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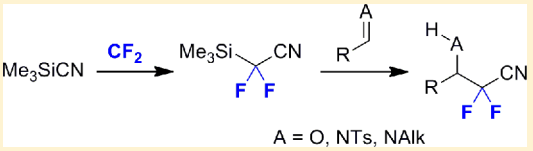
Difluoro(trimethylsilyl)acetonitrile: Synthesis and Fluoroalkylation Reactions

Mikhail D. Kosobokov, Alexander D. Dilman,* Vitalij V. Levin, and Marina I. Struchkova

N. D. Zelinsky Institute of Organic Chemistry, 119991 Moscow, Leninsky prosp. 47, Russian Federation

Supporting Information

ABSTRACT: A new silicon reagent, difluoro(trimethylsilyl)acetonitrile, was prepared by insertion of difluorocarbene into silyl cyanide. The obtained silane served as a good cyanodifluoromethylating reagent toward aldehydes, *N*-tosylimines, *N*-alkylimines, and enamines under basic or acidic conditions.



The importance of organofluorine compounds for pharmaceutical and agrochemical industries has stimulated intense research activity aimed at the development of new methods for the synthesis of fluorinated substances.[1] Though mechanistically diverse processes have been evaluated, reactions employing silicon reagents have received particular attention, since they allow for the smooth introduction of fluorinated carbanions.[2−4] Indeed, silanes are typically air stable and easy-to-handle compounds, with their nucleophilic reactivity being uncovered by Lewis basic activators.

While the major work on nucleophilic fluoroalkylation has been done with CF_3- and higher alkyl silanes,[2] the efforts in the field are moving forward to study fluorinated silanes bearing a functional group.[3] Thus, silanes possessing sulfur,[4] phosphorus,[5] halogen,[6] as well as ester groups[7] have been prepared and used in various C−C bond forming processes (Figure 1). Herein we describe a new silicon reagent, which contains nitrile substituent, and demonstrate that it can be successfully used in fluoroalkylation reactions.

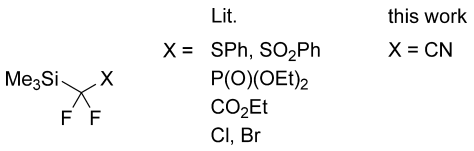
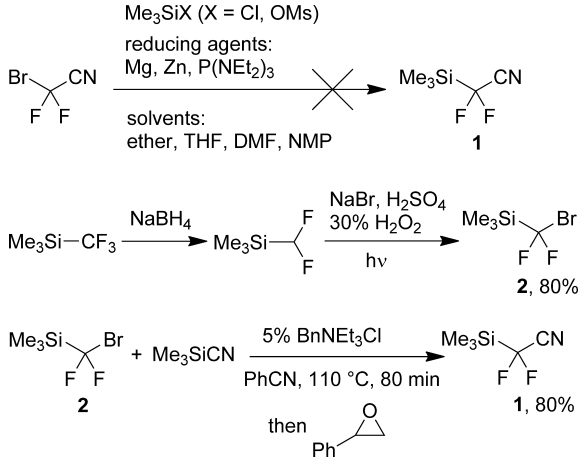


Figure 1. Silicon reagents.

Our original plan to synthesize difluoro(trimethylsilyl)-acetonitrile (**1**) was to silylate readily available bromodifluoroacetonitrile (Scheme 1). However, attempts to perform this transformation failed despite extensive variation of reaction conditions. Even in those cases when silane **1** was detected by NMR spectroscopy, we could not isolate it in individual state. In an alternative approach, we started from $TMSCF_3$, which was converted to the corresponding difluoromethylsilane according to a literature procedure.[8] Subsequent radical bromination of $TMSCHF_2$ using hydrogen bromide/aqueous hydrogen peroxide system[9] irradiating with household incandescent light bulb afforded silane **2**. Heating of silane **2** with trimethylsilyl cyanide in the presence of 5 mol % of

Scheme 1. Synthesis of Slane 1



benzyltriethylammonium chloride led to clean reaction providing an equimolar mixture of silane **1** and Me_3SiBr. The bromosilane byproduct was scavenged by styrene oxide,[10] and subsequent distillation allowed isolation of analytically pure silane **1** in 80% yield as a clear colorless liquid.[11] As a working hypothesis, we assume that the reaction proceeds through the chloride ion induced generation of difluorocarbene from **2**[12] and its insertion into Me_3SiCN.

