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Synthesis and Reactivity of *N*-Trifluoromethyl-*N*-nitrosotrifluoromethanesulfonamide as a New Type of Trifluoromethylating Agent

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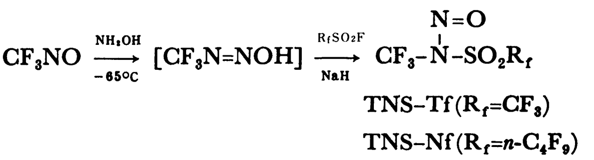
N-Trifluoromethyl-*N*-nitrosotrifluoromethanesulfonamide (TNS-Tf) was synthesized in a 58% yield by the reaction of trifluoronitrosomethane with hydroxylamine followed by the treatment with trifluoromethanesulfonyl fluoride in the presence of a base. TNS-Tf was demonstrated to be an effective trifluoromethylating agent photochemically or thermally for aromatics, thiols, disulfides, and uridine derivatives. The insertion reaction by two trifluoromethyl groups of TNS-Tf to the sulfur–sulfur bonds was observed in the reaction with disulfides having electron-withdrawing groups, giving 2 mols of trifluoromethylthio compounds. Furthermore, TNS-Tf served as a good reagent for mild and convenient in situ generation of trifluoromethylcopper complex which converted iodoaromatics to trifluoromethyl-substituted aromatics in good yields. Similarly, *N*-trifluoromethyl-*N*-nitrosononafluoro-1-butanesulfonamide (TNS-Nf) was synthesized in a 36% yield. The examination of the reactivity indicated that this type of *N*-nitroso sulfonamides became to be sources of both perfluoroalkyl radicals contained.

Much attention has been riveted to trifluoromethyl-containing compounds in the fields of medicine and agricultural chemicals because of the attractive effect of the trifluoromethyl groups on biological activity.[1] Therefore, there have been many investigations for introduction of trifluoromethyl groups into organic compounds. There have been two essential approaches, conversion of trichloromethyl or carboxy groups to trifluoromethyl groups with HF,[2,3] SbF_5,[4] or SF_4[5] and direct introduction of trifluoromethyl groups with trifluoromethyl iodide[6—17] or bromide,[18] trifluoroacetic acid or its salt.[19—21] However, the studies on the syntheses of new reactive trifluoromethylating agents were little reported.[22] Previously we presented the synthesis of *N*-trifluoromethyl-*N*-nitrosobenzenesulfonamide (TNS-B) as a new photochemical trifluoromethylating agent.[23] However the yields for trifluoromethylation were somewhat low and TNS-B was too thermal stable to act as a thermal reagent. In order to enhance the reactivity, we altered it according to our idea that the more the electronegativity of phenyl group of TNS-B rises the more the reactivity increases. Although we replaced the phenyl group of TNS-B with *p*-nitro- or 2,4-dinitrophenyl,[24] their reactivities were rather low. Thus, we expected a great variation in the reactivity by replacement of the aryl group with a perfluoroalkyl group because of its extraordinary high electronegativity.[25] As a result, we could develop a novel and effective trifluoromethylating agent. This paper describes the synthesis and reactivity of *N*-trifluoromethyl-*N*-nitrosotrifluoromethanesulfonamide (TNS-Tf) as a new type of trifluoromethylating agent.

Results and Discussion

TNS-Tf was synthesized in a 58% yield by the reaction of trifluoronitrosomethane with hydroxylamine in DMF/Et_2O (4/1) at -65 °C followed by the treatment with trifluoromethanesulfonyl fluoride at -65—-60 °C for 20 h in the coexistence of sodium hydride.



$$CF_3NO \xrightarrow[-65\,^{\circ}C]{NH_2OH} [CF_3N{=}NOH] \xrightarrow[NaH]{R_fSO_2F} CF_3\text{-}\overset{N=O}{\overset{|}{N}}\text{-}SO_2R_f$$

TNS-Tf(R_f=CF_3)
TNS-Nf(R_f=*n*-C_4F_9)

When trifluoromethanesulfonyl chloride was used instead of the fluoride, TNS-Tf could not be synthesized. TNS-Tf is colorless volatile liquid (mp 3.2—4 °C). Since it is stored in acetonitrile at room temperature for a long time, TNS-Tf can easily and safely be treated as an acetonitrile solution (1—0.5 mol dm^{-3}).

