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Nucleophilic Trifluoromethylation Reactions of Organic Compounds with (Trifluoromethyl)trimethylsilane

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1. Introduction

The introduction of a fluorine atom or perfluoroalkyl group, particularly a trifluoromethyl group, into an organic compound can bring about remarkable changes in the physical, chemical and biological properties that result in new compounds/materials making them suitable for diverse applications in the areas of materials science, agrochemistry, and industry.[1–5] The influence of the trifluoromethyl group in biologically active molecules is often associated with increased lipophilicity that this substituent imparts. In addition, its electronegativity and relatively small size (only two and one-half times the volume of a methyl group) are contributing factors.[6] While a wide variety of methods have been developed for introducing trifluoromethyl groups into organic compounds,[7] the utilization of (trifluoromethyl)trimethylsilane (Me_3SiCF_3) as a nucleophilic trifluoromethylating reagent is rapidly becoming the method of choice.[8]

This review is concerned specifically with the synthesis of compounds that contain the CF_3 group via nucleophilic trifluoromethylation reactions using Me_3SiCF_3. The latest review available[8] covers almost all the trifluoromethylation reactions of organic molecules with Me_3SiCF_3 through 1996. In the past 3 years, a large number of publications involving Me_3SiCF_3 have appeared. This review covers the trifluoromethylation reactions of organic compounds with Me_3SiCF_3 as a nucleophilic trifluoromethylating agent from January 1997 and including a few that were omitted from the previous review.

2. Preparation of Trimethyl(trifluoromethyl)silane

There are several methods available for the synthesis of Me_3SiCF_3 with variable yields. Unfortunately, with the

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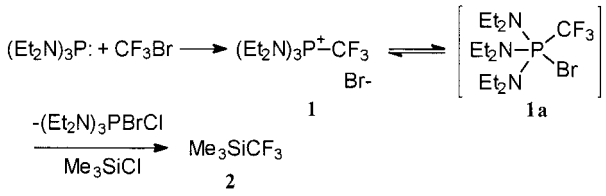


Scheme 1.

phase out of the use of bromotrifluoromethane, because of its high survivabilty in the atmosphere, alternative preparative routes may be required.

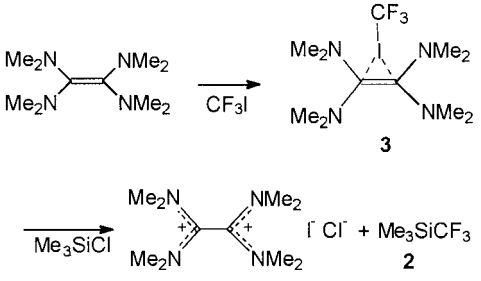
2.1. Ruppert's method and its modifications

Me_3SiCF_3 was first synthesized by Ruppert in 1984.[9] The reaction involved condensation of CF_3Br and Me_3SiCl, with $(Et_2N)_3P$ (HEPT) (Scheme 1). The reaction mechanism involves the formation of the phosphonium salt **1** through bromophilic attack of the phosphorus center of $(Et_3N)_3P$ by CF_3Br. The phosphonium salt **1** which is in equilibrium with intermediate **1a** reacts with Me_3SiCl by in situ transfer to give Me_3SiCF_3 (**2**) as a colorless liquid (bp 54–55°C). Ruppert's procedure was later modified by Prakash and his coworkers[10] but the method still requires utilization of more than 2 equiv. of CF_3Br. The above procedure was then simplified by Gassman et al.[11] in a rather high yield synthesis which only required 1.2 equiv. of CF_3Br per equivalent of HEPT where the reaction was carried out at −78°C. Rather than evaporating the CF_3Br at −30 to −60°C as in the Prakash synthesis, Gassman used balloons to confine the CF_3Br gas thus pressurizing the reaction mixture slightly. This may contribute to a superior yield (85%) in this procedure.

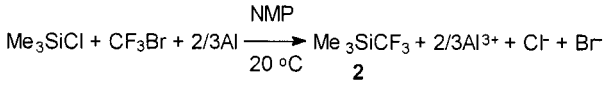
Pawelke has also reported[12] that the reaction of CF_3I and tetrakis(dimethylamino)-ethylene formed a charge transfer complex **3** which acts as a trifluoromethylating agent in reaction with Me_3SiCl producing **2** in 94% yield (Scheme 2). Somewhat surprisingly, CF_3Br was found to be ineffective in this case with the formation of **2** being observed in only trace amounts.

2.2. Aluminum-induced synthesis

The main disadvantage of the methods reported so far is their relative practical inconvenience and high cost of the reagents involved, [$(Et_2N)_3P$ in Ruppert's procedure and CF_3I in Pawelke's]. In order to circumvent these limitations, several aluminum-mediated reductive methods have been



Scheme 2.



Scheme 3.

developed. Although the two electron reduction of CF_3Br gives a highly unstable trifluoromethyl anion, conditions under which it could be efficiently generated and trapped were found. The aluminum anode technique was applied to convert CF_3Br into **2** in good isolated yield.[13,14] Grobe has reported efficient trifluoromethylation of chlorotrimethylsilane with aluminum powder in *N*-methyl pyrrolidinone. **2** was isolated on a preparative scale in 62% isolated yield[15] (Scheme 3).

2.3. Electrochemical synthesis

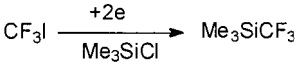
Me_3SiCF_3 (**2**) was also synthesized in 32% yield by the electrochemical reduction of CF_3I in the presence of chlorotrimethylsilane[16] (Scheme 4). Because of the diminishing supply of CF_3Br, work is currently underway to develop a new high yield route to **2** by using CF_3H and other available CF_3-containing moieties.[17]

3. Trifluoromethylation Reactions

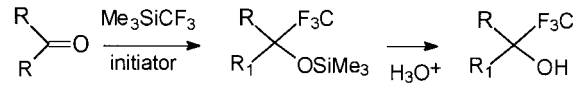
Nucleophilic trifluoromethylation reactions of organic compounds using Me_3SiCF_3 are very similar to nucleophilic allylation or cyanation reactions which involve the use of allyl or cyanotrimethylsilane.[18,19] The Si–CF_3 bond in Me_3SiCF_3 is weak due to the highly electron withdrawing nature of the trifluoromethyl group.[20a,b] It is easily cleaved by fluoride ion to produce Me_3SiF and to liberate CF_3^- as the nucleophile which attacks the electrophilic carbon in the substrate and finally results in transfer of the CF_3 group. Trifluoromethylation reactions with Me_3SiCF_3 are also very much dependent on the electronic nature of the substrates. Because of the electrophilic nature of the carbonyl carbon, simple aldehydes and ketones are very reactive to nucleophilic attack by Me_3SiCF_3 in the presence of a fluoride ion source. Simple esters, amides, imines and lactones are less reactive with Me_3SiCF_3 due to electron donation from the adjacent oxygen or nitrogen atoms causing the deactivation of the C=O or C=N group. With such deactivated substrates, either no reaction took place or the intermediates formed were claimed to be unstable and to decompose[21] to give byproducts or starting materials. The recent reactions of Me_3SiCF_3 with different substrates are summarized below.

3.1. Aldehydes and ketones

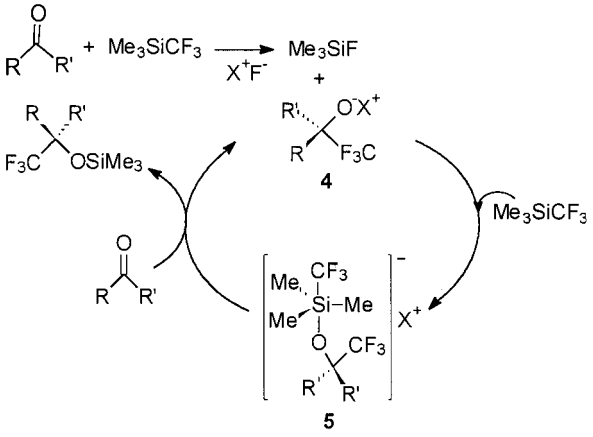
In general, the trifluoromethylation reactions of aldehydes or ketones with Me_3SiCF_3 proceed as shown in Scheme 5. Upon the addition of the appropriate nucleophilic fluoride ion initiator into a mixture of an aldehyde or ketone and



Scheme 4.



Scheme 5.



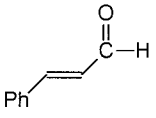
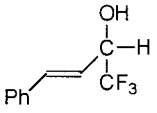
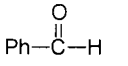
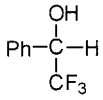
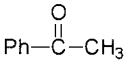
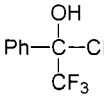
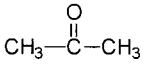
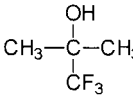
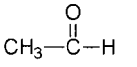
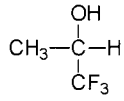
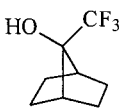
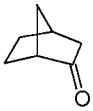
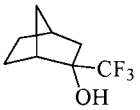
Scheme 6.