Having developed a convenient protocol for the preparation of multigram quantities of silane **1**, we focused on exploration of its chemistry. First, the interaction of benzaldehyde (**3a**), selected as a model electrophile, with silane **1** (1.3 equiv) using THF as solvent was studied (Table 1). Employment of 10 mol % of strong Lewis basic activators such as TBAT ($Bu_4NPh_3SiF_2$), CsF, or Bu_4NOAc induced rapid reactions leading to mixtures containing noticeable amounts of compound **6**, which is likely produced from the nucleophilic addition of **1** to primary product **4a**.[13] Use of alkaline acetate salts allowed decreasing the amount of byproduct **6**, though

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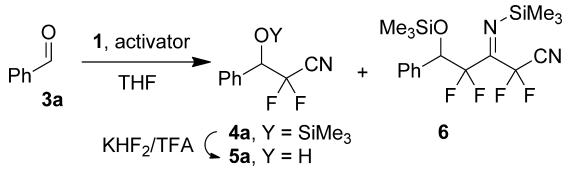
Table 1. Reaction of Silane 1 with Benzaldehyde



#	activator	1, equiv	conditions	conversion (%)	4a:6
1	CsF, 10%	1.3	0 °C, 1 h	80	11:1
2	TBAT, 10%	1.3	0 °C, 1 h	87	15:1
3	Bu_4NOAc, 10%	1.3	0 °C, 1 h	73	14:1
4	AcONa, 10%	1.3	0 °C, 1 h	18	>30:1
5	AcONa, 10%	1.3	rt, 24 h	96	14:1
6	AcOK, 10%	1.3	rt, 18 h	>98	6:1
7[a]	AcOK, 10%	1.3	0 °C, 2 h	84	5:1
8	AcOLi, 10%	1.3	rt, 24 h	78	>30:1
9	AcOLi, 50%	2.0	rt, 18 h	93 (82[b])	>30:1
10	AcOLi, 50%	1.05	50 °C, 3 h	95 (85[b])	>30:1

[a]DMF as solvent. [b]Isolated yield of **5a**.

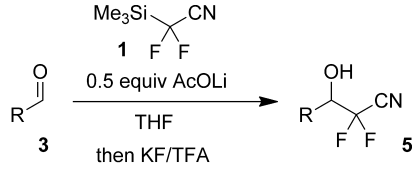
longer reaction times were needed. Lithium acetate proved to be the optimal Lewis base, furnishing the cleanest reaction, and virtually no byproduct **6** could be detected. To achieve high conversion, 2 equiv of the silane were used, and after desilylative workup with KHF_2/trifluoroacetic acid and column chromatography, the final product **5a** was isolated in 82% yield (entry 9). Finally, the fastest and least costly procedure utilizing only 1.05 equiv of the silane was developed by carrying out the reaction at slightly elevated temperature (50 °C) for 3 h (entry 10).

Under the optimized conditions, a series of aldehydes were reacted with silane **1** (Table 2). All tested substrates including aromatic, heteroaromatic, α,β-unsaturated, and aliphatic aldehydes gave good yields of products. Attempted reactions of acetophenone gave only about 70% conversion, while providing complex mixtures, which is likely caused by decreased reactivity of the keto group along with side reactions of primary product.