TNS-Tf was found to be a useful photochemical or thermal trifluoromethylating agent for aromatics, thiols, disulfides, and uridine derivatives. The reactions proceeded with evolution of gas. The photochemical reaction was carried out in acetonitrile by using a high pressure Hg lamp and biacetyl as a sensitizer. The results are summarized in Table 1. The trifluoromethylation smoothly took place in the case of electron-rich aromatic compounds and the substitution occurred preferentially at electron-rich positions as shown in Run 2. In this way, TNS-Tf has electrophilic nature. In addition, the trifluoromethylation showed a high *ortho-para* substitution ratio as shown in the reaction of acetanilide (*o*/*p*=4/1). It is in sharp contrast to classical electrophilic substitution of acetanilide (*o*/*p*=1/19 in the nitration).[26] Our method was successfully applied to the preparation of trifluoromethylated dopamine derivative (Run 6), whereas the trifluoromethylation with gaseous trifluoromethyl iodide needed an excess of the substrate and the yield was low.[27] The reaction with such activated aromatics as *p*-*t*-butylphenol and *p*-dimethoxybenzene was accompanied with the formation of considerable amount of

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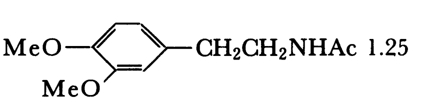
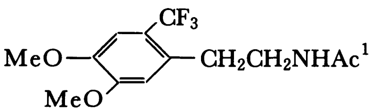
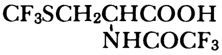
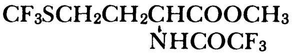
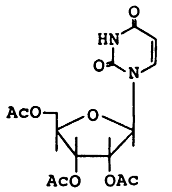
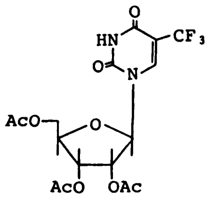
Table 1. Photochemical Trifluoromethylation with TNS-Tf

Run[a]	Substrate	Molar equiv of TNS-Tf	Time h	Product[b]	Yield[c] %	^{19}F-NMR[d]
1	Benzene	0.29	3	$PhCF_3$	49[e]	—
2	Naphthalene	1.0	3.5	CF_3-Naphthalene (α:β-isomers)	41[e] (8.7:1)	60.1(α) 63.1(β)
3	*p*-*t*-Butylphenol	1.0	5	2-CF_3-4-*t*-Butylphenol 2,6-Bis(CF_3)-4-*t*-butylphenol	65[f,g] 17[f](34)[h]	61.3 61.2
4	*p*-Dimethoxybenzene	1.0	2.8	2-CF_3-1,4-Dimethoxybenzene Bis(CF_3)-1,4-dimethoxybenzene[i]	60[e] 16[e](32)[h]	62.9 63.4 55.9
5	Acetanilide	1.0	4.5	CF_3-Acetanilide (*o*:*m*:*p*-isomers)	49[e] (8:1:2)	60.7(*o*) 63.3(*m*) 62.5(*p*)
6		1.25	13	[l]	62[f]	57.8
7	*n*-$C_7H_{15}SH$	1.0	2	*n*-$C_7H_{15}SCF_3$[m]	43[f]	41.6
8	$HSCH_2COOH$	1.0	4	CF_3SCH_2COOH[n]	86[f]	42.0
9	$HSCH_2CH_2COOH$	1.0	4	$CF_3SCH_2CH_2COOH$[d]	89[f]	41.5
10	(n-$C_{10}H_{21}S)_2$	1.0	6.5	*n*-$C_{10}H_{21}SCF_3$[p]	36[f]	41.3
11	$\left(SCH_2\underset{NHCOCF_3}{CH}COOH\right)_2$[j]	1.2	4.5	$CF_3SCH_2\underset{NHCOCF_3}{CH}COOH$	82[f]	40.9(CF_3S) 76.1($COCF_3$)
12	$\left(SCH_2CH_2\underset{NHCOCF_3}{CH}COOCH_3\right)_2$[k]	1.25	5	$CF_3SCH_2CH_2\underset{NHCOCF_3}{CH}COOCH_3$	71[f]	41.4(CF_3S) 76.1($COCF_3$)
13		1.2	1.25	[q]	30[f]	63.8

