Nucleophilic Trifluoromethylation of Carbonyl Compounds and Disulfides with Trifluoromethane and Silicon-Containing Bases

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Provided that DMF (or another *N*,*N*-dialkylformamide) is present in the reaction medium, at least in a catalytic amount, fluoroform trifluoromethylates efficiently carbonyl compounds, even enolizable ones, when opposed to $(TMS)_2N^-\ M^+$, generated in situ from $N(TMS)_3$ and $M^+\ F^-$ or $RO^-\ Na^+$. When F^- is used in a catalytic amount, silylated α-(trifluoromethyl)carbinols are obtained: in this case, the four-component system $HCF_3/N(TMS)_3$/catalytic F^-/catalytic DMF behaves like the Ruppert's reagent, especially as far as nonenolizable carbonyl compounds are concerned (CF_3SiMe_3 remains more efficient for enolizable carbonyl compounds). This process involves an adduct between DMF and $^-CF_3$ which is the true trifluoromethylating agent. In the same way, fluoroform efficiently trifluoromethylates disulfides and diselenides when deprotonated with a strong base selected from *t*-BuOK or $N(SiMe_3)_3/Me_4NF$ (or TBAT). *t*-BuOK is more adapted to the trifluoromethylation of aryl disulfides whereas $N(SiMe_3)_3/F^-$ is well suited to that of aliphatic disulfides.

Introduction

Because of the very peculiar properties of the fluorine atom, the importance of fluorinated products in life sciences is steadily expanding at a high rate. At present, up to 30−40% of agrochemicals and 20−30% of pharmaceuticals contain at least one fluorine atom.[1] Among fluorinated compounds, trifluoromethylated ones constitute an important class because of the stereoelectronic properties of the CF_3 moiety and the important bioavailability brought by this group.[2] For a long time, bioactive trifluoromethylated compounds have been prepared from trifluoromethylated "building blocks" through iterative modifications but, during the past decade, new opportunities appeared with the discovery of reagents and techniques allowing the direct introduction of a CF_3 group on an organic substrate.[3]

Direct electrophilic trifluoromethylation has been scarcely studied and few reagents has been developed for this use. Radical trifluoromethylation has been more extensively studied since the electrophilic $^{\bullet}CF_3$ radical can be produced in a variety of ways from CF_3Br,[4] sodium trifluoromethanesulfinate[5,7,8] or thioesters of trifluoroacetic or triflic acids.[6] Nucleophilic trifluoromethylation is more complex since the "naked" trifluoromethyl anion is strongly destabilized by electrostatic repulsions between the anionic charge and the p-electron pairs of the fluorine atoms (+ I_Π effect). It collapses into fluoride anion and difluorocarbene which, in contrast, is stabilized by an overlap between the vacant orbital of the carbon and the p-orbitals of the fluorine atoms. Thus, equivalents of $^-CF_3$ have been designed in which stabilization is brought by dispersion of the anionic charge either into the vacant orbitals of a transition metal (especially Cu^I) or in a fragile σ bond (typically C−Si). The first approach is essentially devoted to the nucleophilic substitution of aryl halides since strong solvation often lowers the reactivity of trifluoromethylcopper(I) species which need a thermal activation to react.[9−12] (Trifluoromethyl)tri-

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methylsilane (Ruppert's reagent) is presently the most popular tool to carry out the second methodology.[13] When activated by a fluoride anion in the form of an anionic pentacoordinated silicon species, it transfers, under mild conditions, a $^{-}CF_3$ moiety to carbonyl compounds,[13] esters[14] and disulfides[15] or thiocyanates[16] to provide, respectively, α-(trifluoromethyl)carbinols, trifluoromethyl ketones and trifluoromethyl sulfides. Nevertheless, this technique suffers from the fact that CF_3SiMe_3 is presently prepared from ecotoxic CF_3Br. Surprisingly, the use of trifluoromethane (fluoroform) as a source of $^{-}CF_3$ has been reported only recently. The large availability of this cheap and environmentally benign reagent led us to consider its use for synthetic purposes.

The first results concerning trifluoromethylation with fluoroform has been reported by Shono et al.: they treated, at −50 °C, a solution of benzaldehyde in DMF with an excess of HCF_3, in the presence of an electrogenerated base resulting from 2-pyrrolidinone (1.5 equiv), and obtained 2-(trifluoromethyl)benzyl alcohol in good yields.[17] They claimed that such an electrogenerated base was far more efficient than, for example, potassium *tert*-butoxide. However, aryl trifluoromethyl carbinols have been also obtained very recently, in moderate to fair yields, from fluoroform, aromatic aldehydes and potassium dimsylate,[18] phenyl anion (generated by cathodic reduction of iodobenzene),[19] or *t*-BuOK. The latter base delivered good yields, even at −10 °C, providing that it was used in a stoichiometric amount to avoid side-reactions.[20] In all these cases, again, DMF was used as solvent.

Nevertheless, as pointed out by Normant et al.,[18] this result cannot be explained by the only formation of CF_3K or CF_3NBu_4 which are unstable, even at −45 °C.[21] As the reaction failed in THF, they postulated that $^{-}CF_3$ was trapped by DMF as soon as formed, to deliver the adduct **1** (Scheme 1) which was able to transfer a $^{-}CF_3$ equivalent to the carbonyl substrate. For these authors, the occurrence of **1** can be deduced from the formation of fluoral during hydrolysis of such a putative adduct in the absence of benzaldehyde.[18] Soon after, Russel and Roques[20] reported more direct proofs from ^{19}F NMR and trapping experiments: when carefully treated with acetic acid, **1** delivered its conjugated acid and, in the presence of *t*-$BuMe_2SiCl$, its silyl ether was formed and isolated. The latter compound was quite identical to that resulting from the action of CF_3SiMe_3 on DMF (Scheme 1).

Scheme 1. Evidence for the Occurrence of 1

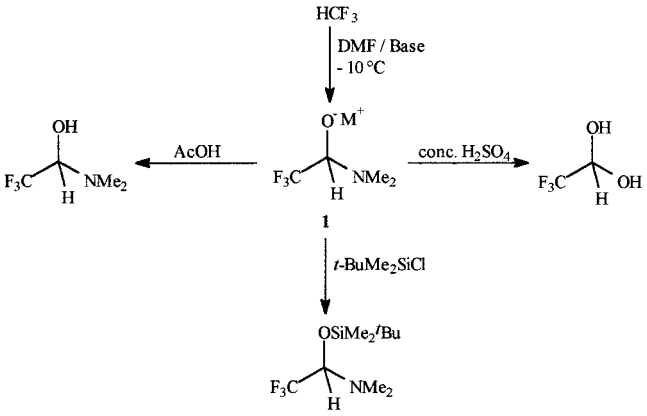

Table 1. Desilylation of $N(TMS)_3$ by Me_4NF at Room Temperature in DMF and THF

$$(Me_3Si)_3N + Me_4N^+ F^- \xrightarrow[rt]{solvent} Me_3SiF + (Me_3Si)_2N^-Me_4N^+ \xrightarrow{H_2O} (Me_3Si)_2NH$$

solvent	time (min)	$N(TMS)_3/HN(TMS)_2$[a] (mol/mol)
DMF	10	90:10
	30	70:30
	60	0:100
THF	30	100:0
	60	98:2
	300	80:20

[a] From GC analysis of the ratio $N(TMS)_3/HN(TMS)_2$ after hydrolysis with water.

Such experiments underlined the crucial role of DMF during trifluoromethylation with fluoroform and strong bases since its adduct **1** acts as a $^{-}CF_3$ reservoir. However, though the system HCF_3/*t*-BuOK/DMF was very efficient to trifluoromethylate benzaldehyde, it completely failed, in our hands, with acetophenone: in this case, enolate formation prevailed over trifluoromethylation. Thus, we tried to deprotonate HCF_3 with a base designed to be generated in situ in low concentrations and slowly enough to decrease enolization.

Results and Discussion

For this purpose, we used a 1:1 mixture of tris(trimethylsilyl)amine and anhydrous tetramethylammonium fluoride since we determined that, in DMF, this system generates very slowly tetramethylammonium bis(trimethylsilyl)amide at room temperature (Table 1).

With such a three-component system [HCF_3 (excess), $N(TMS)_3$ (1.5 equiv), Me_4NF (1.5 equiv)], enolizable ketones were successfully trifluoromethylated in DMF at −10 °C, though in a modest yield except when enolization was disfavored by steric factors as, for example, in 2,6-dimethylcyclohexanone (Scheme 2).