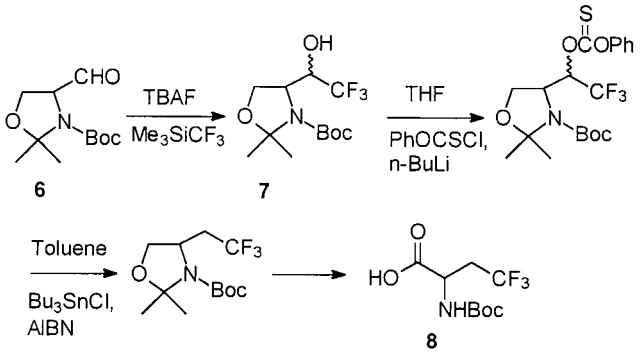
Me_3SiCF_3 the trimethylsilylated ether intermediate was produced. Desilylation of the intermediate with aqueous hydrochloric acid gave the trifluoromethylated alcohol as the final product. Depending on the aldehyde or ketone used, the trifluoromethylation reactions were found to be solvent and initiator dependent. While tetrabutylammonium fluoride (TBAF) is commonly used[22a–d] as an initiator, recently CsF[23a,b] has been found to be at least as effective. THF is most commonly used as a solvent for the trifluoromethylation reaction but glyme has also been found to be a suitable solvent. Many reactions proceed without any solvent.

The detailed mechanism of the nucleophilic trifluoromethylation of the carbonyl compound have been described in the literature.[8] For convenience, it is given in Scheme 6. The addition of a catalytic amount of fluoride initiator to a mixture of carbonyl compound and Me_3SiCF_3 resulted in the initial formation of gaseous Me_3SiF and an alkoxide adduct (**4**). The adduct is stabilized by the X^+ cation. The reaction between the adduct and Me_3SiCF_3 results in the formation of the pentavalent complex **5**. In the next step the CF_3 group is transferred to the electrophilic carbon of the carbonyl functionality until all of the starting material has reacted.

In 1989 Prakash and his coworkers reported the first nucleophilic trifluoromethylation of aldehydes and ketones using Me_3SiCF_3 in the presence of TBAF.[8] Based on that work a variety of aldehydes and ketones have been converted into secondary trifluoromethylated carbinols. These considerable efforts were reviewed.[8] We have recently reported the reactions of Me_3SiCF_3 with aldehydes and ketones[23a] by using a cesium fluoride initiator. In the case of liquid

Table 1. CsF Catalyzed trifluoromethylation reactions of aldehydes and ketones with Me_3SiCF_3 (Ref. 23a)

substrate	solvent	t (h)	products	Yield (%)
	glyme	1.5		92
	neat	6		88
	neat	5		93
	neat	1.5		89
	neat	1		85
	glyme	1		90
	glyme	1.5		95



Scheme 7.

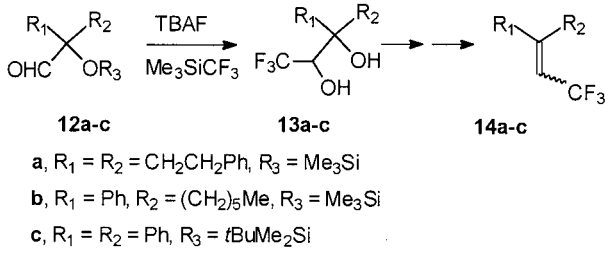
substrates, the reactions go smoothly in the absence of solvent. The reactions also succeeded when monoglyme was used as a solvent for the reactions (Table 1).

Qing and his group have reported[24] the reaction of Me_3SiCF_3 with Garner's aldehyde (**6**) in the presence of TBAF to give the corresponding trifluoromethylated alcohol (**7**). **7** was ultimately converted into (2*R*)-*N*-butoxycarbonyl-2-amino-4,4,4-trifluorobutanoic acid (**8**) (Scheme 7).

The reaction of Me_3SiCF_3 with **9** in the presence of TBAF gave the corresponding trifluoromethylated alcohol derivative (**10**).[25] Interestingly it has been found that Me_3SiCF_3 reacted selectively only with the aldehyde and not with the keto group which is present in **9**. This may arise from the activation of the aldehyde carbon by the presence of two adjacent electron withdrawing groups. Finally, **10** was converted into a trifluoroethylidine derivative (**11**) in good yield (Scheme 8).

These workers have also reported the reactions of **12a–c** with Me_3SiCF_3 to give diols **13a–c** which were finally converted into trifluoroethylidine derivatives (**14a–c**) (Scheme 9).

T. Fuchikami and his coworkers have found[26] that the trifluoromethylation reaction of carbonyl compounds with Me_3SiCF_3 can also be catalyzed by Lewis bases such as Et_3N, *n*-Bu_2NH, pyridine, Ph_3P (Scheme 10). These Lewis base catalyzed reactions proceed more slowly and the yields of the final products are lower than when fluoride ion is



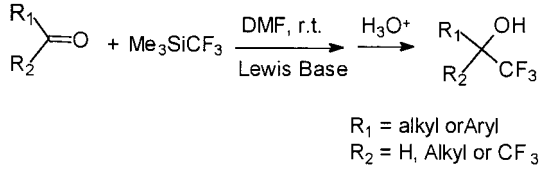
Scheme 9.

utilized. Asymmetric trifluoromethylation of benzaldehyde catalyzed by quinone was also reported but the ee (%) was only 9.

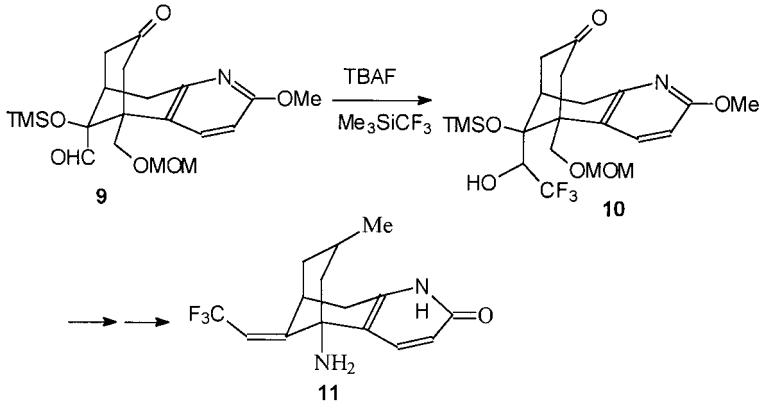
We have recently used Me_3SiCF_3 for the efficient synthesis of 2,2,2-trifluoro-1-(*N*,*N*-dialkylaminophenyl)ethanols and 2,2,2-trifluoro-1-(hydroxy)ethanol derivatives (Table 2).[27]

Portella and his coworkers have utilized Me_3SiCF_3 in the synthesis of 2,2-difluoro-1,5-diketones[28] which are important building blocks for the synthesis of *gem*-difluorinated compounds. The reaction of acylsilanes (**15a,b**) with Me_3SiCF_3 in the presence of fluoride initiator produced difluoroenoxysilanes (**16a,b**) which were allowed to react with enone (**17**) in the presence of a Lewis acid to give 2,2-difluoro-1,5-diketones (**18a,b**) in 66–67% yields (Scheme 11). By the same procedure, compounds **19**, **20** and **21** were isolated in 51–60% yields.

The reaction of **22** with Me_3SiCF_3 in the presence of Bu_4N^+ $Ph_3SnF_2^-$ gives 1-*tert*-butyldimethylsilyloxy-1-phenyl-difluoroethane (**23**) in 88% yield. **23** was treated with benzoyl- or acetyl trimethylsilane (**24a,b**) with $BiCl_3$ activation, leading to aldols (**25a,b**). The latter produced the corresponding 2-difluoro-1,3-diketones (**26a,b**) by treating

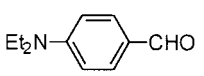
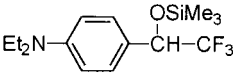
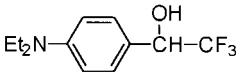
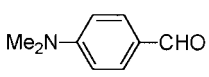
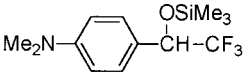
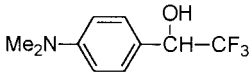
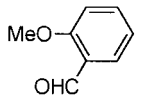
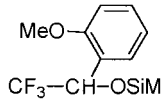
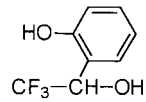
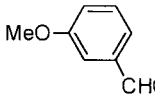
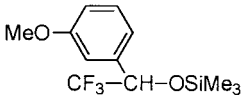
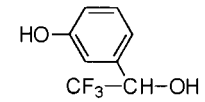
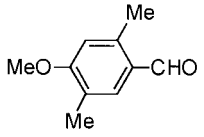
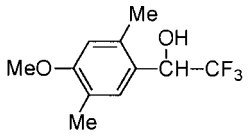
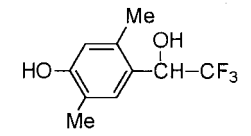
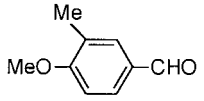
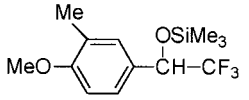
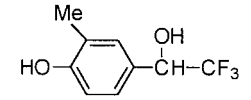
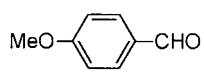
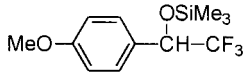
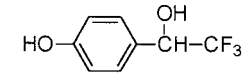


Scheme 10.



Scheme 8.