a) Acetonitrile was used as a solvent except for Run 10 where acetone was used. b) See the experimental section for spectral data of new compounds. The known compounds were spectroscopically in agreement with authentic samples or spectral data reported. c) Yields were calculated on the basis of substrates except for Run 1 in which the yield was on the basis of TNS-Tf. d) Chemical shifts (ppm, upfield from $CFCl_3$ as an internal standard) of trifluoromethyl groups are given. e) ^{19}F-NMR yields. f) Isolated yields. g) 2,6-Bis(CF_3)-4-*t*-butylphenol as another product was isolated in a 17% yield based on the substrate (34% based on TNS-Tf). h) Yields were calculated based on TNS-Tf. i) 2,3-Bis(CF_3)-1,4-dimethoxybenzene and 2,5-bis(CF_3)-1,4-dimethoxybenzene were produced in 7 and 9% ^{19}F-NMR yields based on the substrate, respectively (14 and 18% based on TNS-Tf). Their spectral data are shown in the experimental section. j) This starting material was prepared by treating L-cystine with trifluoroacetic anhydride in trifluoroacetic acid at −10 to +10 °C. k) This starting material was prepared by treating DL-homocystine in the same manner as the case of j) followed by esterification with diazomethane. l) Ref. 24. m) Bp 60 °C/20 mmHg (1 mmHg=133.322 Pa). n) Bp 125 °C/21 mmHg [lit, 88—88.5 °C/15 mmHg, V. V. Boiko, G. M. Shchupak, and L. M. Yagupol'skii, *J. Org. Chem. USSR*, **13**, 972 (1977)]. o) Bp 120 °C/17 mmHg (lit, 108 °C/22 mmHg, J. F. Harris, Jr., USP 3522293). p) BP 106 °C/17 mmHg. q) Ref. 15.

bis(trifluoromethyl)aromatics (34% in Run 3 and 32% in Run 4, based on TNS-Tf). Accordingly, the total yields of trifluoromethylated aromatics in Runs 3 and 4 were 99 and 92% based on TNS-Tf, respectively. It indicated that TNS-Tf is an effective source of trifluoromethyl groups. Deactivated aromatics such as methyl benzoate did not give any trifluoromethylated products. Photochemical decomposition of TNS-Tf itself occurred. TNS-Tf could not trifluoromethylate such nitrogen-containing compounds as pyridine and aniline because TNS-Tf was decomposed by them.

The reaction of mercaptoacetic and 3-mercaptopropionic acids with TNS-Tf afforded (trifluoromethylthio) acetic and -propionic acids in 86 and 89% isolated yields, respectively. It is in contrast to the reaction of the phenyl analogue TNS-B, of which reaction with 3-mercaptopropionic acid yielded only a trace of the product. 1-Heptanethiol, an easily oxidizable thiol, gave a moderate yield of the product. Until now, trifluoromethylation of thiols was the photochemical or thermal action of trifluoromethyl iodide on the thiols under basic conditions.[8,15] TNS-Tf afforded a useful method for thiols or products which are unstable to basic conditions (for example Runs 9, 11, and 12).

TNS-Tf was a good reagent for the conversion of disulfides to trifluoromethylthio compounds. The yields were calculated according to the following equation. Actually the reaction of 2.73 mmol of TNS-

$$R\text{-}S\text{-}S\text{-}R + TNS\text{-}Tf \longrightarrow 2\,CF_3\text{-}S\text{-}R$$

Table 2. Thermal Trifluoromethylation with TNS-Tf

Run[a)]	Substrate	Molar equiv of TNS-Tf	Temp °C	Time h	Product	Yield[b)] %
1[c)]	*t*-Butylphenol	1.0	110	22	2-CF_3-4-*t*-butylphenol[c)]	69
2	$(n\text{-}C_{10}H_{21}S)_2$	1.5	80	1.5	$n\text{-}C_{10}H_{21}SCF_3$	23
3	$(-SCH_2CH_2COOH)_2$	1.0	80	23	$CF_3SCH_2CH_2COOH$	47

a) Acetonitrile was used as a solvent. b) Isolated yields which were calculated on the basis of substrates. c) In addition, 2,6-bis(trifluoromethyl)-4-*t*-butylphenol was isolated in 15.5% yield.