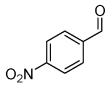
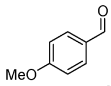
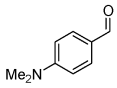
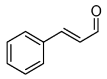
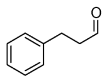
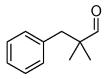
Then we focused on reactions of silane **1** with substrates bearing C=N bond. *N*-Tosylimines (**7**) were first evaluated as electrophilic components. In this case, stoichiometric quantities of Lewis basic activator were required for complete conversion of starting imine. Reactions were performed using 1.3 equiv of both lithium acetate and the silane at room temperature for 18−48 h (Table 3). Notably, no byproduct originating from the consecutive nucleophilic addition at the nitrile group of primary products was observed. This fact, as well as the need for a stoichiometric amount of basic activator, can be explained by the formation of stable anionic adduct after the addition of carbanion at the C=N bond, which does not undergo silylation. High yields of products **8a−e** were obtained starting from nonenolizable imines. At the same time, *N*-tosylimines derived from hydrocinnamaldehyde and isobutyraldehyde bearing acidic α-hydrogen gave complex mixtures. Unactivated imines (*N*-methyl and *N*-phenylimines of benzaldehyde) were completely unreactive and were recovered unchanged.

It was also important to investigate applicability of silane **1** for reactions mediated by in situ generated hydrofluoric acid, since this procedure significantly extends the scope of fluoroalkylation process.[14] Thus, unactivated imines and enamines were treated with silane **1** in the presence of

Table 2. Fluoroalkylation of Aldehydes

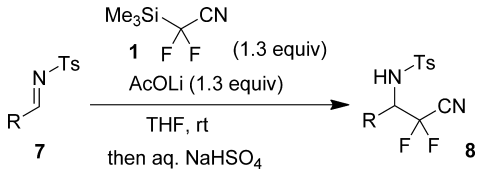


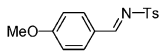
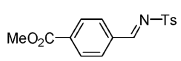
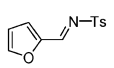
Method A: **1** (2.0 equiv), rt, 18 h
Method B: **1** (1.05 equiv), 50 °C, 3 h

#	aldehyde	method	5	yield of 5,[a] %
1		A	**5b**	70
2		B	**5b**	77
3		A	**5c**	75
4		B	**5d**	60
5		B	**5e**	84
6		B	**5f**	72
7		B	**5g**	73
8		A	**5h**	72
9		A	**5i**	72
10		A	**5j**	72
11		B	**5j**	70
12		A	**5k**	65
13		B	**5k**	66

[a]Isolated yield.

Table 3. Reactions of *N*-Tosylimines



#	imine	time, h	8	yield of 8,[a] %
1		18	**8a**	93
2		48	**8b**	78
3		18	**8c**	91
4		18	**8d**	82
5		48	**8e**	76

[a]Isolated yield.

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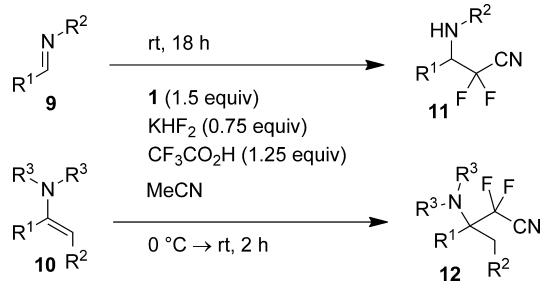
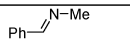
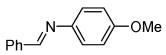
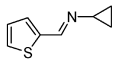
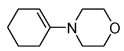
potassium bifluoride and trifluoroacetic acid in acetonitrile (Table 4). Reasonable yields were achieved in all cases, though reactions of enamines proceeded faster and gave higher yields.

Table 4. Fluoroalkylation under Acidic Conditions

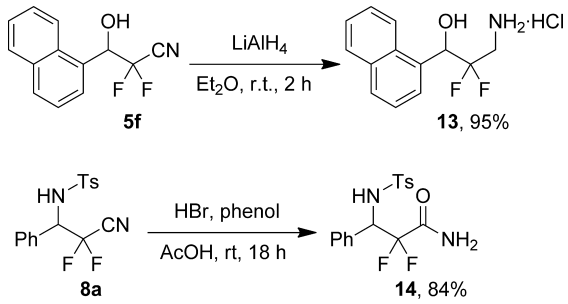


#	substrate	product	yield,[a] %
1		**11a**	66
2		**11b**	68
3		**11c**	78
4		**12a**	95
5		**12b**	82

[a]Isolated yield.