Table 2. Synthesis of 2,2,2-trifluoro-1-(*N*,*N*-dialkylaminophenyl)ethanols and 2,2,2-trifluoro-1-(hydroxyaryl)ethanols using Me_3SiCF_3 (Ref. 27)

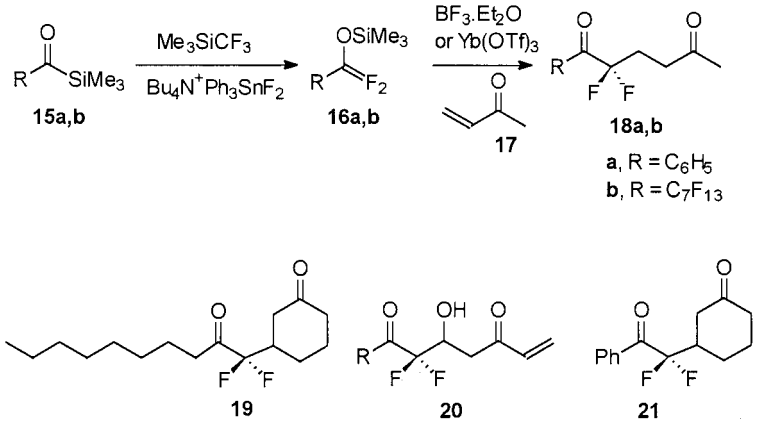
Substrate	Intermediate	Product	Yield (%)
			95
			95
			92
			94
			92
			93
			92

with TBAF in THF/aq. HCl (Scheme 12). The C-silylated cyclic aldols (**29a,b**) were prepared in good yield by the reaction of *tert*-butylacetyl bis-silane (**27a,b**) with Me_3SiCF_3 followed by treating with $BiCl_3$. **29a,b** were converted into the corresponding 2-fluoro-3-hydroxy-cyclohexen-2-ones (**30a,b**) in good yields (Scheme 12).[29]

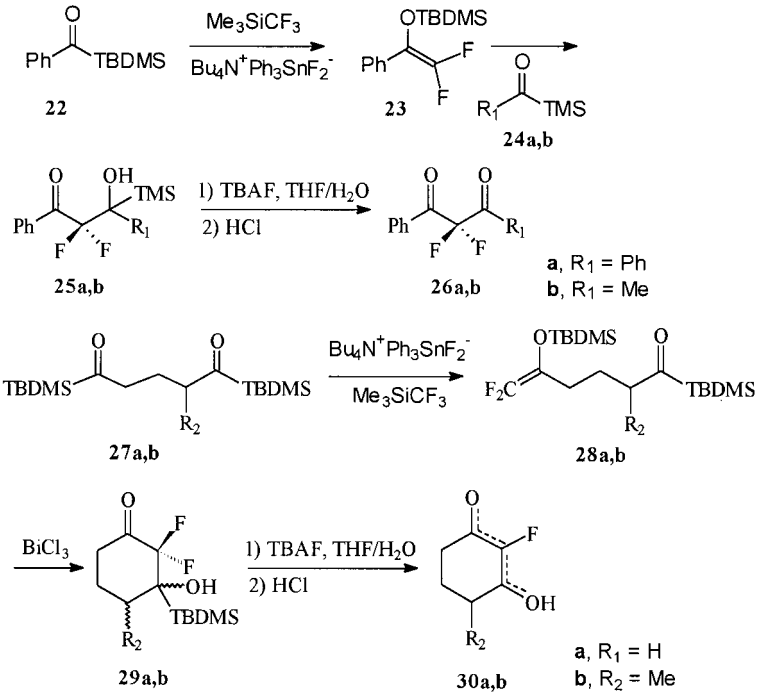
Fuchikami and his coworkers have also found a unique reactivity of amino ketones with Me_3SiCF_3. In DMF in the absence of any promotor the desired trifluoromethylated alcohols were formed in good to moderate yield depending on the substrates (Table 3).[30] It has been observed that the reactivity of the substrate is strongly dependent on the length of the carbon chain between the amino group and the carbonyl group of the amino ketones. In the reaction mechanism, a cyclic intermediate has been proposed (Scheme 13) which is generated by the coordination of both the amino and carbonyl groups to the silicon atom. Some diastereoselectivity in the product has been also obtained.

3.2. Enones and indinones

Fluorinated allylic alcohols are useful intermediates for the synthesis of biologically active compounds. Their syntheses were reported by Shen and his coworkers[31] by reacting the ylide anion of the type $Ph_3P^+C^-HCO^-(CF_3)(CH)_2CH_3$

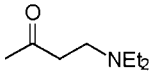
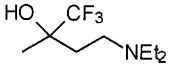
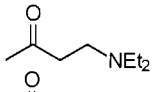
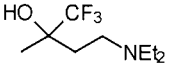
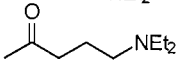
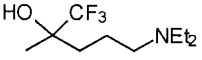
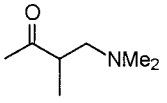
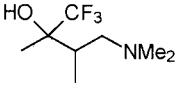
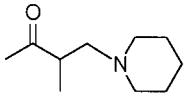
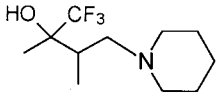
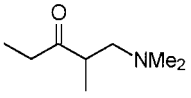
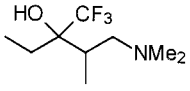
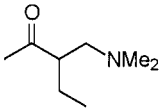
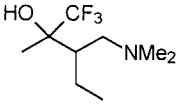
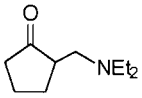
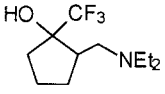
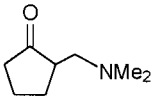
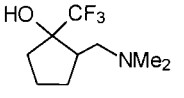
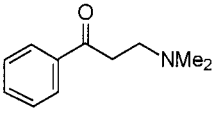
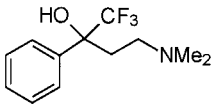


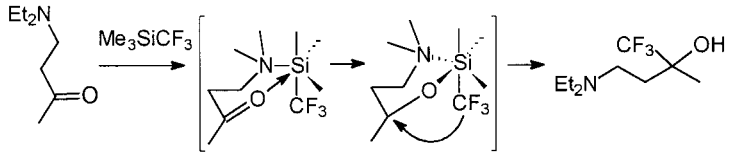
Scheme 11.



Scheme 12.

Table 3. Trifluoromethylation of aminoketones with Me_3SiCF_3 (Ref. 30)

Substrate	Product	Yield (%)
		82
		56
		78
		51
		44
		67
		36
		24
		32
		52



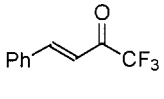
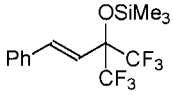
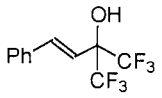
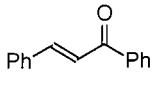
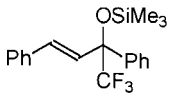
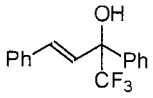
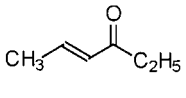
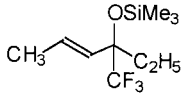
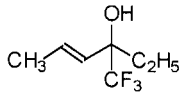
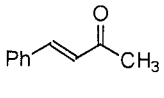
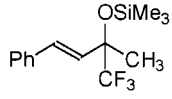
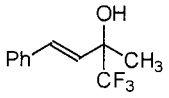
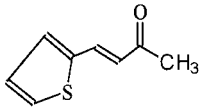
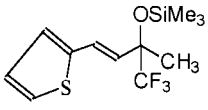
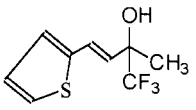
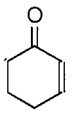
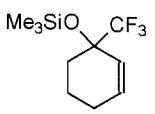
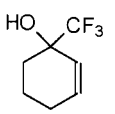
Scheme 13.

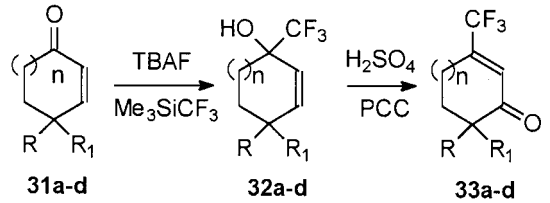
(generated by the reaction of *n*-butyllithium with trifluoroacetylmethylene–triphenylphosphorane) with an aldehyde but the yields are low (40–55%). We have found that the *trans* enones reacted cleanly with Me_3SiCF_3 in the presence of a catalytic amount of cesium fluoride to produce trimethylsilyether intermediates in essentially quantitative yields. Hydrolysis of the intermediates with aqueous HCl gave *trans*-α-trifluoromethylated allylic alcohols in excellent isolated yields (Table 4).[23b]

Several conjugated cyclic enones (**31a–d**) with Me_3SiCF_3 produced the corresponding trifluoromethylated alcohols (**32a–d**).[32] **32a–d** were finally converted into trifluoromethylated tertiary allylic alcohols (**33a–d**) (in 20–34% isolated yields) by the reaction of pyridinium chlorochromate (PCC) in the presence of a small amount of sulfuric acid (Scheme 14).

Compound **34** was also converted into **35** (60% yield) which

Table 4. Trifluoromethylation of enones with Me_3SiCF_3 (Ref. 23b)

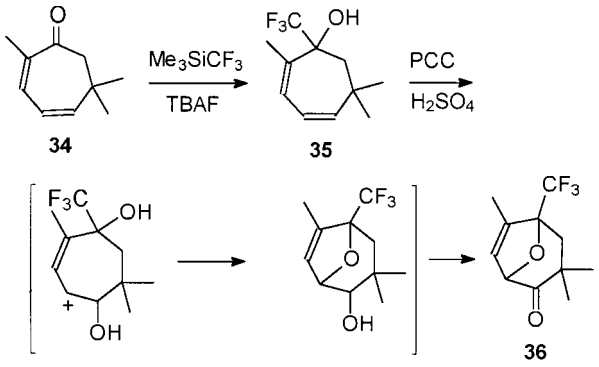
Substrate	Intermediate	Yield (%)	Product	Yield (%)
		98		95
		99		96
		97		91
		98		96
		98		95
		96		92



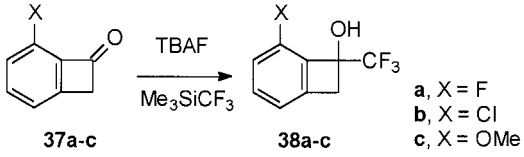
31a-d **32a-d** **33a-d**

a, n = 1, R, R_1 = H
b, n = 1, R, R_1 = Me
c, n = 1, R = H, R_1 = 2-propenyl
d, n = 2, R, R_1 = H

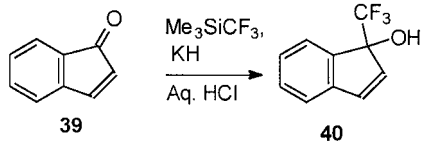
Scheme 14.