Table 3. Preparation of 1-Trifluoromethylnaphthalene from 1-Iodonaphthalene by CF_3 Copper Complex Generated In Situ from TNS-Tf and Copper

Run	Solvent	Temp/°C	Time/h	Yield/%[b)]
1	HMPA/CH_3CN(5/2)[a)]	100	18	86
2	NMP/CH_3CN(5/2)[a)]	100	19	93
3	DMF/CH_3CN(5/2)[a)]	100	19	88
4	CH_3CN	Reflux	19	52

a) The amount of acetonitrile is that of acetonitrile solution (0.5 mol dm^{-3}) of TNS-Tf used. b) ^{19}F-NMR yields.

Tf with 2.28 mmol of *N*-trifluoroacetylcystine gave 3.75 mmol of the product (82% based on the disulfide, Run 11). In this way, two trifluoromethyl groups of TNS-Tf were consumed in the insertion reaction. The trifluoromethionine derivative was prepared in a 71% yield by TNS-Tf (Run 12), whereas the yield by TNS-B was 30% only. This insertion reaction followed by hydrolysis provided an effectual method for the preparation of trifluoromethionine, a competitive inhibitor of methionine activation,[28)] compared with the known method[29)] starting from acrylaldehyde and gaseous trifluoromethanethiol because of easiness of operation, availability of the amino acid as a starting material, high yield, and short steps.

TNS-Tf is the first to make it possible to trifluoromethylate the uridine derivative directly, giving the biologically interesting 5-trifluoromethyluridine derivative (Run 13).[1)] Our method is advantageous compared with the stepwise synthesis.[17)]

The thermal trifluoromethyaltion with TNS-Tf was accomplished by heating an equimolar mixture of TNS-Tf and a substrate in acetonitrile in a sealed tube. The results are shown in Table 2 and are similar to the photochemical reaction.

Interestingly, it was found that an exothermic reaction occurred with evolution of gas when a solution (0.5 mol dm^{-3}) of TNS-Tf (1 equimol) in acetonitrile was added dropwise into a mixture of activated copper powder (2 equimol) in such solvents as HMPA, NMP, DMF, and acetonitrile at room temperature. This is a good example for high reactivity of TNS-Tf. The reaction mixture resulted in an almost homogeneous brown solution. Iodonaphthalene (0.4 equimol) was added into the brown solution and the reaction mixture was heated to give trifluoromethylnapthalene in a high yield without the formation of naphthalene. Advantageously, no reduction of iodine atom by copper occurred. It is due to the complete reaction of TNS-Tf with copper. Reduction of aromatic iodides by copper was reported in the trifluoromethylation with trifluoromethyl iodide and copper.[10)] The results and reaction conditions are shown in Table 3. These facts

$$\text{TNS-Tf} \xrightarrow[\text{R.t.}]{\text{Cu}} \text{CF}_3\text{-Cu Complex} \xrightarrow[\Delta]{\text{ArI}} \text{Ar-CF}_3$$

suggested that the reaction of TNS-Tf with copper formed trifluoromethylcopper complex, because it has been well-known that trifluoromethylcopper reacted with iodoaromatics to give trifluoromethyl compounds.[12,30)] There have been many reports about the methods for the formation of the copper.[6,7,10,12,21,30)] It was demonstrated that trifluoromethylcopper in situ generated afforded high yields and wide application for the preparation of trifluoromethyl compounds, compared with the copper transiently formed.[12,30)] The reaction of trifluoromethylcopper complex generated in situ from TNS-Tf with several kinds of haloaromatics was carried out and the results are summarized in Table 4. Trifluoromethyl compounds were prepared from iodo compounds in good yields, while bromo compounds gave poor yields of the products under our conditions. Dodecyl iodide did not afford the corresponding trifluoromethyl compound under our conditions, although it was reported that trifluoromethylcopper in situ generated from trifluoromethyl iodide and copper in HMPA at 120°C was treated with decyl iodide to give 1,1,1-trifluoroundecane in a 48% yield.[12)] Our method using TNS-Tf is advantageous in generating in situ the copper complex conveniently under very mild conditions compared with the known methods which needed high tempearture or pressure reaction and removal of excess or remaining copper by filtration in a dry box.[12,30)]