Finally, we briefly investigated the behavior of obtained products (Scheme 2). Reduction of nitrile group of product **5f**

Scheme 2. Transformations of Primary Products



with lithium aluminum hydride allowed isolation of amine **13** as hydrochloride salt. We also attempted to liberate amino group by reductive removal of tosyl group from product **8a** upon treatment with hydrobromic acid in the presence of phenol. Disappointingly, even at room temperature the hydration of electrophilic nitrile group occurred faster than the deprotection leading to amide **14**. An attempt to remove *p*-methoxyphenyl group from product **11b** using ceric ammonium nitrate also failed, resulting in complex mixture.

In summary, we obtained a new fluorinated silicon reagent starting from readily available starting materials.[15] The silane works well in nucleophilic cyanodifluoromethylation of carbonyl compounds, imines, and enamines under basic or acidic conditions.

EXPERIMENTAL SECTION

(Bromodifluoromethyl)trimethylsilane (2).[6] The flask equipped with reflux condenser was charged with NaBr (10.8 g, 105 mmol), 30% aqueous H_2O_2 (14.2 g, 125 mmol), and water (7 mL). The mixture was cooled with ice/water bath, and concentrated sulfuric acid (6.7 mL, 125 mmol) was added dropwise. The cooling bath was removed, and $TMSCHF_2$ (12.4 g, 100 mmol) was added to the resulting dark mixture. The reaction flask was immersed into 40 °C water bath and stirred at this temperature under irradiation with household incandescent light bulb (75 W) until bromine color almost disappeared (ca. 1 h). Upper phase was separated, filtered through $MgSO_4$, and distilled. Yield 16.2 g (80%), colorless liquid: bp 106−108 °C.

Difluoro(trimethylsilyl)acetonitrile (1). A mixture of Me_3SiCN (3.96 g, 40 mmol), silane **2** (8.12 g 40 mmol), $BnNEt_3Cl$ (372 mg, 2 mmol), and benzonitrile (15 mL) was heated at 110 °C for 80 min. The mixture was cooled to 0 °C, styrene oxide (5.5 mL, 48 mmol) was added dropwise, and the mixture was stirred for 1 h at room temperature. The reaction flask was immersed into room temperature bath, and volatile components were distilled off under vacuum (1 Torr) collecting into a cold trap (−100 °C). The collected liquid was filtered through cotton wool plug and fractionally distilled at atmospheric pressure using Vigreux column. Yield 4.76 g (80%), colorless liquid: bp 106−108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.8 (t, J = 1.5), 113.3 (t, J = 37.1), 116.4 (t, J = 264.9); ^{19}F NMR (282 MHz, $CDCl_3$) δ −115.4 (s, 2F). Calcd for $C_5H_9F_2NSi$ (149.21): C, 40.25; H, 6.08; N, 9.39. Found: C, 40.50; H, 6.13; N, 9.62.