Scheme 15.



Scheme 16.



Scheme 17.

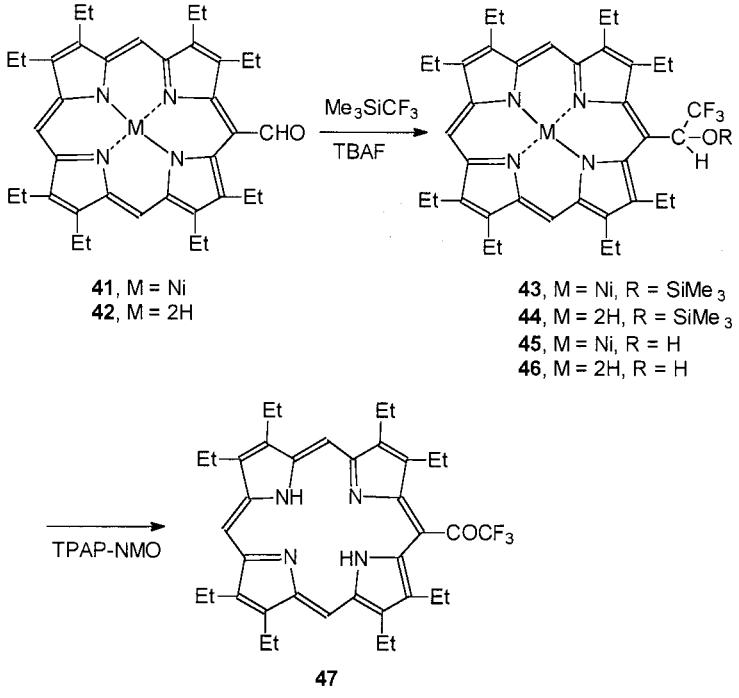
upon action with PCC gave **36** as the final product in 26% isolated yield. It has been proposed that PCC under acidic conditions hydroxylated the double bond which is farthest removed from the CF_3 in **35** and produced a carbocation which is subsequently attacked by the hydroxyl group geminal to the CF_3-containing carbon atom (Scheme 15).

Benzocyclobutenone derivatives (**37a–c**) were converted to the corresponding trifluoromethylcyclobutanols (**38a–c**) in 54–59% yield by reaction with Me_3SiCF_3 in the presence of TBAF (Scheme 16).[33]

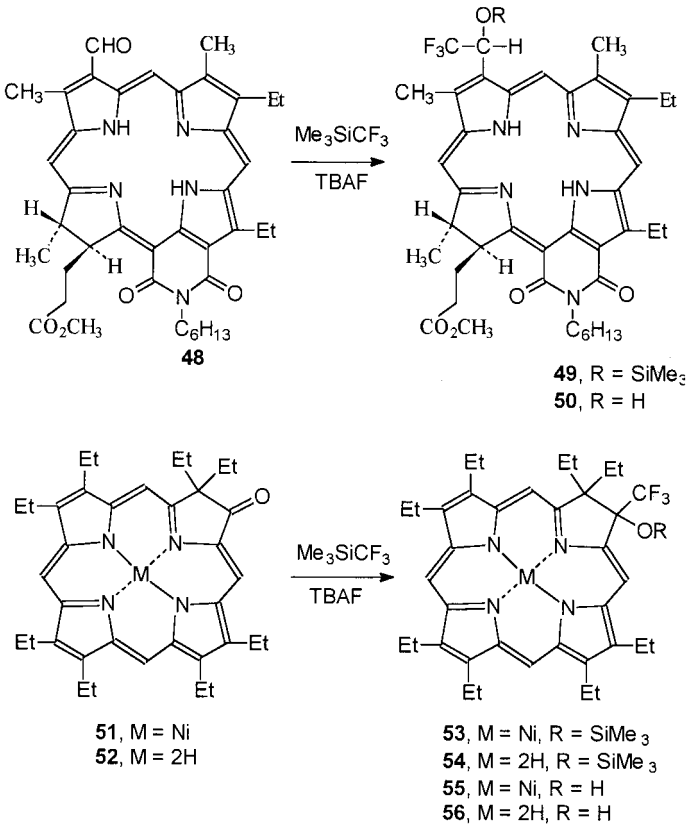
Tidwell and his coworkers have reported[34] the reaction of indenone (**39**) with 2 in the presence of KF to generate the corresponding trifluoromethylated silylether derivative which give the trifluoromethylated alcohol derivative (**40**) after hydrolysis (Scheme 17)

3.3. Porphyrins, chlorins and bacteriochlorins

These days a promising technique known as photodynamic therapy (PDT) technique is used in the treatment of cancer.[35] In this therapy, patients are given intravenous injections of a porphyrin-based drug and accumulates in cancer cells in generally higher concentrations than in surrounding tissue. The photosensitizing agent is then activated by a visible or near IR light at cancer sites through fiber optics and thus the infected site is detected. Compared to non-fluorinated analogs the compounds containing fluorinated moieties generally have shown improved PDT efficiency. Pandey and his coworkers[36] have recently reported the first nucleophilic trifluoromethylations of porphyrins, chlorins and bacteriochlorins with Me_3SiCF_3. They reacted *meso*-formyl-octaethyl porphyrin **41** [Ni(II) complex] and **42** (free base) with Me_3SiCF_3 in the presence of a catalytic amount of TBAF (Scheme 18), which produced the corresponding trimethylsilyl analogs **43** and **44** in excellent yield. After acid hydrolysis the products **45** and **46** were obtained in good yields. The reaction of **46** with



Scheme 18.



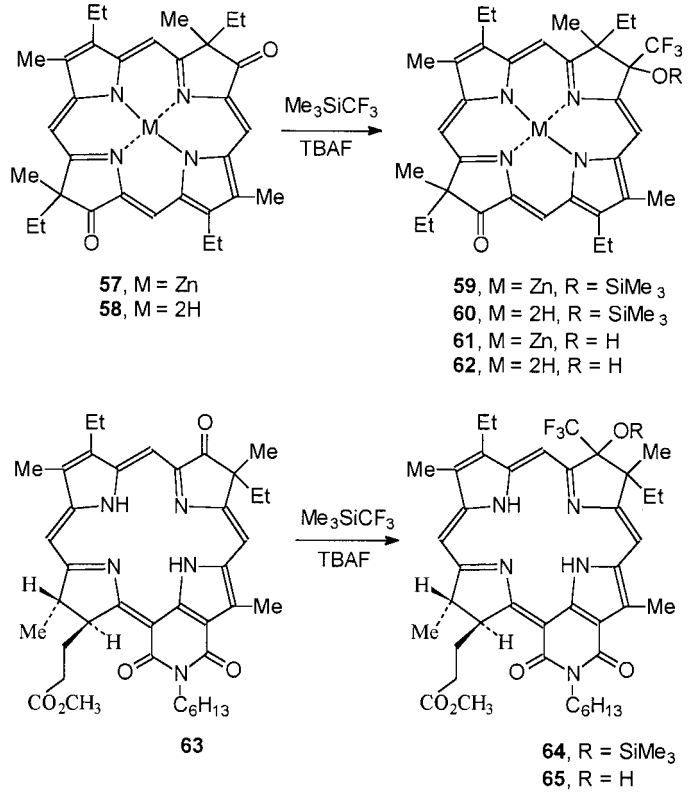
48

49, R = $SiMe_3$
50, R = H

51, M = Ni
52, M = 2H

53, M = Ni, R = $SiMe_3$
54, M = 2H, R = $SiMe_3$
55, M = Ni, R = H
56, M = 2H, R = H

Scheme 19.



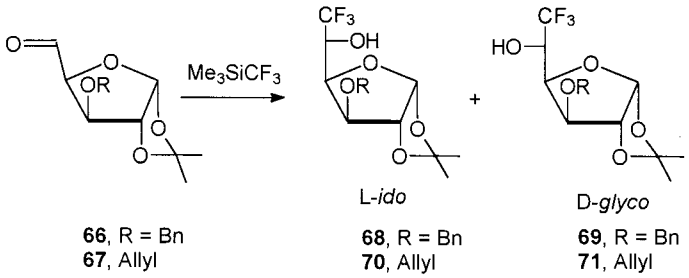
57, M = Zn
58, M = 2H

59, M = Zn, R = $SiMe_3$
60, M = 2H, R = $SiMe_3$
61, M = Zn, R = H
62, M = 2H, R = H

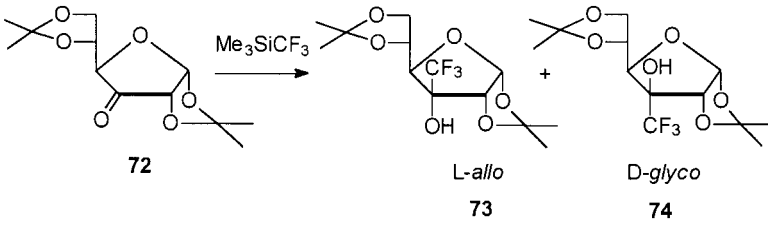
63

64, R = $SiMe_3$
65, R = H

Scheme 20.



Scheme 21.



Scheme 22.

tetrapropylammonium perruthenate-*N*-methyl morpholine-*N*-oxide (TPAP-NMO) gave meso trifluoroacetyl porphyrin **47** in quantitative yield.