Table 4. Trifluoromethylation of Haloaromatics by CF_3 Copper Complex from TNS-Tf

Run	Haloaromatics	Method[a)]	Product[b)]	Yield/%[c)]
1	*p*-Iodonitrobenzene	A	*p*-CF_3-nitrobenzene	68
2	*p*-Iodoanisole	A(B)	*p*-CF_3-anisole	71(66)
3	*m*-Iodoanisole	B	*m*-CF_3-anisole	72
4	*o*-Iodoanisole	B	*o*-CF_3-anisole	88
5	*p*-Iodochlorobenzene	B	*p*-CF_3-chlorobenzene	74
6	*p*-Iodobromobenzene	B	*p*-CF_3-bromobenzene	53
7	*p*-Bromoanisole	A	*p*-CF_3-anisole	5
8	1-Bromonaphthalene	A(B)	1-CF_3-naphthalene	16(3)

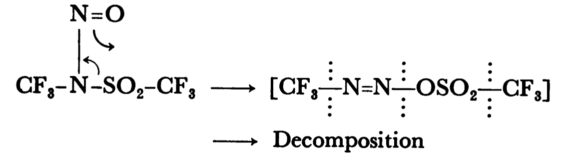
a) Method A=Run 1 in Table 3, B=Run 2 in Table 3. b) Spectral data of products were in agreement with authentic samples. c) ^{19}F-NMR yields.

Table 5. Photochemical or Thermal Reaction with TNS-Nf

Run[a)]	Substrate	Molar equiv of TNS-Nf	Condition	Time/h	Product[b)]	Yield/%[c)]
1	*p-t*-Butylphenol	1.0	*hν*	18	2-CF_3-4-*t*-butylphenol	25
					2-C_4F_9-4-*t*-butylphenol	20
2	*p-t*-Butylphenol	0.8	100°C	7.5	2-CF_3-4-*t*-butylphenol	22
					2-C_4F_9-4-t-butylphenol	42
3	*p*-Dimethoxybenzene	1.0	*hν*	18	2-CF_3-1,4-dimethoxybenzene	30
					2-C_4F_9-1,4-dimethoxybenzene	25
4	*p*-Dimethoxybenzene	0.8	100°C	13	2-CF_3-1,4-dimethoxybenzene	11
					2-C_4F_9-1,4-dimethoxybenzene	47

a) All the reactions were carried out in acetonitrile. b) See the experimental section for spectral data of new compounds. c) Isolated yields which were calculated on the basis of TNS-Tf.

We also synthesized *N*-trifluoromethyl-*N*-nitroso-nonafluoro-1-butanesulfonamide (TNS-Nf) in a 36% yield in a similar manner as TNS-Tf. The results of the thermal and photochemical reactions with *p-t*-butylphenol and *p*-dimethoxybenzene are shown in Table 5. In every case, two kinds of products, trifluoromethyl and nonafluorobutyl compounds were formed, indicating that both trifluoromethyl and nonafluorobutyl radicals were generated from TNS-Nf, probably, by homolytic fission. It suggested that both trifluoromethyl groups in TNS-Tf participated in the trifluoromethylation. The mass spectrum of the gas evolved from the photoreaction of TNS-Tf with *p-t*-butylphenol in acetonitrile (Run 3 in Table 1) indicated that nitrogen and hexafluoroethane were contanined in the gas as main components but dinitrogen monoxide wasn't. The formation of nitrogen and hexafluoroethane suggested the isomerization of TNS-Tf to the azo compound followed by decomposition through the homolytic cleavage. It was reported that hydrocarbon analogues of nitrososulfonamides, *N*-alkyl-*N*-nitrosotoluenesulfonamides, easily isomerized to the corresponding azo compounds which decomposed through heterolytic fission.[31)] Although the acetonitrile solution didn't contain triflic acid after the reaction, the solution became acidic. Probably it is due to the formation of sulfur trioxide as a by-product. It was reported that trifluoromethanesulfonyloxyl radical easily decomposed to release sulfur trioxide.[32)]



$$CF_3\text{-}\overset{N=O}{N}\text{-}SO_2\text{-}CF_3 \longrightarrow [CF_3 \vdots N{=}N \vdots OSO_2 \vdots CF_3] \longrightarrow \text{Decomposition}$$