Mixture of Compounds 4a and 6 (Ratio 1.6:1). AcOK (220 mg, 2.25 mmol) was added to a solution of benzaldehyde (159 mg, 1.5 mmol) and silane **1** (514 mg, 3.45 mmol), and the mixture as stirred for 18 h at room temperature. The volatile components were evaporated under vacuum in a bath not exceeding 25 °C, and the residue was diluted with hexane (10 mL) and filtered. The filtrate was concentrated under vacuum, and the residue was distilled in a short path apparatus at 85−100 °C (bath temp.)/0.078 Torr to give 200 mg of the mixture of **4a** and **6**. Colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 9H), 0.20 (s, 14H), 0.36 (s, 9H), 4.99 (t, 2H, J = 8.5), 5.14 (dd, 1H, J = 17.8, 5.9), 7.39−7.57 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.34, −0.26, 0.1 (br), 75.3 (dddd, J = 32.2, 24.8, 2.9, 1.0), 75.6 (dd, J = 27.6, 25.9), 105.3 (t, J = 254.8), 111.0 (t, J = 259.6), 111.1 (tm, J = 44.1), 111.4 (t, J = 44.9), 116.1 (ddt, J = 259.1, 250.5, 2.0), 127.7, 128.17, 128.24, 128.5, 129.1, 129.7, 134.0 (dd, J = 3.5), 135.4 (d, J = 1.7), 151.5 (dddd, J = 56.4, 34.5, 28.4); ^{19}F NMR (282 MHz, $CDCl_3$) δ −89.6 (ddd, 1F, J = 308.4, 17.8, 8.5), −92.5 (dt, J = 308.4, 8.5), −98.2 (dd, J = 284.0, 8.5), −102.9 (dd, J = 284.0, 8.5), −104.7 (ddd, J = 260.3, 17.8, 8.5), −114.1 (dm, J = 260.3).

Reaction of Silane 1 with Aldehydes 3. General Procedure. *Method A.* AcOLi (17 mg, 0.25 mmol) was added to a solution of aldehyde **3** (0.5 mmol) and silane **1** (149 mg, 1.0 mmol) in dry THF (1 mL) at 0 °C, and the mixture was stirred for 18 h at room temperature. For the workup, the volatile components were evaporated under vacuum in a bath not exceeding 25 °C, and the residue was dissolved in acetonitrile (1 mL), treated with CF_3CO_2H (77 μL, 1.0 mmol) and KHF_2 (47 mg, 0.6 mmol), and stirred for 30 min. The mixture was diluted with water (5 mL) and extracted with *tert*-butyl methyl ether (3 × 3 mL). The organic phase was dried over Na_2SO_4 and concentrated, and the residue was purified by chromatography.

Method B. AcOLi (17 mg, 0.25 mmol) was added to a solution of aldehyde **3** (0.5 mmol) and silane **1** (78 mg, 0.525 mmol) in dry THF (1 mL) at room temperature, and the mixture was stirred for 3 h at 50 °C. The workup is the same as that used in Method A.

*2,2-Difluoro-3-hydroxy-3-phenylpropanenitrile (**5a**).* Method A, 78 mg, 84% yield. Method B, 77 mg, 85% yield. Oil: R_f 0.31 (hexanes/EtOAc 5:1); bp 100−105 °C (bath temp.)/0.091 Torr; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.98−3.06 (br, 1H), 5.04 (t, 1H, J = 8.6), 7.43−7.56 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 74.9 (t, J = 26.2), 110.7 (t, J = 249.3), 111.0 (t, J = 44.6), 127.5, 128.9, 130.2, 132.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ −99.4 (dd, 1F, J = 290.3, 8.6), −102.5 (dd, 1F, J = 290.3, 8.6). Calcd for $C_9H_7F_2NO$ (183.15): C, 59.02; H, 3.85; N, 7.65. Found: C, 58.83; H, 3.65; N, 7.54.

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*2,2-Difluoro-3-hydroxy-3-(4-nitrophenyl)propanenitrile (**5b**).* Method A, 80 mg, 70% yield. Method B. 88 mg, 77% yield. Pale yellow crystals: mp 87−89 °C (hexanes); R_f 0.20 (hexanes/EtOAc 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.37−3.47 (br, 1H), 5.24 (t, 1H, J = 8.4), 7.74 (d, 2H, J = 8.6), 8.31 (d, 2H, J =8.6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 73.9 (t, J = 27.1), 110.3 (t, J = 250.5), 110.4 (t, J = 44.3), 123.9, 128.7, 139.3, 149.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ −99.2 (dd, 1F, J = 290.3, 8.4), −102.6 (dd, 1F, J = 290.3, 8.4). Calcd for $C_9H_6F_2N_2O_3$ (228.15): C, 47.38; H, 2.65; N, 12.28. Found: C, 47.60; H, 2.66; N, 12.35.