The same three-component reagent was also satisfactorily used to trifluoromethylate benzophenone (**2**). 1,1-Diphenyl-2,2,2-trifluoroethanol (**3**) was obtained in yields comparable to those resulting from HCF_3 and NaH, *t*-BuOK, or $KN(TMS)_2$ (Table 2). Moreover, as anhydrous Me_4NF is not readily available nor easy to handle because of its hygroscopic character, it was advantageously replaced by sodium alcoholates. Table 2 clearly shows that, under these conditions, alcoholates acted as desilylating agents rather than bases since, in the absence

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Scheme 2. Trifluoromethylation of Enolizable Ketones with $HCF_3/N(TMS)_3/F^-$/DMF

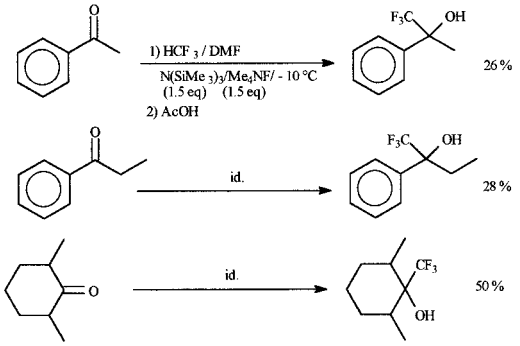
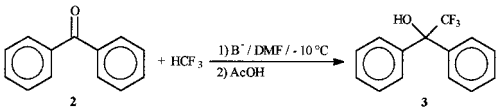


Table 2. Trifluoromethylation of Benzophenone with HCF_3/B^-/DMF



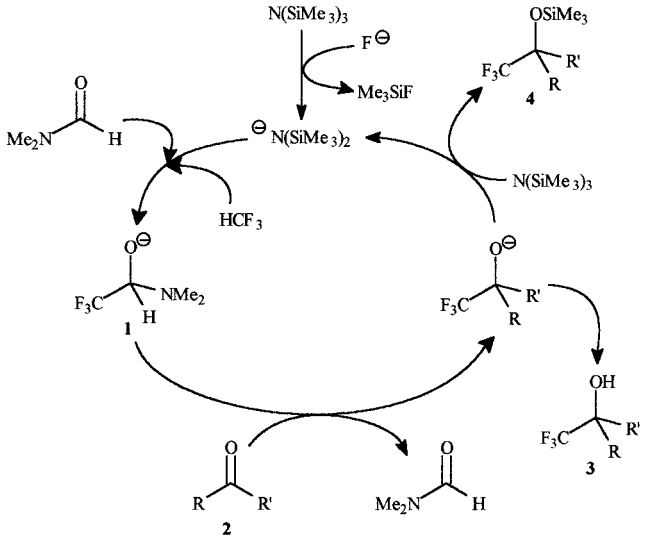
entry	base (equiv)	yield of **3**[a] (%)
1	NaH (1.1)[b]	85
2	*t*-BuOK (1.1)[b]	100
3	$(TMS)_2NK$ (1.1)[b]	79
4	$(TMS)_2NNa$ (1.1)[b]	49
5	CF_3CH_2ONa (1.5)[c]	0
6	MeONa (1.5)[c]	29
7	EtONa (1.5)[c]	23
8	*i*-PrONa (1.5)[c]	20
9	$(TMS)_3N$ (1.5)/Me_4NF (1.5)	72
10	$(TMS)_3N$ (1.5)/CF_3CH_2ONa (1.5)[c]	25
11	$(TMS)_3N$ (1.5)/MeONa (1.5)[c]	80
12	$(TMS)_3N$ (1.5)/EtONa (1.5)[c]	96
13	$(TMS)_3N$ (1.5)/i-PrONa (1.5)[c]	81

[a] From ^{19}F NMR analysis with an internal standard. [b] Commercial reagent. [c] Preformed in situ from NaH + ROH.

of $N(TMS)_3$, they did not deprotonate efficiently fluoroform. In this procedure, even sodium trifluoroethylate, which is a very weak base, delivered **3** in a significant yield (entry 10). The best yields were obtained with EtONa (entry 12), which is more nucleophilic than MeONa (entry 11) and less hindered than *i*-PrONa (entry 13). Comparison of entries 4 and 11−13 also indicates that commercial $(TMS)_2NNa$ was less efficient than the same salt generated in situ from $(TMS)_3N$/RONa. An explanation could be that fluoroform was directly deprotonated by ($[Me_3Si(OR)N(TMS)_2]^-$ Na^+), resulting from addition of RONa on $N(TMS)_3$.

In further experiments, we also obtained **3** in good yields when Me_4NF, or other anhydrous fluorides such as CsF or tetrabutylammonium difluorotriphenylsilicate (TBAT), was used in a catalytic amount only. Under these conditions, **3** was mainly isolated in the form of its silylated ether **4**, indicating that $N(TMS)_3$ acted as an efficient silylating agent. Analogous results were obtained in *N*,*N*-dimethylethyleneurea (DMEU) or *N*,*N*-dimethylpropyleneurea (DMPU) instead of DMF. Moreover, in contrast with Normant's results, trifluoromethylation of benzophenone with fluoroform, $N(TMS)_3$ and catalytic amounts of fluorides was also successfully carried out in THF, provided that DMF (or another *N*,*N*-dialkylformamide, such as *N*-formylmorpholine) was present in small amounts (Table 3). Again, **4** was the main product of the reaction. Thus, the multicomponent system HCF_3 (excess)/$N(TMS)_3$ (1.5 equiv)/Me_4NF (0.2 equiv)/DMF (0.3 equiv) behaves, in THF, like the Ruppert's reagent (CF_3SiMe_3/catalytic F^-), as far as nonenolizable carbonyl compounds are concerned, in the sense that it allows the addition of the elements of CF_3-SiMe_3 on a C=O double bond under mild conditions. The Ruppert's reagent remains, however, far more efficient than ours for the trifluoromethylation of enolizable ketones. The fact that DMEU, DMPU and *N*-formylmorpholine plaid the same role as DMF probably indicates that they also add $^-CF_3$ to give "$^-CF_3$ reservoirs".

Scheme 3. Mechanism of Trifluoromethylation with $HCF_3/N(TMS)_3$/Cat. F^-/Cat. DMF



Trifluoromethylation with HCF_3, $N(TMS)_3$, and catalytic amounts of Me_4NF and DMF could be rationalized as indicated in Scheme 3. The first key-step (in which DMF is recovered) is the transfer of $^-CF_3$ from **1** to the carbonyl function. The second one is the silylation of the resulting α-(trifluoromethyl)alcoholate by $N(TMS)_3$ which enables the regeneration of bis-(trimethylsilyl)amide.

The most intriguing point arising from Table 3 is the relative variation of compounds **3** and **4** between crude and isolated yields. It might result from a "silicon dance" between **4** and DMF, through an equilibrium which could be shifted toward **4** when DMF was extracted by water from the organic phase during the workup (Scheme 4).

Trifluoromethylation with $HCF_3/N(TMS)_3$ (1.5 equiv)/F^- (0.2 equiv) has been also successfully applied to chalcone **8a**, (dibenzylidene)acetone **8b**, 4,4′-difluorobenzophenone **8c**, and fluorenone **8d** (Table 4). The relative variation between crude and isolated yields of **9a**−**c** and **10a**−**c** can be explained as above.

As shown from conjugated ketones **8a** or **8b**, nucleophilic trifluoromethylation with HCF_3 exclusively resulted in a 1,2-addition (CF_3SiMe_3 is known to behave in the same way). Nevertheless, an exclusive 1,4-trifluoromethylation occurred from *trans*-1-benzoyl-2-(dimethylamino)ethylene **8e** (prepared from acetophenone and dimethylketal of DMF).[22] The resulting *N*,*N*-dimethyl-1-trifluoromethyl-2-benzoylethylamine **11** was transformed into *trans*-1-benzoyl-2-(trifluoromethyl)ethylene **12** by acidic treatment[23] (Scheme 5).