In the chlorin system, the reactions of *N*-hexyl purpurin imide **48** and Me_3SiCF_3 are catalyzed by TBAF to produce **49** which gave **50** as the final product after hydrolysis (Scheme 19). The reactions of hindered keto chlorins **51** and **52** were also examined with Me_3SiCF_3. The trimethylsilyl ether derivatives **53** and **54** produced trifluoromethyl alcohol derivatives **55** and **56** in good yields.

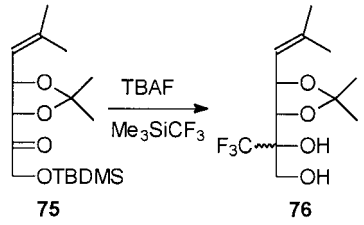
Diketobacteriochlorins **57** and **58** were reacted with Me_3SiCF_3 and afforded the expected trifluoromethyl derivatives **59**–**62** (Scheme 20). Interestingly, the bacteriochlorins **57** and **58** containing two keto groups at diagonal pyrrole units, under various reaction conditions, afforded only the mono trifluoromethyl analogs. Under similar reaction conditions, 7-ketobacteriochlorin **63** reacted with Me_3SiCF_3 and produced the corresponding trifluoromethylsiloxy analog **64** in 92% yield. After hydrolysis the final hydroxy derivative **65** was obtained.

3.4. Carbohydrates

Fluorine-containing carbohydrates have their applications in the synthesis of stereocontrolled glycosidation,[37] in enzymatic studies,[38] in molecular recognition studies,[39] and as bioactive compounds.[40] In this context, pentodialdoses (**66** and **67**) were trifluoromethylated by Me_3SiCF_3 at 0°C in methylene chloride in the presence of a catalytic amount of *n*-tetrabutylammonium difluorotriphenylstannate.[41] This reaction yielded a mixture of intermediate silylethers quantitatively which was easily hydrolyzed to give a mixture of the two epimeric L-ido (**68/69**) and D-gluco (**70/71**) products in an 80/20 ratio (Scheme 21). The epimers were separated by flash column chromatography and the stereochemical assignment was determined.

Trifluoromethylation of 3-oxo-glucose (**72**) also proceeded smoothly with Me_3SiCF_3. In contrast to the addition of pentodialdoses, Me_3SiCF_3 added with complete stereoselectivity to the b-face, and produced the L-allo (**73**) and D-gluco (**74**) in the ratio of 75:25, respectively (Scheme 22).

Ribulose derivative (**75**) reacted with Me_3SiCF_3 in the presence of TBAF to give trifluoromethylated alcohol analog (**76**) in 69% yield[42] as a mixture of D-robo and L-lyxo in 4:1 ratio (Scheme 23).



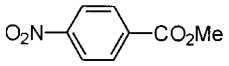
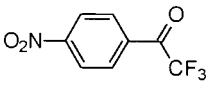
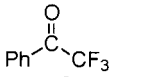
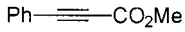
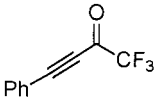
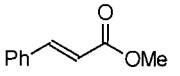
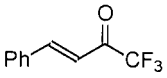
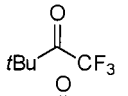
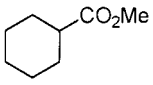
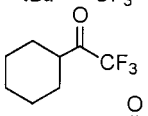
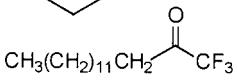
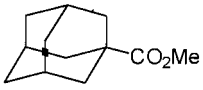
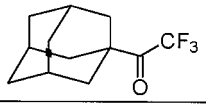
Scheme 23.

3.5. Esters, sulfonic, sulfinic and selenic esters and α-ketoesters

It was suggested earlier that simple esters are not sufficiently electrophilic to react with Me_3SiCF_3 even when stoichiometric amounts of fluoride ion initiators were used.[8] Recently, Prakash and his coworkers[43] synthesized trifluoromethyl ketones by reacting Me_3SiCF_3 with carboxylic esters in the presence of TBAF (Table 5). The success of reactions between esters and Me_3SiCF_3 required careful drying of all solvents and reagents. A commercial solution of TBAF (1 M in THF) was dried for 4 h under a dry argon atmosphere over activated 4 Å molecular sieves (4 mL of solution per gram of molecular sieves). One failure of this methodology was with methyl propiolate where the desired trifluoromethylated product did not form and extensive polymerization occurred (Table 5).

Recently we have reported a more effective route to trifluoromethyl ketones from carboxylic esters with Me_3SiCF_3.[23a] In

Table 5. Reactions of Me_3SiCF_3 (1.25 equiv.) with various esters induced by 2.5 mol% TBAF in THF (Ref. 43)

Reagent	Solvent	*t* [h]	Product	Yield (%)
	CH_2Cl_2	18		81
$PhCO_2Me$	toluene	18		95
	pentane	24		0[a]
	pentane	24		85
$tBuCO_2Me$	toluene	72		68
	pentane	48		72
$CH_3(CH_2)_{12}CO_2Me$	toluene	24		75
	pentane	72		70

[a] Extensive polymerization

our procedure, CsF was used as an initiator and glyme was the solvent of choice. Methyl propiolate cleanly gave the desired product in excellent isolated yield (Table 6).

We found that CsF also catalyzed the trifluoromethylation reactions of sulfonic, sulfinic and selenic esters (Table 7) in good yields.[23a]

Nucleophilic trifluoromethylation of aliphatic α-ketoesters was reported by Prakash and his coworkers.[44] By using the same procedure, a recently issued patent claimed the reaction of several aromatic (bearing different substituents on the ring) α-ketoesters with Me_3SiCF_3 to produce the corresponding trifluoromethylated silylether derivatives.[45] The reactions of the silylether intermediates were further carried

Table 6. CsF catalyzed trifluoromethylation of esters with Me_3SiCF_3 (Ref. 23a)

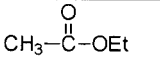
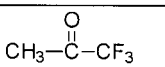
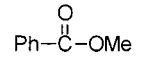
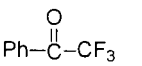
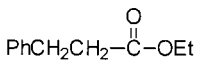
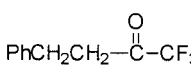
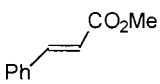
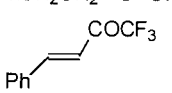
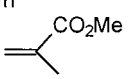
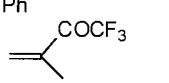
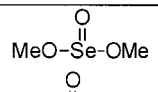
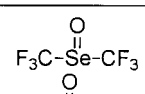
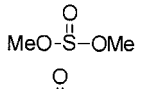
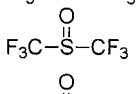
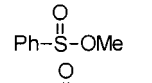
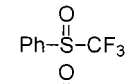
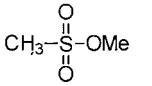
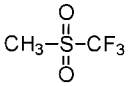
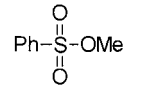
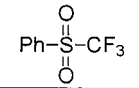
substrate	solvent	T (°C)	t (h)	product	yield (%)
	neat	25	1		86
	neat	25	1		90
	neat	25	4		90
	glyme	25	3		90
	neat	25	3		84
$Ph{-}{\equiv}{-}CO_2Me$	neat	25	3	$Ph{-}{\equiv}{-}COCF_3$	86
$Ph{-}{\equiv}{-}CO_2Et$	neat	25	3	$Ph{-}{\equiv}{-}COCF_3$	87

Table 7. CsF catalyzed trifluoromethylation of sulfonic, sulfinic and selenic esters with Me_3SiCF_3 (Ref. 23a)

substrate	solvent	T (°C)	t (h)	product	yield (%)
	neat/PhCN	50	2		84
	neat/PhCN	50	0.5		77
	neat	25	6		95
	PhCN	100	6		88
	neat	100	6		85

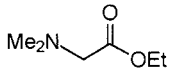
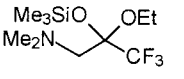
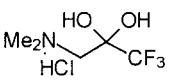
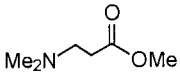
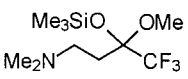
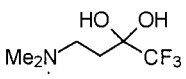
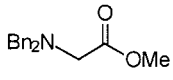
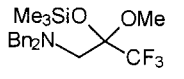
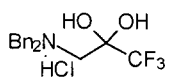
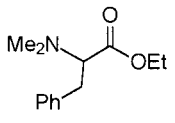
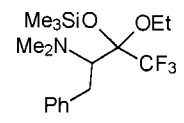
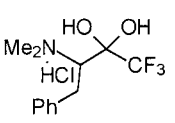
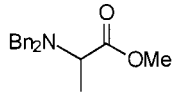
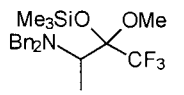
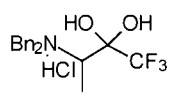
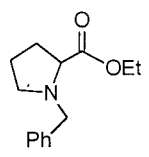
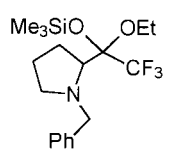
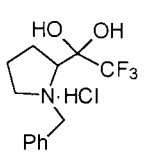
out with alcoholate and alkylating agents to produce α-alkoxy-α-trifluoromethyarylacetic acids and esters.