*2,2-Difluoro-3-hydroxy-3-(4-methoxyphenyl)propanenitrile (**5c**).* Method A, 80 mg, 75% yield. Colorless oil: R_f 0.32 (hexanes/EtOAc 3:1); bp 110−120 °C (bath temp.)/0.015 Torr; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.04−3.10 (br, 1H), 3.84 (s, 3H), 4.98 (t, 1H, J = 8.6), 6.96 (d, 2H, J = 8.8), 7.43 (d, 2H, J = 8.8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.3, 74.5 (t, J = 26.8), 110.8 (t, J = 249.0), 111.1 (t, J = 44.6), 114.3, 124.7, 128.8, 160.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ −99.6 (dd, 1F, J = 288.2, 8.6), −102.5 (dd, 1F, J = 288.2, 8.6). Calcd for $C_{10}H_9F_2NO_2$ (213.18): C, 56.34; H, 4.26; N, 6.57. Found: C, 56.23; H, 4.21; N, 6.51.

*3-[4-(Dimethylamino)phenyl]-2,2-difluoro-3-hydroxypropanenitrile (**5d**).* Method B, 68 mg, 60% yield. Orange crystals: mp 56−58 °C (hexanes/EtOAc 10:1); R_f 0.28 (hexanes/EtOAc 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.99 (s, 6H), 3.15−3.39 (br, 1H), 4.87 (t, 1H, J = 8.7), 6.75 (d, 2H, J = 8.8), 7.33 (d, 2H, J = 8.8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.3, 74.7 (t, J = 26.8), 110.9 (t, J = 249.0), 111.4 (t, J = 44.9), 112.3, 120.0 (d, J = 3.6), 128.4, 151.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ −99.4 (dd, 1F, J = 288.2, 8.7), −102.3 (dd, 1F, J = 288.2, 8.7). HRMS (ESI) Calcd for $C_{11}H_{13}F_2N_2O$ (M + H): 227.0990. Found: 227.0991.

*3-(2-Bromophenyl)-2,2-difluoro-3-hydroxypropanenitrile (**5e**).* Method B, 110 mg, 84% yield. Colorless oil: R_f 0.35 (hexanes/EtOAc 5:1); bp 110−125 °C (bath temp.)/0.095 Torr; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.02−3.10 (br, 1H), 5.70 (t, 1H, J = 7.6), 7.26−7.37 (m, 1H), 7.40−7.50 (m, 1H), 7.60−7.68 (m, 1H), 7.71−7.79 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 73.0 (t, J = 27.0), 110.8 (t, J = 250.2), 111.0 (t, J = 44.3), 124.1, 128.1, 129.3, 131.5, 132.5 (d, J = 3.5), 133.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ −98.2 (dd, 1F, J = 291.4, 7.6), −102.5 (dd, 1F, J = 291.4, 7.6). Calcd for $C_9H_6BrF_2NO$ (262.05): C, 41.25; H, 2.31; N, 5.35. Found: C, 41.24; H, 2.24; N, 5.41.

*2,2-Difluoro-3-hydroxy-3-(1-naphthyl)propanenitrile (**5f**).* Method B, 84 mg, 72% yield. Colorless crystals: mp 72−73 °C (hexanes); R_f 0.28 (hexanes/EtOAc 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.08 (d, 1H, J = 4.0), 5.86−6.00 (m, 1H), 7.51−7.64 (m), 7.88−8.02 (m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.5 (t, J = 27.4), 111.1 (t, J = 44.6), 111.6 (t, J = 250.5), 122.4 (d, J = 2.9), 125.2, 125.9, 126.1, 127.0, 128.8 (d, J = 3.5), 129.1, 130.7, 131.1, 133.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ −96.4 (dd, 1F, J = 290.3, 8.5), −101.0 (dd, 1F, J = 288.2, 6.4). Calcd for $C_{13}H_9F_2NO$ (233.21): C, 66.95; H, 3.89; N, 6.01. Found: C, 66.81; H, 3.88; N, 5.96.