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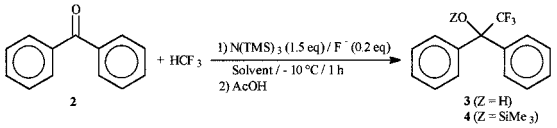
Table 3. Trifluoromethylation of Benzophenone with HCF_3 and Catalytic Amounts of Fluoride



F^-	solvent	yield of **3**[a] (%)	yield of **4**[a] (%)	**3** + **4**[a] (%)
anhyd Me_4NF	DMF	28 (33)	57 (47)	85 (80)
anhyd Me_4NF	DMEU	41	34	75
anhyd Me_4NF	DMPU	51	16	67
anhyd Me_4NF	THF	0	0	0
anhyd Me_4NF	THF + DMF (0.3 equiv)	52 (7)	38 (60)	90 (67)
CsF	DMF	37	62	99
$Bu_4N^+[Ph_3SiF_2]^-$ (TBAT)	DMF	20	69	89
$Bu_4N^+[Ph_3SiF_2]^-$ (TBAT)	THF + DMF (0.3 equiv)	91 (36)	3 (55)	94 (91)
$Bu_4N^+[Ph_3SiF_2]^-$ (TBAT)	THF + *N*-formylmorpholine (0.3 equiv)	60 (46)	40 (47)	100 (93)

[a] From ^{19}NMR with internal standard; in parentheses: isolated yield.

Scheme 4. "Silicon Dance" between 4 and DMF

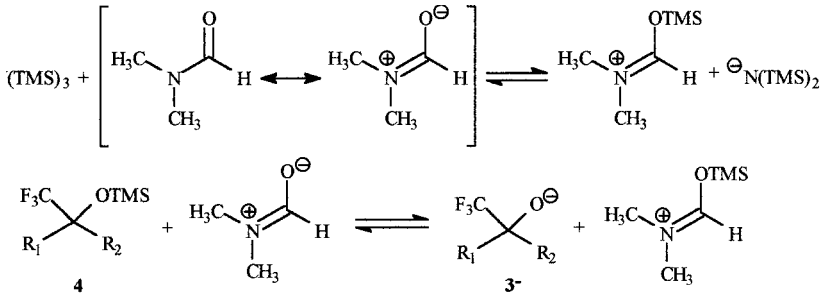
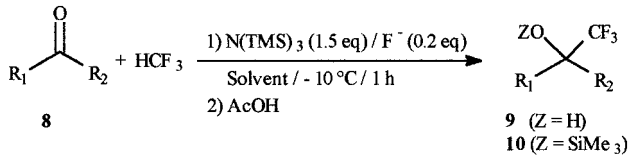
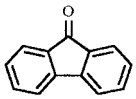


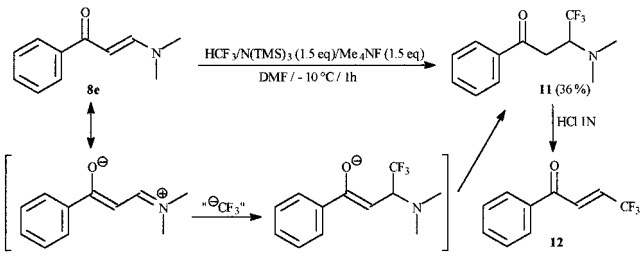
Table 4. Trifluoromethylation of Nonenolizable Ketones with $HCF_3/N(TMS)_3$ (1.5 Equiv)/F^- (0.2 Equiv)



substrate					**9**[a]	**10**[a]	**9** + **10**
no.	R_1	R_2	solvent	F^-	(%)	(%)	(%)
8a	Ph-CH=CH	Ph	DMF	Me_4NF	0 (26)	68 (42)	68 (68)
8b	Ph-CH=CH	Ph-CH=CH	DMF	Me_4NF	40 (0)	22 (45)	62 (45)
8c	4-F-C_6H_4	4-F-C_6H_4	DMF	CsF	43 (0)	44 (64)	87 (64)
8d			DMF	CsF	0	72 (57)	72 (57)
			THF + DMF (0.3 equiv)	Me_4NF	0	83 (75)	83 (75)

[a] From ^{19}NMR with internal standard; in parentheses: isolated yield.

Scheme 5. Conjugated Trifluoromethylation of 3-Acylenamines



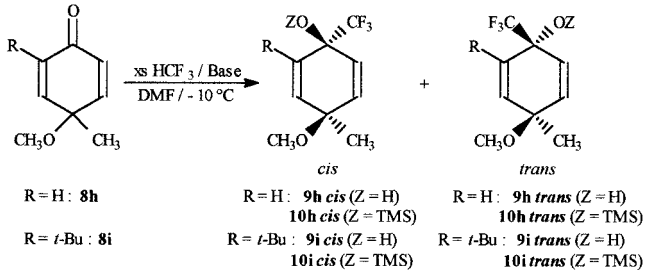
4-Substituted 4-methoxy-2,5-cyclohexadien-1-ones (easily prepared from 4-substituted phenols with $I^{(III)}$ in the presence of methanol)[24] were also submitted to nucleophilic trifluoromethylation with $HCF_3/N(TMS)_3/F^-$. 4,4-dimethoxy-2,5-cyclohexadien-1-one **8f** delivered excellent crude yields but the isolated product was dependent on the aqueous workup (Scheme 6).

Under the same conditions, 4-methoxy-4-methyl-2,5-cyclohexadien-1-one (**8h**) and its 2-*tert*-butyl analogue (**8i**) delivered the expected trifluoromethylated adducts as a mixture of two diastereomers in which the *cis*-isomer (**9h**−**i** ***cis*****, 10h**−**i** ***cis***) was always predominant over the *trans*-isomer (**9h**−**i** ***trans*****, 10h**−**i** ***trans***).[25] Diastereoselectivity was dramatically dependent on steric hindrance: it ranged from 12 to 19% for **8h** to 69% for **8i** (Table 5). The major formation of the cis isomer from **8h**−**i** should

(24) (a) McKillop, A.; McLaren, L.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2047. (b) Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677.

(25) The relative configurations of compounds **9i** ***cis*****−*****trans***, **10h** ***cis*****−*****trans*** and **10i** ***cis*****−*****trans*** have been deduced from ^{13}C NMR spectra which exhibited through-space ^{13}C-^{19}F coupling constants (from 1.0 to 1.9 Hz) between CF_3 and either CH_3 (cis series) or OCH_3 (trans series). The configuration of **10i** ***cis*** has been also confirmed by an NOE experiment. The configurations of **9h** ***cis*** and **9h** ***trans*** have been attributed by comparison with compounds resulting from desilylation of **10h** ***cis*** and **10h** ***trans***, respectively.

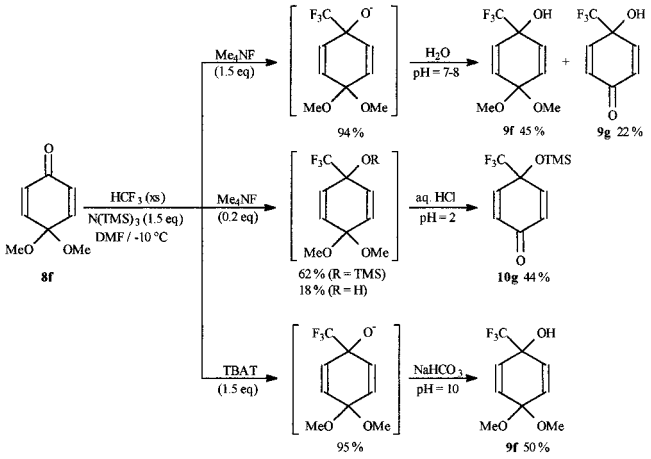
Table 5. Trifluoromethylation of 4-Methoxy-4-methyl-2,5-cyclohexadien-1-one



substrate **8**	base	yield **9**−**10** ***cis***[c] (%)	yield **9**−**10** ***trans***[c] (%)	cis + trans[c] (%)	de (%)
8h	$N(TMS)_3/Me_4NF$[a]	**10h** ***cis*** 38 (21)	**10h** ***trans*** 26 (22)	**10h** 64 (43)	19
8h	*t*-BuOK[b]	**9h** ***cis*** 42 (42)	**9h** ***trans*** 33 (33)	**9h** 75 (75)	12
8i	$N(TMS)_3/CsF$[a]	**10i** ***cis*** 44 (26)	**10i** ***trans*** 8 (7)	**10i** 52 (33)	69
8i	*t*-BuOK[b]	**9i** ***cis*** 50 (47)	**9i** ***trans*** 9 (9)	**9i** 59 (56)	69

[a] $N(TMS)_3$ (1.5 equiv)/F^- (0.2 equiv). [b] *t*-BuOK (1.1 equiv). [c] From ^{19}NMR with internal standard; in parentheses: isolated yield.