3.6. Aminoesters and oxazolidinones

N-Protected amino esters reacted with Me_3SiCF_3 to produce trimethylsilylether intermediates. Hydrolysis with aqueous HCl led to the formation of α- or β-amino trifluoromethylketones as hydrated hydrochloride salts in good yield (Table 8).[46]

Synthesis of α-amino trifluoromethylketones resulted from the nucleophilic trifluoromethylation of oxazolidines with Me_3SiCF_3 in the presence of CsF as initiator followed by hydrolysis with Amberlite IR-120 in acetonitrile (Scheme 24).[47]

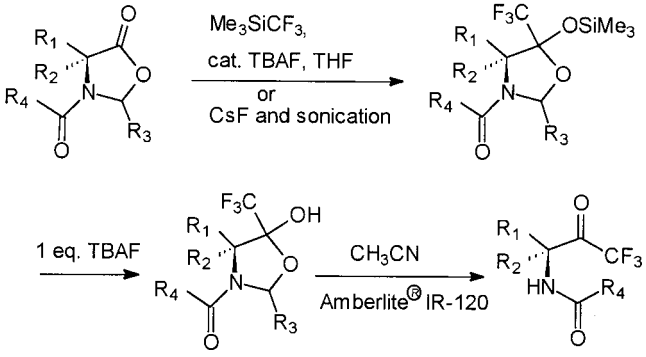
Table 8. Reaction of *N*-protected amino esters with Me_3SiCF_3 (Ref. 46)

Substrate	Intermediate	Product	Yield (%)
			85
			85
			83
			81
			82
			82

A proposed mechanism for the trifluoromethylation of oxazolidine-5-ones (Scheme 25) is similar to that described for aldehyde and ketones in Scheme 6. In the case of oxazolidin-5-one, the precoordination of Me_3SiCF_3 to the oxazolidin-5-one activates the carbonyl group toward nucleophilic attack and may lead to the formation of a complex such as **86**.

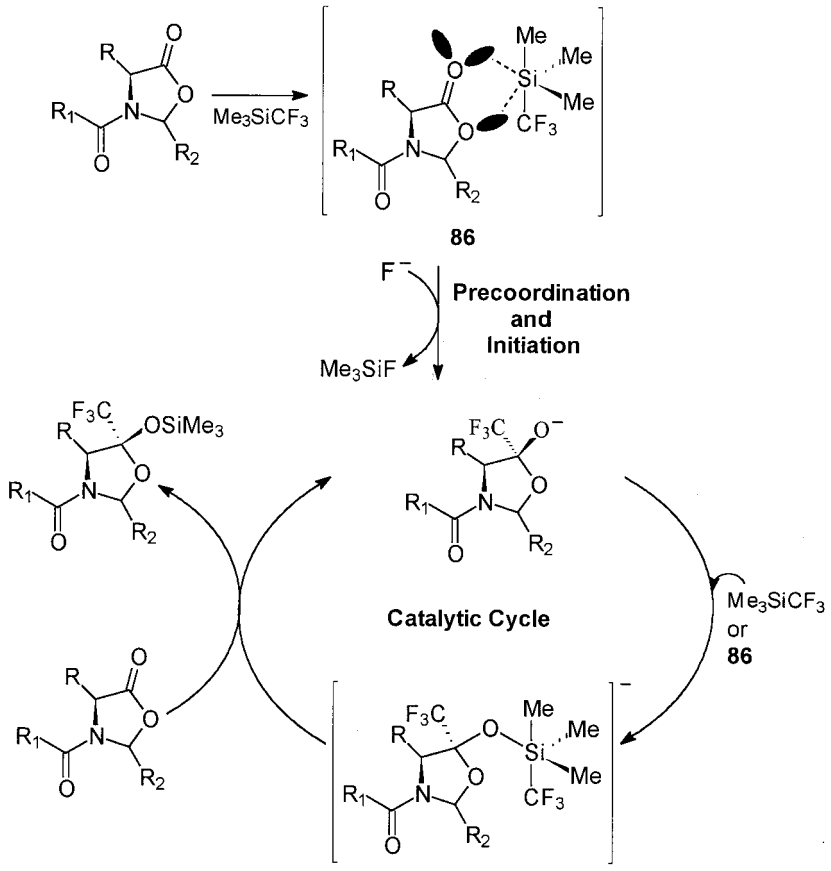
3.7. Amides and α-ketoamides

The reactivity of simple amides with Me_3SiCF_3 has been described.[8] It has been mentioned that benzamide and acetamide did not react with Me_3SiCF_3 even when equimolar amounts of initiator were used. However, we have recently observed[48] that an exothermic reaction occurred when *N*,*N*-dimethylacetamide or *N*,*N*-dimethylbenzamide was reacted with Me_3SiCF_3 in the presence of a catalytic amount of CsF.



77, R_1 = Me, R_2 = H, R_3 = *para*-$MeOC_6H_4$, R_4 = $PhCH_2O$
78, R_1 = $PhCH_2$, R_2 = H, R_3 = *para*-$MeOC_6H_4$, R_4 = $PhCH_2O$
79, R_1 = Me_2CH, R_2 = H, R_3 = *para*-$MeOC_6H_4$, R_4 = $PhCh_2O$
80, R_1 = Me, R_2 = H, R_3 = *para*-$MeOC_6H_4$, R_4 = Ph
81, R_1 = H, R_2 = H, R_3 = *para*-$MeOC_6H_4$, R_4 = Ph
82 R_1 = Me, R_2 = Me, R_3 = *para*-$MeOC_6H_4$, R_4 = Ph
83, R_1 = Me, R_2 = H, R_3 = *para*-$MeOC_6H_4$, R_4 = $PhCH_2$
84, R_1 = Me, R_2 = H, R_3 = *para*-$MeOC_6H_4$, R_4 = $PhOCH_2$
85, R_1 = $PhCH_2$, R_2 = H, R_3 = *t*-Bu, R_4 = Ph

Scheme 24.



Scheme 25.

The details of the reactions are unclear. Prakash and his coworkers[49] have reported the synthesis of trifluoromethylated amides from ketones and Me_3SiCF_3 via the Ritter reaction with acetonitrile (Scheme 26). The yields are good to average (Table 9).

We have reported the reactions of α-ketoamides with Me_3SiCF_3 in the presence of a catalytic amount of TBAF in THF.[50] The reactivity of α-ketoamides were found to be similar to the α-keto esters. The α-keto group was found to be reactive at room temperature and produced α-hydroxy α-trifluoromethylated amides in excellent isolated yields after acid hydrolysis (Table 10).

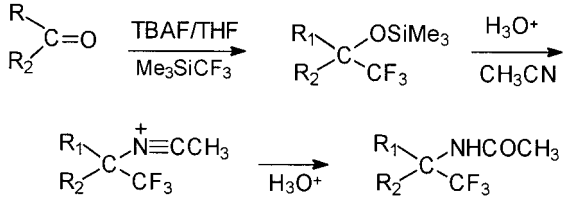
3.8. Imines and nitrones

Just as with amides, imines were reported[8] to be unreactive towards Me_3SiCF_3. However, recently Blazejewski and his coworkers reported[51] the nucleophilic trifluoromethylation of various imines with Me_3SiCF_3. This success was based on preventing the decomposition of the intermediate by trapping it with a suitable electrophile (*N*-trimethylsilylimidazole). Thus, the reaction of imines (**87a–j**) with Me_3SiCF_3 in the presence of CsF and TMS-imidazole gave unisolable intermediates but gave the desired products (**88a–j**) in moderate yields. The concomitant formation of bistrifluoromethylated amine derivatives (**89a,c–f**) in poor yields (Scheme 27) was also observed. The lower yields of **88h–j** are associated with the high basicity of the amines.

The formation of the byproducts (**89a,c–f**) is thought to be due to trifluoromethylation of the trifluoromethylated imine as shown in Scheme 27. The oxidation step in Scheme 28 giving **89a,c–f** to get imines is not understood.

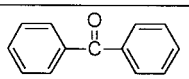
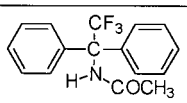
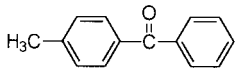
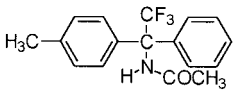
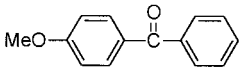
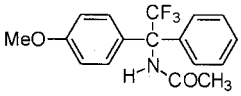
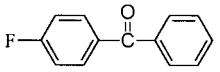
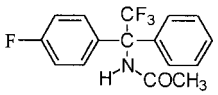
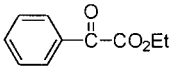
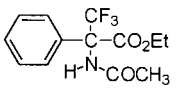
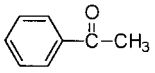
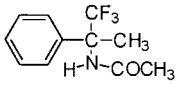
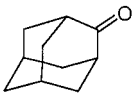
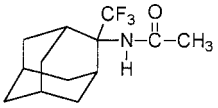
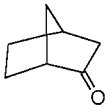
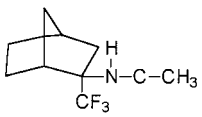
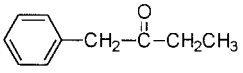
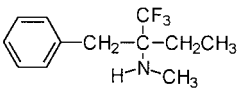
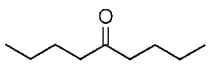
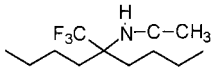
Nelson and his coworkers have reported[52] the nucleophilic trifluoromethylation of nitrones with Me_3SiCF_3. Reaction of nitrones **90a–f** with Me_3SiCF_3 proceeded smoothly at −78°C, but the limited solubility of the nitrones necessitated the use of higher temperature (Scheme 29). The reactions were initiated by the addition of potassium butoxide slurry in THF at regular intervals. The silyl ether adducts, **91a–f**, were found to be quite stable and were characterized by GC and GC–MS, but decomposition has been observed upon exposure to UV light (λ=254 nm). The yields of the products are in the range of 50–90% depending on the substituents.

When the substituent is a furyl group, the silyl ether adduct



Scheme 26.