*2,2-Difluoro-3-hydroxy-3-pyridin-2-ylpropanenitrile (**5g**).* Method B, 67 mg, 73% yield. Colorless crystals: mp 56−61 °C (hexanes); R_f 0.23 (hexanes/EtOAc 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.05 (t, 1H, J = 8.2), 5.63−5.82 (br, 1H), 7.39−7.53(m, 2H), 7.80−7.89 (m, 1H), 8.66−8.71 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 72.7 (t, J = 26.8), 110.7 (t, J = 250.8), 110.8 (t, J = 44.3), 123.1, 125.0, 137.5, 148.7, 149.7 (d, J = 5.2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −98.8 (dd, 1F, J = 292.5, 8.2), −103.2 (dd, 1F, J = 290.3, 8.2). Calcd for $C_8H_6F_2N_2O$ (184.14): C, 52.18; H, 3.28; N, 15.21. Found: C, 52.39; H, 3.31; N, 15.32.

*2,2-Difluoro-3-hydroxy-3-thien-2-ylpropanenitrile (**5h**).* Method A, 68 mg, 72% yield. Colorless oil: R_f 0.27 (hexanes/EtOAc 5:1); bp 80−100 °C (bath temp.)/0.075 Torr; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.04−3.19 (br, 1H), 5.25−5.39 (m, 1H), 7.05−7.19 (br, 1H), 7.23−7.35 (br, 1H), 7.42−7.52 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 71.6 (t, J = 27.9), 110.0 (t, J = 249.9), 110.8 (t, J = 44.6), 127.4, 127.8, 127.9, 134.7 (d, J = 3.4); ^{19}F NMR (282 MHz, $CDCl_3$) δ −99.9 (d, 1F, J = 288.2), −102.4 (d, 1F, J = 288.2). Calcd for $C_7H_5F_2NOS$ (189.19): C, 44.44; H, 2.66; N, 7.40. Found: C, 44.21; H, 2.55; N, 7.27.

*(4E)-2,2-Difluoro-3-hydroxy-5-phenylpent-4-enenitrile (**5i**).* Method A, 75 mg, 72% yield. Colorless oil: Chromatography was performed at −30 °C; R_f 0.29 (hexanes/EtOAc 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80−2.98 (br, 1H), 4.68 (q, 1H, J = 7.4), 6.19 (dd, 1H, J = 15.8, 7.4), 6.95 (d, 1H, J = 15.8), 7.34−7.51 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 73.7 (t, J = 26.8), 110.7 (t, J = 249.6), 111.2 (t, J = 44.3), 119.1 (dd, J = 3.5, 1.7), 127.0, 128.8, 129.1, 135.0, 137.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −100.9 (dd, 1F, J = 290.3, 7.4), −103.7 (dd, 1F, J = 290.3, 7.4). Calcd for $C_{11}H_9F_2NO$ (209.19): C, 63.16; H, 4.34; N, 6.70. Found: C, 63.08; H, 4.45; N, 6.81.

*2,2-Difluoro-3-hydroxy-5-phenylpentanenitrile (**5j**).* Method A, 76 mg, 72% yield. Method B, 74 mg, 70% yield. Colorless oil: R_f 0.25 (hexanes/EtOAc 10:1); bp 90−100 °C (bath temp.)/0.051 Torr; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91−2.25 (m, 2H), 2.41−2.58 (m, 1H), 2.72−2.88 (m, 1H), 2.92−3.10 (m, 1H), 3.84−4.08 (m, 1H), 7.20−7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.7, 30.8 (dd, J = 2.3, 1.2), 71.8 (dd, J = 26.5, 25.3), 111.2 (t, J = 44.6), 111.5 (t, J = 247.9), 126.6, 128.4, 128.7, 139,8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −101.7 (dd, 1F, J = 294.6, 10.6), −104.5 (dd, 1F, J = 292.5, 8.5). Calcd for $C_{11}H_{11}F_2NO$ (211.21): C, 62.55; H, 5.25; N, 6.63. Found: C, 62.57; H,5.31; N, 6.61.