Scheme 6. Trifluoromethylation of 4,4-Dimethoxy-2,5-cyclohexadien-1-one



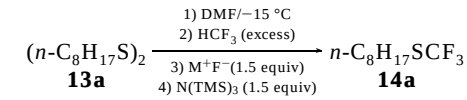
be consistent with the occurrence of two six-membered transition states during the $^-CF_3$ transfer; the *cis*-isomer could result from the one in which electrostatic repulsions (between p-electrons of O and F) were minimized. This interpretation is in accordance with a very recent paper concerning nucleophilic additions to 4,4-disubstituted-2,5-cyclohexadienones.[26]

The trifluoromethylation of other carbonyl compounds with $HCF_3/N(TMS)_3/Me_4NF$/DMF was also investigated: under the usual conditions, esters were unreactive and benzaldehyde was transformed into its *N*-trimethylsilyl imine. For the trifluoromethylation of such substrates, Ruppert's reagent remains the most adapted tool.

Because trifluoromethyl sulfides can be prepared by nucleophilic trifluoromethylation of disulfides or thiocyanates, as we demonstrated with CF_3SiMe_3,[15,16] we were also interested in studying the ability of fluoroform to trifluoromethylate such substrates, all the more so since Roques and Russell reported very briefly some preliminary results from diphenyl disulfide.[20] Thus, we examined the ability of fluoroform to trifluoromethylate a panel of disulfides and diselenides, under the same conditions as carbonyl compounds. Preliminary experiments, carried out from dioctyl disulfide **13a**, HCF_3, and commercial $LiN(TMS)_2$ (1.1 equiv) in DMF at −15 °C, gave octyl trifluoromethyl sulfide **14a** in a fair yield

(26) Wipf, P.; Jung, J. K. *Chem. Rev.* **1999**, *99*, 1469.

Table 6. Trifluoromethylation of 13a with HCF_3 and $N(TMS)_3/F^-$ in DMF at −10 °C



$M^+ F^-$	yield of **14**[a] (%)
n-$Bu_4N^+ [Ph_3SiF_2]^-$	60 (50)
anhydr Me_4NF	73 (65)

[a] From ^{19}F NMR with internal standard; in parentheses: isolated yield.

(crude: 51%, isolated: 45%), provided that $LiN(TMS)_2$ was buffered with hexamethyldisilazane (0.2 equiv) to avoid competitive deprotonation of the substrate. When using *t*-BuOK in place of $LiN(TMS)_2$, **14a** was obtained in almost the same crude yield (54%). However, the side formation of octyl difluoromethyl sulfide **15a** and *N*,*N*-bis(trimethylsilyl)octanesulfenamide could not be avoided. Thus, we turned again to $N(TMS)_3/Me_4NF$ and $N(TMS)_3$/TBAT systems to minimize the steady-state concentration of base. As expected, **14a** was formed in yields up to 73% (Table 6) and no trace of **15a** was detected with such systems, even used in excess.

Nevertheless, the trifluoromethylation of disulfides with $HCF_3/N(TMS)_3/Me_4NF$ contrasted with that of carbonyl compounds. First, it required a stoichiometic amount of Me_4NF because the resulting thiolates were unable to react with $N(TMS)_3$, as we verified under the reaction conditions. Second, whereas the trifluoromethylation of carbonyl compounds could not be carried out in the absence of DMF, that of dioctyl disulfide was successfully carried out, at −10 °C, either in DMF (crude yield **14a** = 73%) or in pure THF (crude yield **14a** = 66%). Since desilylation of $N(TMS)_3$ by F^- in far slower in THF than in DMF (Table 1), this means that, in THF, $^-CF_3$ was generated in such a low concentration that it was trapped very rapidly by the disulfide before collapsing. Apparently, the soft nucleophile $^-CF_3$ interacted better with the soft electrophile RSSR than with the harder carbonyl moiety and was more efficiently trapped by the former. Thus, different mechanisms can be proposed in DMF and in THF (Scheme 7).

Other disulfides **13b**−**f**, as well as diphenyl diselenide **16f**, were also trifluoromethylated with fluoroform under the different conditions studied with **13a**. The results are summarized in Table 7.

Scheme 7. Possible Mechanisms for the Trifluoromethylation of Disulfides with $HCF_3/N(TMS)_3/Me_4NF$

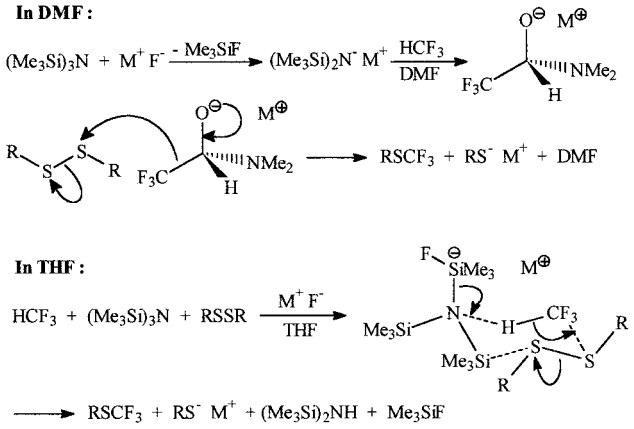


Table 7. Trifluoromethylation of Different Disulfides and Diselenides with HCF_3

RYYR (Y = S, Se) + HCF_3 (excess) $\xrightarrow{\text{basic system I, II, or III}}$ $RYCF_3$
DMF/−15 °C/5.5 h

I: $LiN(TMS)_2$ (1.1 equiv)/$HN(TMS)_2$ (0.2 equiv)
II: $N(TMS)_3$ (1.5 equiv)/Me_4NF (1.5 equiv)
III: *t*-BuOK (1.1 equiv)

RSSR or RSeSeR	$RSCF_3$ or $RSeCF_3$	base	yield[a] (%)
$(C_8H_{17}S)_2$	$C_8H_{17}SCF_3$	I	51
13a	**14a**	II	73 (65)
		III	54 (34)
$(c\text{-}C_6H_{11}S)_2$	$c\text{-}C_6H_{11}SCF_3$	I	2[b]
13b	**14b**	II	54 (50)
		III	45
$(t\text{-BuS})_2$	$t\text{-BuSCF}_3$	I	0
13c	**14c**	II	23
		III	0
$(PhCH_2S)_2$	$PhCH_2SCF_3$	II	0
13d	**14d**	III	0
$(EtO_2CCH_2CH_2S)_2$	$CF_3SCH_2CH_2CO_2Et$	II	0
13e	**14e**		
PhSSPh	$PhSCF_3$	I	4[c]
13f	**14f**	II	6[d]
		III	82 (75)
PhSeSePh	$PhSeCF_3$	II	61 (47)
16f	**17f**	III	77

[a] From ^{19}F NMR with internal standard; in parentheses: isolated yield. [b] $c\text{-}C_6H_{11}SCF_2H$ (**15b**): 1%. [c] $PhSCF_2H$ (**15f**): 23%; $PhSN(TMS)_2$: (46%). [d] $PhSCF_2H$ (**15f**): 0%; $PhSN(TMS)_2$: detected.

As shown from Table 7, $N(TMS)_3/Me_4NF$ was more efficient than *t*-BuOK with aliphatic disulfides, except with substrates which were too sensitive to proton abstraction (**13d**) or β-elimination (**13e**). Though the yield was sensitive to steric hindrance, this reagent was even able to deliver *tert*-butyl trifluoromethyl sulfide **14c** from *tert*-butyl disulfide, in contrast to other trifluoromethylation processes.[6,15a] On the contrary, *t*-BuOK was far more adapted to aromatic disulfides. Concerning diphenyl diselenide, which is less electrophilic but more polarizable than **13f**, both techniques were almost equivalent.

Conclusion

The work reported here enlarges the limited previous reports on trifluoromethylation of carbonyl compounds with fluoroform. We demonstrated that this reaction can be carried out with milder bases than $KN(TMS)_2$ or *t*-BuOK by using mixtures of $N(TMS)_3$ and fluorides or alcoholates which generate amides slowly enough to allow the trifluoromethylation of enolizable ketones. Moreover, the system $HCF_3/N(TMS)_3$/catalytic F^-/catalytic DMF constitutes an environmentally benign alternative to CF_3SiMe_3 for the preparation of α-trifluoromethyl silyl ethers, especially from nonenolizable ketones. Nevertheless, in contrast to CF_3SiMe_3, it is not yet adapted to the trifluoromethylation of aldehydes and esters. Our work confirms that, under these conditions, trifluoromethylation occurs through the formation of an adduct between $^-CF_3$ and DMF, which acts as the true trifluoromethylating agent. Concerning the trifluoromethylation of disulfides with fluoroform, we also demonstrated that the binary system $N(SiMe_3)_3/Me_4NF$ is especially adapted to the treatment of aliphatic disulfides, whereas *t*-BuOK is more suited to that of aryl disulfides. In the former case, the reaction can be carried out in pure THF.