Table 9. Preparation of trifuloromethylated amides (Ref. 49)

Substrate	Product	M.p. (°C)	Yield
		187-188	68
		161-162	81
		130	66
		180	57
			59
		128	54
		152	40
		152	32
			49
			32

decomposes in the presence of the excess butoxide to give the trifluoromethylated imine in 63% yield.

3.9. Thiocyanate and selenocyanate

Earlier Langlois and his coworkers described[53] a one-pot synthesis of trifluoromethyl sulfides (or selinides) by using disulfides (or diselenides) and 2 equiv. each of Me_3SiCF_3 and of TBAF. The technique suffers from the use of an excess of TBAF which behaves as an undesirable base or nucleophile and more importantly that only one-half of the disulfide and (diselenides) was consumed in giving the desired compound with the other half being wasted as a thiolate (or selenoate). However, the synthesis of trifluoromethyl sulfides (or selenides) (**93a–j**) from the reaction of thiocyanate or selenocyanate (**92a–j**) with Me_3SiCF_3 in the presence of catalytic amounts of TBAF resulted in moderate to good yields[53] (Scheme 30).

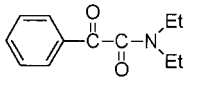
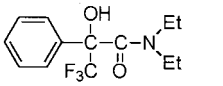
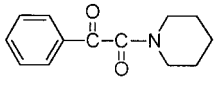
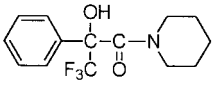
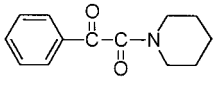
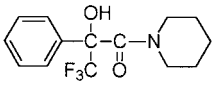
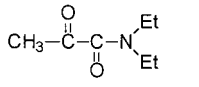
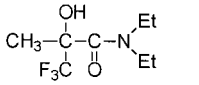
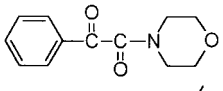
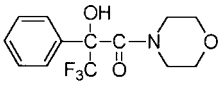
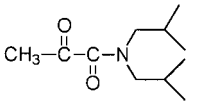
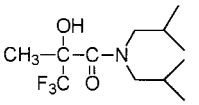
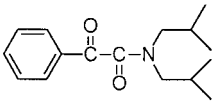
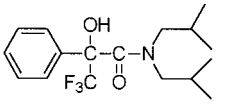
In the proposed mechanism (Scheme 31) for the synthesis of trifluoromethyl sulfides or selenides, it has been assumed that the Si–CN bond is stronger than the Si–CF_3 bond. This assumption is based on the fact that only a catalytic amount of fluoride ion is required to reach the desired results.[54]

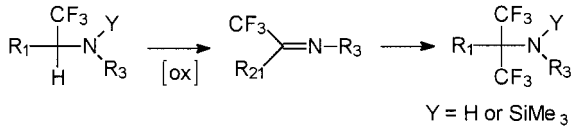
Praly et al. reported the synthesis of trifluoromethylthio-sugar derivatives from thiocyanate precursors.[55] Various protected sugar derivatives (**94a–d**) with thiocyanato groups attached at different positions were reacted with Me_3SiCF_3 in THF in the presence of TBAF to give the corresponding trifluoromethylthio derivatives (**95a–d**) in good yields (Scheme 32).

3.10. Organophosphorus compounds

Recently we have reported the novel synthesis of hexakis-(trifluororomethyl)-cyclotriphosphazene in 90% yield (**97**) via the reaction of hexafluorotricyclophosphazene (**96**) with Me_3SiCF_3 in the presence of a catalytic amount of CsF in THF (Scheme 33).[56] **97** was reported earlier[57] in 12% isolated yield. We have characterized **97** by spectral and single crystal X-ray analyses.

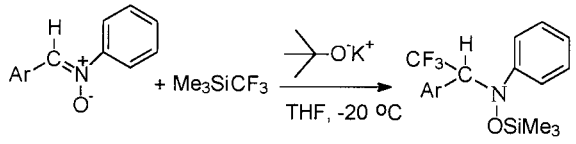
Table 10. Trifluoromethylation of α-keto amides with Me_3SiCF_3 catalyzed by TBAF in THF at room temperature for 3 h (Ref. 50)

Substrate	Product	Yield (%)
		91
		96
		94
		93
		95
		92
		95



Y = H or $SiMe_3$

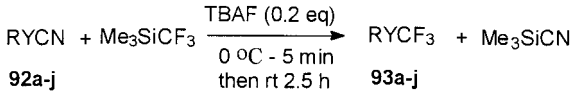
Scheme 28.



90a-f **91a-f**

a, Ar = 4-$MeOC_6H_4$- **d**, 2-Naphthyl
b, Ph, **e**, 2-Furyl
c, 3-$O_2NC_6H_4$- **f**, 4-ClC_6H_4-

Scheme 29.



92a-j **93a-j**

a, R = $PhCH_2$, Y = S **f**, R = 2,4-$(MeO)_2C_6H_4$, Y = S
b, R = $PhCH_2$, Y = S **g**, R = 1-Me-2-pyrolyl, Y = S
c, R = *n*-C_8H_{13}, Y = S **h**, R = PhCH2, Y = Se
d, R = Ph, Y = S **i**, R = *n*-C_8H_{13}, Y = Se
e, R = 4-O_2N-C_6H_4, Y = S **j**, R = Ph, Y = Se

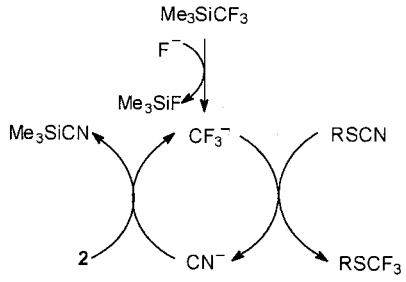
Scheme 30.

4. Miscellaneous Trifluoromethylation Reactions

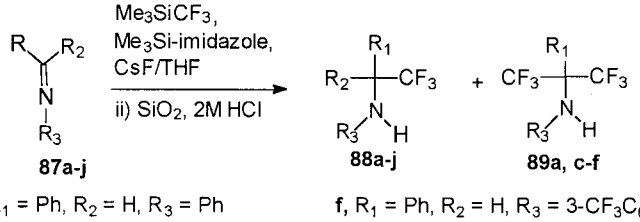
Recently Me_3SiCF_3 was shown to be a very effective reagent for introducing a fluorocarbon ligand into a metal complex.[58] The reaction of Me_3SiCF_3 with $RuHF(CO)L_2$ (L=P^tBu_2Me) (**98**) in the presence of CsF at 25°C led to the generation of a quantitative amount of Me_3SiF and the formation of a six coordinate complex (**99**) via $RuH(CF_3)(CO)L_2$ as the intermediate (Scheme 34).

Clark and his coworkers have reported[59] that tetramethylammonium fluoride reacts with Me_3SiCF_3 in acetonitrile to form a pentacoordinate silicon species (**100**) which can act as a source of fluoride ion, depending on the substrate (Scheme 35).

Naumann has characterized the reaction intermediates **101** and **102** by NMR (^{19}F and ^{29}Si).[60] The reaction of Me_3SiCF_3 with $[Me_4N]^+F^-$ in THF was studied from −90 to −60°C (Scheme 36). A trigonal bipyramidal structure has been proposed for both **101** and **102**.



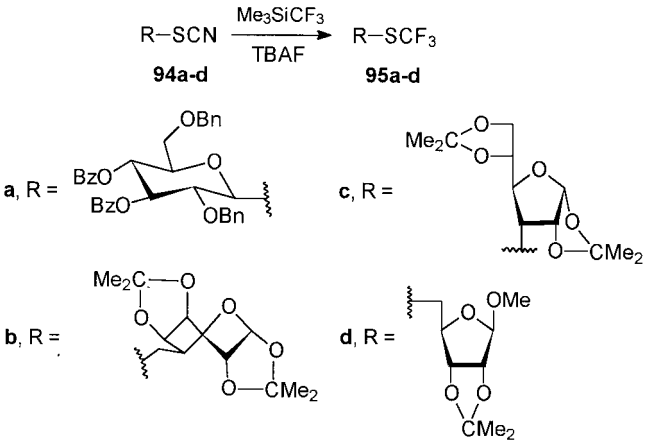
Scheme 31.



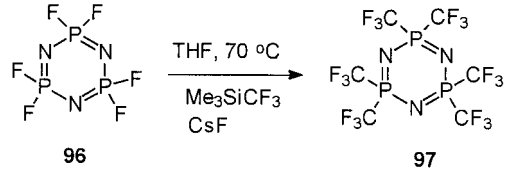
87a-j **88a-j** **89a, c-f**

a, R_1 = Ph, R_2 = H, R_3 = Ph
b, R_1 = 2-naphthyl, R_2 = H, R_3 = Ph
c, R_1 = 2-furyl, R_2 = H, R_3 = Ph
d, R_1 = 3-$MeOC_6H_4$, R_2 = H, R_3 = Ph
e, R_1 = PhCH=CH, R_2 = H, R_3 = Ph
f, R_1 = Ph, R_2 = H, R_3 = 3-$CF_3C_6H_4$
g, R_1 = Ph, R_2 = CF_3, R_3 = Ph
h, R_1 = Ph, R_2 = Me, R_3 = Ph
i, R_1-R_2 = -$(CH_2)_5$-, R_3 = Ph
j, R_1 = Ph, R_2 = H, R_3 = $PhCH_2$

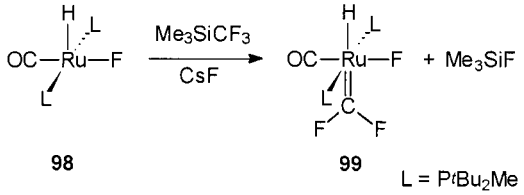
Scheme 27.