Experimental

Melting and boiling points were uncorrected. ^{1}H NMR spectra were determined with a Varian HA-100 NMR spectrometer or a Varian EM 390 NMR spectrometer. ^{19}F NMR spectra were determined with a Varian XL-100A NMR spectrometer or a Hitachi R-20B NMR spectrometer. ^{19}F Chemical shifts are given in ppm upfield from trichlorofluoromethane as an internal standard. IR spectra were measured on a Jasco A-202 diffraction grating infrared spectrometer. Mass spectra were recorded on a Hitachi RMU-6MG spectrometer at 70 eV. GLC analyses were carried out with Ohkura 802 Gas Chromatograph, using a column (2 mm×3 m) packed with Silicone SE-30 (10%) on Chromosorb WAW DMCS. Riko Kagaku UVL-400P Hg lamp was used for the photoreaction. *N,N*-Dimethylformamide (DMF) used was distilled on a small amount of triphenylchlorosilane to remove amines contained, after drying with molecular sieve 3A.

Material. Trifluoronitrosomethane was prepared according to our method reported previously.[33)]

Caution. Neat TNS-Tf or TNS-Nf must not be allowed to stand at room temperature because of possible violent decomposition and can be stored for a long time (more than one year) in a deep freezer (−20°C). As mentioned earlier, TNS-Tf can easily and safely be treated as an acetonitrile solution (1—0.5 mol dm^{-3}) at room temperature.

***N*-Trifluoromethyl-*N*-nitrosotrifluoromethanesulfonamide (TNS-Tf).** At −65 °C, trifluoronitrosomethane (16.1 g, 0.163 mol) was blown into a solution of hydroxylamine which was prepared by the treatment of hydroxylamine hydrochloride (10.9 g, 0.156 mol) with potassium *t*-butoxide (17.5 g, 0.156 mol) in 207 ml of a mixture of DMF/diethyl ether (4/1). An excess of the nitrosomethane was removed by flowing argon. After the introduction of 25.0 g (0.165 mol) of trifluoromethanesulfonyl fluoride, sodium hydride (50% in oil, 8.25 g, 0.172 mol) was added in several portions. All operations described above were performed at −65—−60 °C. The mixture was stirred for 20 h at −65 °C and warmed to −50 °C. At this temperature, pentane (20 ml) was added and then the mixture was allowed to warm to −20 °C. The mixture was poured into water and extracted with pentane (60 ml×3). The pentane solution was washed with water, dried ($MgSO_4$), and filtered. The filtrate (room temperature) was transfered to a trap cooled to −78 °C by trap-to-trap distillation in vacuo to remove high boiling materials (nujol and others) from the filtrate. Then the distillate was cooled to −90 °C—−100 °C. TNS-Tf crystallized from the solution and then was isolated as colorless crystals by removing the solvent with a syringe at the low temperature. Further purification by the trap-to-trap method in vacuo from −78 °C to −196 °C gave 22.3 g of colorless volatile crystals (58%); mp 3.2—4 °C; ^{19}F NMR ($CDCl_3$, ppm) 69.7 (3F, m, N–CF_3), 76.5 (3F, bs, SO_2CF_3); IR (neat, cm^{-1}) 1545 (N=O), 1415 (SO_2). Elemental analysis was not done because of instability at room temperature.