Experimental Section

Prior to use, DMF was distilled over calcium hydride and THF over sodium/benzophenone. Both were stored over 3 Å molecular sieves under N_2. CsF was ground and dried at 250 °C for 24 h. Other reagents were used as received. TLC analyses were carried out on Kieselgel 60F 254 deposited on aluminum plates, detection being done by UV (254 nm), phosphomolybdic acid (10% in ethanol), or ninhydrine (1% in ethanol). Flash chromatographies were performed on silica gel Geduran SI 60. Uncorrected melting points were determined in capillary tubes. Unless stated otherwise, NMR spectra were recorded in $CDCl_3$. ^1H NMR were recorded at 200 MHz or 300 MHz and ^{13}C NMR spectra at 50 or 75 MHz. The substitution pattern of the different carbons were determined by a "DEPT 135" sequence. ^{19}F NMR spectra were recorded at 188 MHz. Chemical shifts (δ) are given in ppm vs TMS (^1H, ^{13}C) or $CFCl_3$ (^{19}F) used as internal references. Coupling constants are given in hertz. Crude yields were determined by ^{19}F NMR vs $PhOCF_3$ used as standard. GC was carried out on an apparatus fitted with a semi-capillar column (length: 15 m, Φ: 0.53 mm, film thickness (DB1): 1 μm) and a catharometric detector. Mass spectrometry, coupled with gas chromatography, was carrried out under electron impact at 70 eV. Elemental analyses were carried out by the "Service Central d'Analyses du CNRS".

(*E*)-3-(*N*,*N*-dimethylamino)-1-phenyl-2-propen-1-one (8e). Prepared according to ref 22. Dimethylketal of DMF (4.3 mL, 30 mmol) was added to a solution of acetophenone (1.20 g, 10 mmol) in DMF (10 mL) and the mixture was brought to reflux for 15 h. After hydrolysis with water (10 mL), the aqueous phase was extracted with diethyl ether. The combined organic phases were washed with brine then water and dried over Na_2SO_4. After filtration and concentration at room temperature in vacuo, chromatography on silica gel (petroleum ether (PE)/acetone 50:50) yielded **8e** (1.09 g, 62%) as a yellow solid: mp 90−92 °C; ^1H NMR (200 MHz) δ 7.90 (d, J = 8.0, 2H), 7.77 (d, J = 12.3, 1H), 7.34−7.44 (M, 3H), 5.69 (d, J = 12.3, 1H), 3.04 (broad s, 3H), 2.87 (broad s, 3H); ^{13}C NMR (50 MHz) δ 188.50, 154.23, 140.55, 130.84, 128.11, 127.45, 92.12, 44.88, 37.22; MS *m*/*z* 175 ($M^{\bullet+}$), 158, 143, 131, 105, 98, 91, 77, 70, 55, 42, 28, 15.

4-Methoxy-4-methyl-2,5-cyclohexadien-1-one (8h). Prepared according to ref 24. Bis(trifluoroacetoxy)iodo-benzene (5.00 g, 11 mmol) was added, at −10 °C, to a solution of *p*-cresol (1.10 g, 10 mmol) in methanol (32 mL). The mixture was stirred at 0 °C for 1 h then hydrolyzed with water (32 mL). The aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with water and then dried over Na_2SO_4. After filtration and concentration at room temperature in vacuo, chromatography on silica gel (PE/ethyl ether (EE) 40:60) yielded **8h** (0.840 g, 61%) as a pale yellow solid: mp 57−59 °C; ^1H NMR (200 MHz) δ 6.80 (d, J = 9.8, 2H), 6.32 (d, J = 9.8, 2H), 3.21 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (50

MHz) δ 184.98, 151.72, 130.32, 72.53, 53.09, 26.13; MS *m*/*z* 138 ($M^{\bullet+}$), 123, 110, 107, 95, 79, 77, 67.

2-*tert*-Butyl-4-methoxy-4-methyl-2,5-cyclohexadien-1-one (8i). This compound was prepared in the same way as **8h**, from $PhI(OCOCF_3)_2$ (5.00 g, 11 mmol) and 2-*tert*-butyl-4-methylphenol (1.65 g, 10 mmol). The latter was completely converted within 1.5 h at 0 °C. **8i** (1.34 g, 69%) was obtained as a pale yellow solid: mp 57−58 °C; ^{1}H NMR (200 MHz) δ 6.64 (d, J = 3.0, 1H), 6.51 (dd, J = 9.9 and 3.0, 1H), 6.21 (d, J = 9.9, 1H), 3.15 (s, 3H), 1.40 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (50 MHz) δ 185.38, 149.07, 147.94, 144.86, 132.15, 72.86, 52.76, 34.66, 29.25, 26.72; MS *m*/*z* 194 ($M^{\bullet+}$), 179, 163, 151, 138, 123, 121, 105, 91, 77.

Di-*n*-octyl Disulfide 13a. *n*-Octanethiol (20.0 g, 0.14 mol) was dropped in a solution of NaOH (5.6 g, 0.14 mol) in water (32 mL). Then, iodine (17.8 g, 0.07 mol) was added by portions within 15 min. The mixture was stirred for 7 h at room temperature then **13a** was extracted with toluene. After washing the organic phase with saturated aqueous $Na_2S_2O_3$ and drying it over $MgSO_4$, the solvent was evaporated in vacuo at room temperature. **13a** was obtained as a pure colorless liquid (19.3 g, 95%): ^{1}H NMR δ 0.88 (t, J = 6.8, 6H), 1.27 (m, 20H), 1.66 (quint, J = 7.1, 4H), 2.66 (t, J = 7.1, 4H); ^{13}C NMR δ 14.10, 22.66, 28.56, 29.20, 29.22, 29.25, 31.83, 39.23; MS *m*/*z* 290 ($M^{\bullet+}$), 178, 145, 71, 57, 43.

Trifluoromethylation of Benzophenone with HCF_3/$(Me_3Si)_2NK$. Fluoroform (200 to 600 mg, 1.4 to 8.6 mmol) was bubbled into a solution of benzophenone (1 mmol) in anhydrous DMF (2 mL), maintained at −10 °C. Then, $HN(TMS)_2$ (45 μL, 0.2 mmol)[27] and $KN(TMS)_2$ (1.1 mL of a 1M solution in THF, 1.1 mmol) were successively added at −10 °C. The resulting mixture was stirred at −10 °C for 1 h, warmed to room temperature and stirred at this temperature for 5 h. At this stage, ^{19}F NMR analysis was performed on a small sample, in the presence of $PhOCF_3$ as internal standard. Then, the crude mixture was hydrolyzed with 1 N aqueous HCl until neutral. The aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine then water and dried over Na_2SO_4. After filtration and concentration at room temperature in vacuo, chromatography on silica gel delivered the expected α-(trifluoromethyl)carbinol in a 79% yield.

Trifluoromethylation of Ketones with HCF_3/*t*-BuOK. General Procedure. The same procedure was used to trifluoromethylate **2**, **8h** and **8i**, except that $KN(TMS)_2$ and $HN(TMS)_2$ were replaced by *t*-BuOK (1.1 mL of a 1 M solution in THF, 1.1 mmol). Yields are indicated in Tables 2 and 5.

Trifluoromethylation of Benzophenone with HCF_3 and Sodium Alcoholates (MeONa, EtONa, *i*-PrONa). General Procedure. NaH (72 mg, used as a 50% suspension in oil) was added to a solution of the alcohol (1.5 mmol) in anhydrous DMF (1 mL). The mixture was warmed to 60 °C then cooled to −10 °C. Benzophenone (180 mg, 1 mmol), dissolved in DMF (1 mL), was added at −10 °C then HCF_3 (200 to 600 mg, 1.4 to 8.6 mmol) was bubbled at this temperature. The resulting mixture was stirred at −10 °C for 1 h, warmed to room temperature and stirred at this temperature for 5 h. At this stage, ^{19}F NMR analysis was performed on a small sample, in the presence of $PhOCF_3$ as internal standard. Then, the crude mixture was hydrolyzed with 1 N aqueous HCl until neutral. The aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine then water and dried over Na_2SO_4. After filtration and concentration at room temperature in vacuo, chromatography on silica gel delivered **3** in yields indicated in Table 2.