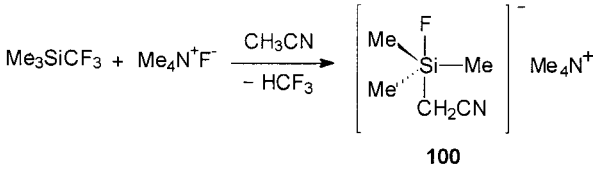
Scheme 32.



Scheme 33.



Scheme 34.



Scheme 35.

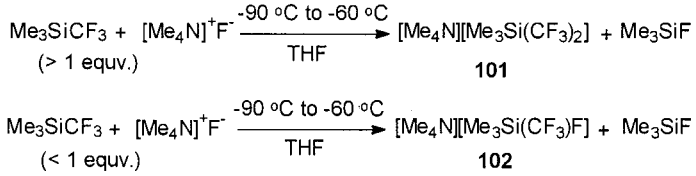
Recently Röschenthaler has succeeded in isolating a hypervalent silicon species, $[(CF_3)_2SiMe_3]^-$, with five Si–C bonds at low temperature.[61] Reaction of Me_3SiCF_3 with **103a–d** in 2:1 molar ratio in monoglyme at −50°C or in THF at −78°C led to the formation of **105a–d** in 95% yields (Scheme 37); **105a** was characterized by single crystal X-ray analysis and was found to be stable up to 0°C but to decompose at 0–5°C with the formation of **103a**; **105b–d** were also isolable but less stable than **105a** and decomposes with the formation of **103b–d** presumably as a function of the counter ion. Compounds **104a–d** are proposed as reaction intermediates.

He has also recently reported that the reaction of bis-(dimethyamino)difluomethame (**106**) with dimethylaminotrimethylsilane in acetonitrile lead to the formation of hexamethylguanidinium fluoride (**107**) in 95% yield (Scheme 38).[62] Interestingly, compound **107** reacted with Me_3SiCF_3 in monoglyme at −80°C gave the stable hypervalent silicate (**108**) as the sole product. Compound **108** was found to be stable in monoglyme solution to −60°C. Upon warming to −50°C, **18** produced **109** and **2** (Scheme 38).[62]

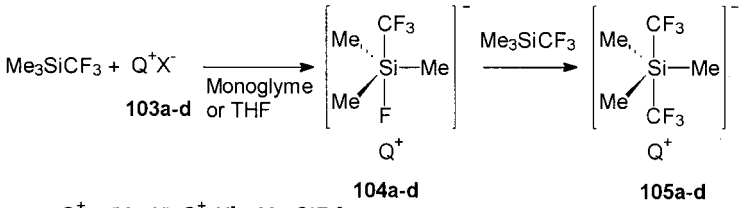
Naumann reported that tris(trifluoromethyl)bismuth (**110**) reacted with the CF_3 anion intermediate (produced from the reaction of Me_3SiCF_3 with $[NMe_4]^+F^-$) in ether, THF or glyme at −70 to −50°C to form the tetrakis(trifluoromethyl)bismuthate (**111**) at −70 to −50°C (Scheme 39).[63]

Clark has found that Me_3SiCF_3 can be activated by KF to produce trifluoromethide which has the ability to replace aromatic nitro or cyano groups under nucleophilic conditions.[64] In these reactions a large excess of KF was used and the yields of the products were low (Table 11).

Recently effective nucleophilic trifluoromethylation reactions by using fluoroform (CF_3H)[65] instead of Me_3SiCF_3 in the presence of base (Scheme 40) have been reported.

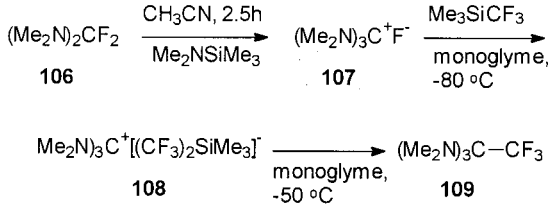


Scheme 36.



a, $Q^+ = (Me_2N)_3S^+$, $X^- = Me_3SiF_2^-$
b, $Q^+ = Me_4N^+$, $X^- = F^-$
c, $Q^+ = (Me_2N)_3C^+$, $X^- = F^-$
d, $Q^+ = (Me_2N)_4P^+$, $X^- = F^-$

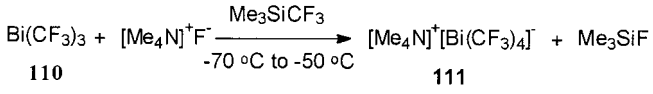
Scheme 37.



Scheme 38.

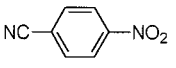
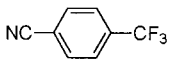
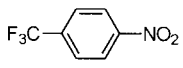
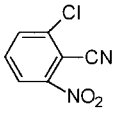
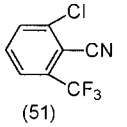
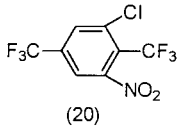
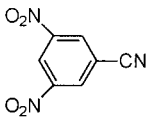
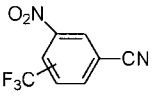
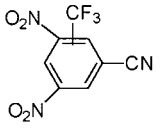
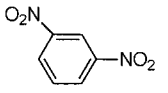
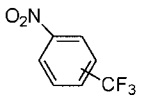
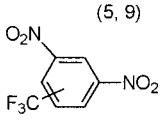
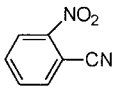
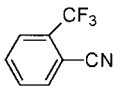
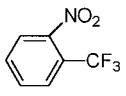
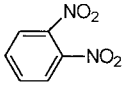
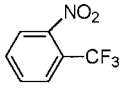
Fluoroform has also been used as an efficient precursor for trifluoromethylation of aldehydes (Scheme 41).[66,67]

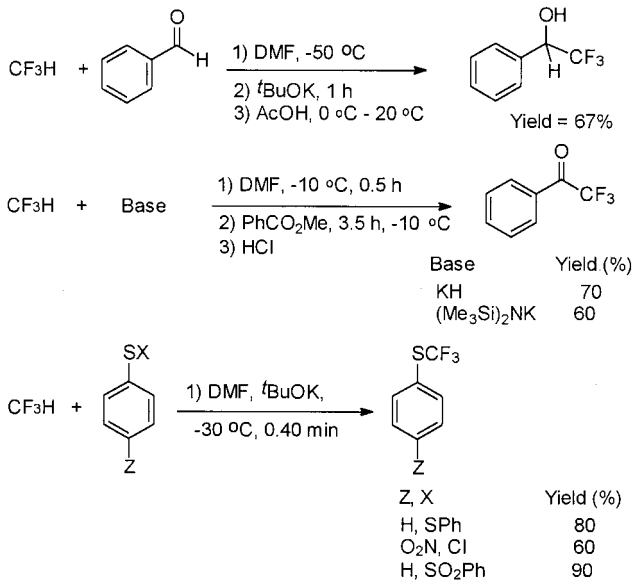
Tomoko and his coworkers have reported application of **2** in materials science; **2** forms a kind of insulating film with O_2, which has a small dielectric constant, low hygroscopic properties and adheres very well to metal surfaces.[68]



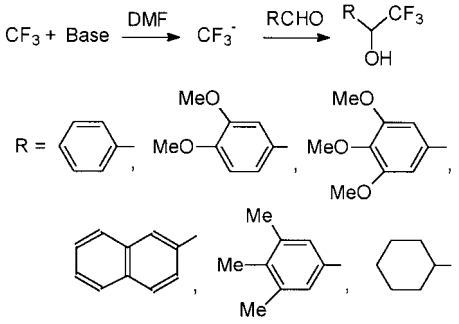
Scheme 39.

Table 11. Product distribution from reactions of nitroaromatics with Me_3SiCF_3 (Ref. 64)

Substrate	Product	[yield (%)]
	 (7)	 (Trace)
	 (51)	 (20)
	 Two isomers (2, 3)	 Two isomers (5, 9)
	 Two isomers (14, 1)	 Two isomers (6, 4)
	 (10)	 (5)
	 (16)	



Scheme 40.



Scheme 41.

5. Conclusions

This review has highlighted the recent advances in nucleophilic trifluoromethylation reactions by using Me_3SiCF_3 from January 1997 to March 2000. Some of the substrates (such as esters, imines, nitrones) which were thought to be deactivated or inert towards Me_3SiCF_3, were found to be reactive. But there are still a variety of areas that remain essentially untapped such as many biological and inorganic derivatives, which have valuable applications. We hope that more rapid progress will be made in trifluoromethylation reactions using Me_3SiCF_3 as the reagent of choice. We expect that the search for effective reaction conditions for the trifluoromethylation and perfluoroalkylation of various substrates will remain an important area in fluorine chemistry.

References

1. For the general applications of organofluorine compounds see: *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum: New York, 1994.

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Jean'ne M. Shreeve is a Montana native. She received her BA in Chemistry from the University of Montana, MS in Analytical Chemistry from the University of Minnesota, and PhD in Inorganic Chemistry from the University of Washington, Seattle. She joined the University of Idaho faculty in 1961, rising to become department head in 1973, and in 1987 assumed the role of Vice-President for Research and Graduate Studies. In January 2000, she returned to full-time research. She has had the privilege of having worked with three of the finest gentlemen of fluorine chemistry, Prof. George H. Cady, Prof. Harry J. Emeléus, and Prof. Oskar Glemser. Her research interests include the syntheses, characterization and reactions of new compounds that contain fluorine as exemplified by more than 300 refereed publications.