***N*-Trifluoromethyl-*N*-nitrosononafluoro-1-butanesulfonamide (TNS-Nf).** Trifluoronitrosomethane was allowed to react with hydroxylamine followed by the treatment with nonafluoro-1-butanesulfonyl fluoride in the same manner as the case of TNS-Tf. The reaction mixture was extracted with diethyl ether. The ethereal layer was washed with water till the aqueous layer was neutral (pH 6—7), dried ($MgSO_4$), filtered and then concentrated on an ice bath by using an aspirator. The residue (yellow oil) was purified by the trap-to-trap method at low temperature to give TNS-Nf as colorless liquid in a 36% yield. ^{19}F NMR ($CDCl_3$, ppm) 69.4 (3F, bs, CF_3N), 81.0 (3F, m, CF_3), 109.9 (2F, m, CF_2), 120.0 (2F, m, CF_2), 125.3 (2F, m, CF_2); IR (Neat, cm^{-1}) 1540 (N=O), 1420 (SO_2). Elemental analysis was not done because of instability at room temperature.

Photochemical Trifluoromethylation with TNS-Tf or -Nf. A Typical Experimental Procedure: A solution of 75 mg (0.50 mmol) of 4-*t*-butylphenol, 43.2 mg (0.50 mmol) of biacetyl, and 127.9 mg (0.52 mmol) of TNS-Tf in 2 ml of acetonitrile was degassed by a freeze-thaw cycle, sealed in a Pyrex tube equipped with a stopcock, and was irradiated under water bath cooling for 5 h with a 400W high pressure Hg lamp. The reaction mixture was chromatographed over silica gel (10% Et_2O/pentane) to give 24.9 mg (17%) of 2,6-Bis(CF_3)-4-*t*-butylphenol and 71 mg (65%) of 2-CF_3-4-*t*-butylphenol.

2,6-Bis(CF_3)-4-*t*-butylphenol: Oil; ^{1}H NMR ($CDCl_3$) δ= 1.33 (9H, s, 3×CH_3), 5.93 (1H, broad peak, OH), 7.68 (2H, bs, ArH); ^{19}F NMR ($CDCl_3$, ppm) 61.2 (s, CF_3).

2,5-Bis(CF_3)-1,4-dimethoxybenzene: Mp 131—132 °C; ^{1}H NMR (CCl_4) δ=3.88 (6H, s, 2×CH_3), 7.13 (2H, s, ArH); ^{19}F NMR (CCl_4, ppm) 63.4 (s, CF_3); MS (*m/z*) 274 (M$^+$).

2,3-Bis(CF_3)-1,4-dimethoxybenzene: Mp 71—74 °C; ^{1}H NMR (CCl_4) δ=3.83 (6H, s, 2×CH_3), 7.08 (2H, s, ArH); ^{19}F NMR (CCl_4, ppm) 55.9 (s, CF_3); MS (*m/z*) 274 (M$^+$).

***N*-Acetyl-*O,O′*-dimethyl-6-CF_3-dopamine:** Mp 118.5—120.5 °C; ^{1}H NMR ($CDCl_3$) δ=1.95 (3H, s, CH_3CO), 2.93 (2H, t, $ArCH_2$), 3.48 (2H, m, CH_2N), 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 5.70 (1H, broad peak, NH), 6.81 (1H, bs, ArH), 7.07 (1H, s, ArH); IR (KBr, cm^{-1}) 3350 (NH), 1640 (C=O); MS (*m/z*) 291 (M$^+$).

***N*-Trifluoroacetyl-*S*-trifluoromethylcysteine:** Mp 69—72 °C; ^{1}H NMR ($CDCl_3$) δ=3.27—3.73 (2H, m, CH_2), 4.80—5.07 (1H, m, CH), 7.10—7.40 (1H, m, NH), 9.77 (1H, bs, COOH); IR (Nujol, cm^{-1}) 3325 (NH), 1720 (C=O).

***N*-Trifluoroacetyltrifluoromethionine Methyl Ester (*N*-Trifluoroacetyl-*S*-trifluoromethylhomocysteine):** Oil; ^{1}H NMR ($CDCl_3$) δ=2.27 (2H, m, CH_2), 2.93 (2H, t, *J*=7.5 Hz, CH_2), 3.80 (3H, s, OCH_3), 4.72 (1H, dt, *J*=6.0, 7.5 Hz, CH), 7.42 (1H, d, *J*=7.5 Hz, NH); IR (Neat, cm^{-1}) 3350 (NH), 1750 (sh) (C=O), 1720 (C=O). Found: C, 30.52; H, 2.85; N, 4.52%. Calcd for $C_8H_9NO_3SF_6$: C, 30.68; H, 2.90; N, 4.47%.