Trifluoromethylation of Benzophenone with HCF_3/NaH. NaH (53 mg, 1.1 mmol, used as a 50% suspension in oil) was added at −10 °C to a solution of benzophenone (1 mmol) in anhydrous DMF (2 mL). Then, HCF_3 (200−600 mg, 1.4−8.6 mmol) was bubbled at this temperature. The resulting mixture was stirred at −10 °C for 1 h, warmed to room temperature, and stirred at this temperature for 5 h. At this stage, ^{19}F NMR analysis was performed on a small sample, in the presence of $PhOCF_3$ as internal standard. Hydrolysis and workup were carried out as above. **3** was obtained in a 85% yield (Table 2).

Trifluoromethylation of Benzophenone with HCF_3/$N(TMS)_3$/Sodium Alcoholates (CF_3CH_2ONa, MeONa, EtONa, *i*-PrONa). General Procedure. NaH (72 mg, used as a 50% suspension in oil) was added to a solution of the alcohol (1.5 mmol) in anhydrous DMF (1 mL). The mixture was warmed to 60 °C then cooled to −10 °C. $N(SiMe_3)_3$ (350 mg, 1.5 mmol), dissolved in anhydrous THF (1 mL), then benzophenone (180 mg, 1 mmol), dissolved in anhydrous DMF (1 mL), were successively dropped at −10 °C. HCF_3 (200−600 mg, 1.4−8.6 mmol) was bubbled at the same temperature. The resulting mixture was stirred at −10 °C for 1 h, warmed to room temperature and stirred for 5 h. At this stage, ^{19}F NMR analysis was performed on a small sample, in the presence of $PhOCF_3$ as internal standard. Hydrolysis and workup were carried out as above. **3** was obtained in yields indicated in Table 2.

Trifluoromethylation of Ketones with HCF_3/$N(TMS)_3$/Stoichiometric M^+F^- (MF = $Me_4N^+F^-$, Cs^+F^-, $Bu_4N^+[Ph_3SiF_2]^-$). General Procedure. HCF_3 (200−600 mg, 1.4−8.6 mmol) was bubbled at −10 °C into a mixture of the ketone (1 mmol), DMF (2 mL), and anhydrous fluoride (1.5 mmol) [Me_4NF (140 mg), CsF (230 mg), TBAT (810 mg)]. Then, a solution of $N(TMS)_3$ (352 mg, 1.5 mmol) in anhydrous THF (1.5 mL) was dropped at −10 °C. The resulting mixture was stirred at −10 °C for 1 h, warmed to room temperature and stirred for 5 h. At this stage, ^{19}F NMR analysis was performed on a small sample, in the presence of $PhOCF_3$ as internal standard. Hydrolysis and workup were carried out as above. The α-(trifluoromethyl)carbinol was obtained in yields indicated in Schemes 3 and 7 as well as in Table 2.

Trifluoromethylation of Ketones with HCF_3/$N(TMS)_3$/Catalytic M^+F^- (MF = $Me_4N^+F^-$, Cs^+F^-, $Bu_4N^+[Ph_3SiF_2]^-$). General Procedure. The same procedure was carried out until hydrolysis, except that 0.24 mmol of fluoride was used [Me_4NF (22 mg), CsF (30 mg), TBAT (108 mg)] and DMF can be replaced by the solvents (2 mL) indicated in Tables 3 and 4. Hydrolysis can be performed either with pure water (to obtain the α-(trifluoromethyl)carbinol along with its silyl ether) or with water after previous treatment with TMSCl (130 μL) (to obtain the silyl ether only) or with 1 N aqueous HCl (to obtain the α-(trifluoromethyl)carbinol only). In all cases, the aqueous phase was extracted with Et_2O, and the combined organic phases were washed with brine then water and finally dried over Na_2SO_4. After filtration and concentration at room temperature in vacuo, chromatography on silica gel delivered the α-(trifluoromethyl)carbinol and/or its silyl ether in yields indicated in Tables 3−5.

1,1-Diphenyl-2,2,2-trifluoroethanol (3). Oil. Purification by chromatography with PE/acetone (20:1) as eluent. Spectral features were in accordance with those reported in the literature:[28] ^{1}H NMR (200 MHz) δ 7.46−7.50 (M, 4H), 7.31−7.34 (M, 6H), 3.09 (broad s, 1H); ^{13}C NMR (50 MHz) δ 139.54, 128.74, 128.36, 127.55 (q, J = 1.6), 125.46 (q, J = 286), 79.57 (q, J = 28.7); ^{19}F NMR δ −74.70 (s); MS *m*/*z* 252 ($M^{\bullet+}$), 189, 105, 77. Anal. Calcd for $C_{14}H_{11}F_3O$: C, 66.67; H, 4.39. Found: C, 66.68; H, 4.55.

1,1-Diphenyl-1-trimethylsilyloxy-2,2,2-trifluoroethane (4). Oil. Purification by chromatography with PE/acetone (7:1) as eluent. Spectral features were in accordance with those reported in the literature:[28] ^{1}H NMR (300 MHz) δ 7.45−7.46 (M, 4H), 7.34−7.37 (M, 6H), −0.002 (s, 9H); ^{13}C NMR (75 MHz) δ 140.98, 128.32, 128.23 (q, J = 1.5), 127.88, 125.24 (q, J = 287), 82.03 (q, J = 28.3), 1.32; ^{19}F NMR δ −73.10 (s); MS *m*/*z* 324 ($M^{\bullet+}$), 255, 239, 213, 185, 165, 105, 77, 73. Anal. Calcd for $C_{17}H_{19}F_3OSi$: C, 62.94; H, 6.32; F, 17.57. Found: C, 63.05; H, 5.84; F, 17.72.

(*E*)-1-Trifluoromethyl-1,3-diphenyl-2-propen-1-ol (9a). Oil. Purification by chromatography with PE/EE (90:10) as

(27) $HN(TMS)_2$ was added as a buffer to ensure the reproducibilty of the results whatever the origin of $KN(TMS)_2$.

(28) Krishnamurti, R.; Bellew, D. R.; Prakash, G. K. S. *J. Org. Chem.* **1991**, *56*, 984.

eluent: ^{1}H NMR (200 MHz) δ 7.64 (d, J = 9.5, 2H), 7.22−7.43 (m, 8H), 6.88 (d, J = 16.0, 1H), 6.71 (d, J = 16.0, 1H), 2.79 (broad s, 1H); ^{13}C NMR (50 MHz) δ 137.57, 135.68, 133.71, 128.97, 128.90, 128.80, 128.54, 127.08, 126.98 (q, J = 1.2), 126.64, 125.20 (q, J = 286), 80.35 (q, J = 28.5); ^{19}F NMR δ −78.97 (s); MS m/z 278 ($M^{\bullet+}$), 209, 191, 131, 105, 103, 77. Anal. Calcd for $C_{16}H_{13}F_3O$: C, 69.06; H, 4.71. Found: C, 69.42; H, 4.98.

(*E*)-1-Trifluoromethyl-1-trimethylsilyloxy-1,3-diphenyl-2-propene (10a). Oil. Purification by chromatography with PE/acetone (14:1) as eluent: ^{1}H NMR (300 MHz) δ 7.63 (d, J = 9.5, 2H), 7.40−7.43 (M, 8H), 6.73 (d, J = 16.3, 1H), 6.59 (d, J = 16.3, 1H), 0.18 (s, 9H); ^{13}C NMR (75 MHz) δ 138.03, 135.74, 135.30, 128.87, 128.69, 128.61, 127.99, 126.93 (q, J = 1.1), 126.89, 125.37 (q, J = 331), 79.98 (q, J = 28.8), 2.07; ^{19}F NMR δ −77.95 (s); MS m/z 350 ($M^{\bullet+}$), 281, 260, 239, 191, 183, 161, 133, 131, 105, 103, 77, 73. Anal. Calcd for $C_{19}H_{21}F_3OSi$: C, 65.12; H, 6.04; F, 16.26. Found: C, 65.37; H, 6.09; F, 16.19.

(*E*,*E*)-3-Trifluoromethyl-3-trimethylsilyloxy-1,5-diphenyl-1,4-pentadiene (10b). Oil. Purification by chromatography with PE/acetone (7:1) as eluent: ^{1}H NMR (200 MHz) δ 7.37−7.56 (m, 10H), 6.97 (d, J = 16.0, 2H), 6.51 (d, J = 16.0, 2H), 0.29 (s, 9H); ^{13}C NMR (50 MHz) δ 135.93, 135.19, 128.93, 128.69, 127.09, 125.32, 124.99 (q, J = 286), 78.57 (q, J = 29.0), 2.36; ^{19}F NMR δ −80.41 (s); MS m/z 376 ($M^{\bullet+}$), 361, 307, 286, 217, 205, 131, 103, 91, 77, 73.

1-Trimethylsilyloxy-1,1-bis(4-fluorophenyl)-2,2,2-trifluoroethane (10c). Oil. Purification by chromatography with PE/acetone (90:10) as eluent: ^{1}H NMR (200 MHz) δ 7.41 (dd, J = 8.5, 5.3, 4H), 7.05 (dd, J = 8.5, 5.3, 4H), −0.04 (s, 9H); ^{13}C NMR (50 MHz) δ 162.73 (d, J = 249), 136.73 (d, J = 3.4), 130.15 (dq, J = 8.2, 1.7), 125.06 (q, J = 287), 114.95 (d, J = 21.5), 81.40 (q, J = 28.8), 1.30; ^{19}F NMR δ −73.45 (s, 3F), −113.83 (s, 2F); MS m/z 360 ($M^{\bullet+}$), 291, 249, 221, 201, 73.

9-Trifluoromethyl-9-(trimethylsilyloxy)fluorene (10d). White solid. Purification by chromatography with PE/acetone (90:10) as eluent: ^{1}H NMR (200 MHz) δ 7.73 (d, J = 7.6, 2H), 7.69 (d, J = 7.6, 2H), 7.50 (t, J = 7.6, 2H), 7.37 (t, J = 7.6, 2H), −0.20 (s, 9H); ^{13}C NMR (50 MHz) δ 141.91, 141.16, 130.64, 128.13, 126.26 (q, J = 1.5), 125.23 (q, J = 284), 120.31, 83.10 (q, J = 32.9), 1.20; ^{19}F NMR δ −80.26 (s); MS m/z 322 ($M^{\bullet+}$), 253, 233, 211, 183, 77, 73.

4,4,4-Trifluoro-3-*N*,*N*-dimethylamino-1-phenyl-1-butanone (11). Chromatography on silica gel did not allow us to isolate this compound: ^{19}F NMR δ −69.97 (d, J = 6.7); MS m/z 245 ($M^{\bullet+}$), 176, 142, 126, 105, 77, 42.

(*E*)-4,4,4-Trifluoro-1-phenyl-2-buten-1-one (12). Oil. Purification by chromatography with PE/EE (70:30) as eluent: ^{1}H NMR (200 MHz) δ 7.99 (d, J = 7.0, 2H), 7.50−7.71 (M, 4H), 6.80 (dq, J = 14.5, 6.5, 1H); ^{19}F NMR δ −65.67 (d, J = 6.5); MS m/z 200 ($M^{\bullet+}$), 105, 77, 51.

1-Trifluoromethyl-1-hydroxy-4,4-dimethoxy-2,5-cyclohexadiene (9f). Oil. Purification by chromatography with PE/EE (50:50) as eluent: ^{1}H NMR (200 MHz) δ 6.06−6.19 (m, 4H), 3.99 (broad s, 1H), 3.28 (s, 3H), 3.24 (s, 3H); ^{13}C NMR (50 MHz) δ 131.74, 128.21, 124.11 (q, J = 285), 92.87, 68.53 (q, J = 30.9), 50.16, 49.87; ^{19}F NMR δ −80.78 (s).

4-Trifluoromethyl-4-hydroxy-2,5-cyclohexadien-1-one (9g). Oil. Purification by chromatography with PE/EE (50:50) as eluent. Spectral features were in accordance with those reported in the literature:[29] ^{1}H NMR (200 MHz) δ 6.87 (d, J = 10.3, 2H), 6.43 (d, J = 10.3, 2H), 3.25 (broad s, 1H); ^{13}C NMR (50 MHz) δ 184.50, 141.80, 131.74, 123.54 (q, J = 286), 69.49 (q, J = 31.0); ^{19}F NMR δ −79.67 (s).

4-Trifluoromethyl-4-trimethylsilyloxy-2,5-cyclohexadien-1-one (10g). White solid. Purification by chromatography with PE/EE (90:10) as eluent. Spectral features were in accordance with those reported in the literature:[29] ^{1}H NMR (200 MHz) δ 6.84 (d, J = 10.0, 2H), 6.40 (d, J = 10.0, 2H), 0.14 (s, 9H); ^{13}C NMR (50 MHz) δ 183.92, 142.73, 132.05, 123.30 (q, J = 287), 71.52, 1.74; ^{19}F NMR δ −80.16 (s); MS m/z 235 ($M^{\bullet+}$), 185, 181, 139, 111, 83, 77, 73.

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(*Z*)-1-Trifluoromethyl-1-trimethylsilyloxy-4-methoxy-4-methyl-2,5-cyclohexadiene (10h *cis*). Oil. Purification by chromatography with PE/EE (80:20) as eluent: ^{1}H NMR (200 MHz) δ 6.07 (d, J = 10.5, 2H), 5.98 (d, J = 10.5, 2H), 3.10 (s, 3H), 1.31 (s, 3H), 0.19 (s, 9H); ^{13}C NMR (50 MHz) δ 137.57, 127.16 (q, J = 5.6), 124.38 (q, J = 285), 71.28 (q, J = 30.9), 71.21, 52.95, 27.50, (q, J = 1.0), 2.04; ^{19}F NMR δ −81.78 (s); MS m/z 280 ($M^{\bullet+}$), 265, 249, 233, 211, 195, 173, 157, 91, 77, 73.

(*E*)-1-Trifluoromethyl-1-trimethylsilyloxy-4-methoxy-4-methyl-2,5-cyclohexadiene (10h *trans*). Oil. Purification by chromatography with PE/EE (80:20) as eluent: ^{1}H NMR (200 MHz) δ 6.07 (d, J = 10.5, 2H), 5.98 (d, J = 10.5, 2H), 3.20 (s, 3H), 1.37 (s, 3H), 0.16 (s, 9H); ^{13}C NMR (50 MHz) δ 137.54, 127.80, 124.45 (q, J = 285), 70.64, 70.56 (q, J = 30.4), 52.07 (q, J = 1.2), 26.70, 1.94; ^{19}F NMR δ −81.11 (s); MS m/z 280 ($M^{\bullet+}$), 265, 249, 233, 211, 195, 173, 157, 91, 77, 73.

***(Z)*-1-Trifluoromethyl-1-hydroxy-4-methoxy-4-methyl-2,5-cyclohexadiene (9h *cis*).** White solid. Purification by chromatography with PE/EE (60:40) as eluent: mp 58−59 °C; ^{1}H NMR (200 MHz) δ 6.06 (d, J = 10.5, 2H), 5.99 (d, J = 10.5, 2H), 3.07 (s, 3H), 3.01 (broad s, 1H), 1.33 (s, 3H); ^{13}C NMR (50 MHz) δ 138.35, 125.86 (q, J = 1.0), 124.50 (q, J = 285), 70.99, 68.16 (q, J = 30.5), 52.22, 27.49; ^{19}F NMR δ −80.63 (s); MS m/z 208 ($M^{\bullet+}$), 193, 177, 173, 157, 139, 124, 109, 108, 91, 77, 69. Anal. Calcd for $C_9H_{11}F_3O_2$: C, 51.92; H, 5.33; F, 27.38. Found: C, 52.27; H, 5.53; F, 26.40.

(*E*)-1-Trifluoromethyl-1-hydroxy-4-methoxy-4-methyl-2,5-cyclohexadiene (9h *trans*). White solid. Purification by chromatography with PE/EE (60:40) as eluent: mp 57−58 °C; ^{1}H NMR (200 MHz) δ 6.02 (d, J = 10.6, 2H), 5.95 (d, J = 10.6, 2H), 3.40 (broad s, 1H), 3.11 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (50 MHz) δ 137.64, 125.39, 124.44 (q, J = 285), 71.22, 68.72 (q, J = 30.7), 52.28, 27.24; ^{19}F NMR δ −81.29 (s); MS m/z 208 ($M^{\bullet+}$), 193, 177, 173, 157, 139, 124, 109, 108, 91, 77, 69. Anal. Calcd for $C_9H_{11}F_3O_2$: C, 51.92; H, 5.33; F, 27.38. Found: C, 51.30; H, 5.33; F, 26.42.