4-*t*-Butyl-2-C_4F_9-phenol: Oil; ^{1}H NMR (CCl_4) δ=1.33 (9H, s, 3×CH_3), 5.48 (1H, m, OH), 6.86 (1H, d, *J*=8.7 Hz, ArH), 7.30 (1H, d, *J*=2.4 Hz, ArH), 7.42 (1H, dd, *J*=8.7, 2.4 Hz, ArH); ^{19}F NMR (CCl_4, ppm) 81.0 (3F, t, *J*=10 Hz, CF_3), 107.6 (2F, m, CF_2), 122.3 (2F, m, CF_2), 125.3 (2F, m, CF_2); IR (Neat, cm^{-1}) 3450 (OH).

1,4-Dimethoxy-2-C_4F_9-benzene: Oil; ^{1}H NMR (CCl_4) δ=3.75 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 6.91 (3H, m, ArH); ^{19}F NMR (CCl_4, ppm) 81.4 (3F, bs, CF_3), 107.6 (2F, m, CF_2), 121.7 (2F, m, CF_2), 125.9 (2F, m, CF_2); IR (Neat, cm^{-1}) 2850 (OCH_3), 1590 (Ar), 1510 (Ar).

Thermal Trifluoromethylation with TNS-Tf or -Nf. A Typical Procedure: A solution of 300 mg (2.0 mmol) of 4-*t*-butylphenol and 491 mg (2.0 mmol) of TNS-Tf in 10 ml of acetonitrile was degassed by a freeze-thaw cycle, sealed in a Pyrex tube, and was heated at 110 °C for 22 h. The reaction mixture was cooled, poured into water, and extracted with diethyl ether. The ethereal layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over silica gel (10% Et_2O/pentane) to give 88.7 mg (15.5%) of 2,6-bis(CF_3)-4-*t*-butylphenol and 300.4 mg (69%) of 2-CF_3-4-*t*-butylphenol.

Hydrolysis of *N*-Trifluoroacetyltrifluoromethionine Methyl Ester to Trifluoromethionine(*S*-trifluoromethylhomocysteine). 2 mol dm^{-3} Sodium hydroxide (1.5 ml) was dropwise added to a solution of 0.35 g of *N*-trifluoroacetyltrifluoromethionine methyl ester in 4 ml of methanol. The mixture was stirred for 5 h at room temperature. After evaporation of the solvent, a small amount of water was added to the residue and the solution was neutralized to pH=ca. 6 with hydrochloric acid. The resulting white precipitates were collected by filtration and washed with acetone. Yield 0.17 g (75%). Recrystallization from methanol gave pure crystals; mp 224—225 °C (with decomp) (lit, mp 229 with decomp),[29] ^{19}F NMR (CD_3OD, ppm) 40.9 (s, CF_3). Found: C, 29.74; H, 3.91; N, 6.78%. Calcd for $C_5H_8NO_2SF_3$: C, 29.56; H, 3.97; N, 6.89%.

Trifluoromethylation of Aromatic Iodides by Using TNS-Tf and Copper. A Typical Procedure: TNS-Tf (4 ml, 0.5 mol dm^{-3} in acetonitrile, 2.0 mmol) was dropwise added to a mixture of 250 mg (3.93 mmol) of activated copper powder[34] and 10 ml of dry *N*-methylpyrrolidinone (NMP) at room temperature under argon atmosphere. Then the mixture was stirred for 3 h at room temperature. 1-Iodonaphthalene (200 mg, 0.788 mmol) was added to the resulting brown solution which was almost homogeneous, and the mixture was heated at 100 °C for 19 h. After addition of water and ether to the cooled reaction mixture, the resulting solution was filtered through Celite layer, and extracted with ether. Combined ethereal layer was washed with water, dried ($MgSO_4$), and concentrated at 40—50 °C under atmosphere. To the remaining crude product was added $CClBr_2CF_3$ (145.9 mg, 0.528 mmol) as an internal standard, and then the yield of 1-CF_3-naphthalene based on the relative intensity of ^{19}F NMR signal was 0.491 mmol (93%).

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