(*Z*)-1-Trifluoromethyl-1-trimethylsilyloxy-2-*tert*-butyl-4-methoxy-4-methyl-2,5-cyclohexadiene (10i *cis*). Oil. Purification by chromatography with PE/EE (90:10) as eluent: ^{1}H NMR (200 MHz) δ 5.94−6.02 (M, 3H), 3.12 (s, 3H), 1.26−1.32 (M, 12H), 0.22 (s, 9H); NOE ^{1}H-{^{1}H} irradiation of the $Si(CH_3)_3$ signal (0.22 ppm) increased the intensity (+3.5%) of the CH_3O signal (3.12 ppm); ^{13}C NMR (50 MHz) δ 145.04, 135.97 (q, J = 1.1), 134.72 (q, J = 1.1), 129.31 (q, J = 2.0), 124.56 (q, J = 288), 75.39 (q, J = 30.5), 71.84, 52.23, 36.73, 32.77 (q, J = 1.9), 26.72 (q, J = 1.1), 2.15; ^{19}F NMR δ −75.66 (s); MS m/z 321 ($M^{\bullet+} - CH_3$), 279, 245, 211, 77, 73, 57.

(*E*)-1-Trifluoromethyl-1-trimethylsilyloxy-2-*tert*-butyl-4-methoxy-4-methyl-2,5-cyclohexadiene (10i *trans*). Oil. Purification by chromatography with PE/EE (90:10) as eluent: ^{1}H NMR (200 MHz) δ 5.79−6.87 (m, 3H), 2.90 (s, 3H), 1.11−1.17 (m, 12H), 0.00 (s, 9H); ^{13}C NMR (50 MHz) δ 146.48, 135.11 (q, J = 1.1), 134.92 (q, J = 1.1), 130.58 (q, J = 1.9), 124.73 (q, J = 288), 75.39 (q, J = 30.5), 71.46, 52.00 (q, J = 1.9), 36.65, 32.77 (q, J = 1.9), 29.70, 1.91; ^{19}F NMR δ −73.51 (s); MS m/z 321 ($M^{\bullet+} - CH_3$), 279, 245, 211, 77, 73, 57.

(*Z*)-1-Trifluoromethyl-1-hydroxy-2-*tert*-butyl-4-methoxy-4-methyl-2,5-cyclohexadiene (9i *cis*). Oil. Purification by chromatography with PE/acetone (90:10) as eluent: ^{1}H NMR (300 MHz) δ 5.80−5.95 (m, 3H), 3.36 (broad s, 1H), 3.04 (s, 3H), 1.27 (s, 9H), 1.24 (s, 3H); ^{13}C NMR (75 MHz) δ 144.00, 135.54 (q, J = 1.1), 134.85 (q, J = 1.1), 129.59 (q, J = 2.1), 124.65 (q, J = 287), 73.71 (q, J = 30.3), 72.45, 51.60, 32.36 (q, J = 1.7), 32.35, 26.22 (q, J = 1.1); ^{19}F NMR δ −75.22 (s).

(*E*)-1-Trifluoromethyl-1-hydroxy-2-*tert*-butyl-4-methoxy-4-methyl-2,5-cyclohexadiene (9i *trans*). Oil. Purification by chromatography with PE/acetone (90:10) as eluent: ^{1}H NMR (300 MHz) δ 5.85−5.97 (m, 3H), 3.24 (broad s, 1H), 3.01 (s, 3H), 1.27 (s, 9H), 1.24 (s, 3H); ^{13}C NMR (75 MHz) δ 145.63, 135.10, 134.41, 130.28 (q, J = 3.2), 124.80 (q, J = 287), 72.54 (q, J = 30.1), 71.97, 51.98 (q, J = 1.7), 32.36 (q, J = 1.7), 32.35, 28.23; ^{19}F NMR δ −72.53 (s).

1-Methyl-1-phenyl-2,2,2-trifluoroethanol. Oil. Purification by chromatography with PE/EE (70:30) as eluent. Spectral

features were in accordance with those reported in the literature:[28] ^{1}H NMR (200 MHz) δ 7.38−7.57 (m, 5H), 2.62 (broad s, 1H), 1.79 (s, 3H); ^{13}C NMR (50 MHz) δ 138.44, 128.59, 128.32, 126.01 (q, J = 1.0), 125.0 (q, J = 280), 74.60 (q, J = 30.0), 23.91; ^{19}F NMR δ −81.45 (s); MS m/z 190 ($M^{\bullet+}$), 121, 105, 77, 51, 43.

1-Trifluoromethyl-2,6-dimethylcyclohexanol. Oil. Purification by chromatography with PE/acetone (90:10) as eluent: ^{1}H NMR (200 MHz) δ 1.97−2.17 (m, 2H), 1.26−1.49 (m, 6H), 1.06 (m, 3H), 0.95 (m, 3H); ^{13}C NMR (50 MHz) δ 126.62 (q, J = 289), 76.96 (q, J = 25.0), 34.29 (q, J = 1.1), 30.34 (q, J = 1.1), 30.13 (q, J = 1.1), 28.29 (q, J = 1.1), 19.66, 15.75 (q, J = 1.9), 14.64 (q, J = 1.9); ^{19}F NMR δ −74.25 (s); MS m/z 196 ($M^{\bullet+}$), 178, 163, 127, 109, 97, 83, 71, 70, 69, 57, 56, 55, 43, 42, 41, 39, 29, 27.

Trifluoromethylation of Disulfides and Diselenides with HCF_3 and Bases. General Procedures. With $LiN(TMS)_2$ as Base. HCF_3 (200−600 mg, 1.4−8.6 mmol) was bubbled at −15 °C in a solution of disulfide or diselenide (1 mmol) in DMF (2 mL). Then, hexamethyldisilazane (45 μL, 0.2 mmol) and a 1 M solution of $LiN(TMS)_2$ in THF (1.1 mL, 1.1 mmol) were successively dropped at the same temperature. After addition, the reaction mixture was stirred at −15 °C for 5.5 h and then warmed to room temperature and kept at this temperature under stirring for 12 h. After reaction, the crude mixture was analyzed by ^{19}F NMR with an internal standard ($PhOCF_3$).

With $N(TMS)_3$/Me_4NF as Base. HCF_3 (200−600 mg, 1.4−8.6 mmol) was bubbled at 0 °C in a mixture of disulfide or diselenide (1 mmol), anhydrous Me_4NF (140 mg, 1.5 mmol), and anhydrous solvent (DMF or THF, 2 mL). Then, a solution of $N(TMS)_3$ (352 mg, 1.5 mmol) in THF (1.5 mL) was added at 0 °C. After addition, the reaction mixture was stirred at 0 °C for 5.5 h and then warmed to room temperature and kept at this temperature under stirring for 12 h. After reaction, the crude mixture was analyzed by ^{19}F NMR with an internal standard ($PhOCF_3$).

With *t*-BuOK as Base. HCF_3 (200−600 mg, 1.4−8.6 mmol) was bubbled at −15 °C in a solution of disulfide or diselenide (1 mmol) in DMF (2 mL). Then, a 1 M solution of *t*-BuOK in THF (1.1 mL, 1.1 mmol) was dropped at the same temperature. After addition, the reaction mixture was stirred at −15 °C for 5.5 h then warmed to room temperature and kept at this temperature under stirring for 12 h. After reaction, the crude mixture was analyzed by ^{19}F NMR with an internal standard ($PhOCF_3$).

Common Workup of These Procedures. Water (2 mL) and 1 N aqueous HCl (0.5 mL) were added to the reaction mixture. After separation, the aqueous phase was extracted with diethyl ether. The combined organic phases were washed with brine and then water, dried over Na_2SO_4, and evaporated in vacuo at room temperature to deliver a crude oil which was purified by column chromatography with petroleum ether as eluent.

Compounds **14a**,**b**,**f** and **17f** exhibited spectral features in accordance with the well documented literature,[6,16a,20,30] as well as **15f**,[31] and will not be detailed again.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra of compounds **3**, **4**, **8e**,**h**,**i**, **9a**,**f**−**i**, **10a**−**d**,**g**−**i**, **11**, **12**, **13a**, 1-methyl-1-phenyl-2,2,2-trifluoroethanol, and 1-trifluoromethyl-2,6-dimethylcyclohexanol. This material is available free of charge via the Internet at http://pubs.acs.org.

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