*2,2-Difluoro-3-hydroxy-4,4-dimethyl-5-phenylpentanenitrile (**5k**).* Method A, 78 mg, 65% yield. Method B, 79 mg, 66% yield. Colorless oil: R_f 0.26 (hexanes/EtOAc 5:1); bp 90−100 °C (bath temp.)/0.078 Torr; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.18 (s, 3H), 2.64 (d, 1H, J = 13.2), 2.75 (d, 1H, J = 6.6), 2.92 (d, 1H, J = 13.2), 3.70 (td, 1H, J = 10.8, 6.2), 7.16−7.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 23.3 (dd, J = 2.3, 4.0), 38.1, 45.9, 76.7 (t, J = 23.9), 112.2 (dd, J = 253.9, 247.0), 112.3 (t, J = 44.6), 126.6, 128.2, 130.7, 136.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ −91.1 (dd, 1F, J = 296.7, 10.6), −98.6 (dd, 1F, J = 296.7, 10.6). Calcd for $C_{13}H_{15}F_2NO$ (239.26): C, 65.26; H, 6.32; N, 5.85. Found: C, 65.21; H, 6.38; N, 5.68.

Reaction of Silane 1 with *N*-Tosylimines 7. General Procedure. AcOLi (43 mg, 0.65 mmol) was added to a solution of *N*-tosylimine **7** (0.5 mmol) and silane **1** (97 mg, 0.65 mmol) in THF (1 mL) at 25 °C, and the mixture was stirred at room temperature for the time indicated in Table 3. The mixture was treated with saturated aq $NaHSO_4$ (1 mL) and stirred for additional 30 min. The mixture was diluted with water (5 mL) and extracted with *tert*-butyl methyl ether (3 × 3 mL). The organic phase was dried over Na_2SO_4 and concentrated, and the residue was purified by chromatography.

*N-(2-Cyano-2,2-difluoro-1-phenylethyl)-4-methylbenzenesulfonamide (**8a**).* 156 mg, 93% yield. Colorless crystals: mp 166−168 °C (hexanes/EtOAc 10:1); R_f 0.29 (hexanes/EtOAc 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H), 4.96 (q, 1H, J = 11.0), 6.27 (d, 1H, J = 11.0), 7.11−7.36 (m, 7H), 7.64 (d, 2H, J = 8.2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 61.6 (t, J = 25.6), 109.5 (t, J = 251.0), 111.0 (t, J = 44.6), 127.0, 128.1, 129.0, 129.6, 129.8, 130.3, 136.6, 144.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.6 (dd, 1F, J = 287.2, 11.0), −99.1 (dd, 1F, J = 287.2, 11.0). Calcd for $C_{16}H_{14}F_2N_2O_2S$ (336.36): C, 57.13; H, 4.20; N, 8.33. Found: C, 57.04; H, 4.20; N, 8.20.

*N-[2-Cyano-2,2-difluoro-1-(4-methoxyphenyl)ethyl]-4-methylbenzenesulfonamide (**8b**).* 143 mg, 78% yield. Colorless crystals: mp 136−137 °C (hexanes/EtOAc 10:1); R_f 0.30 (hexanes/EtOAc 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.77 (s, 1H), 4.90 (td, 1H, J = 11.7, 9.7), 6.15 (d, 1H, J = 9.7), 6.77 (d, 2H, J = 8.8), 7.11 (d, 2H, J = 8.4), 7.17 (d, 2H, J = 8.2), 7.63 (d, 2H, J = 8.4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 55.3, 61.1 (t, J = 25.6), 109.6 (t, J = 251.1), 111.1 (t, J = 44.6), 114.5, 122.2, 127.0, 129.4, 129.6, 136.7, 144.0, 160.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −98.5 (m, 2F). HRMS (ESI) Calcd for $C_{17}H_{16}F_2N_2O_3SNa$ (M + Na): 389.0742, $C_{17}H_{16}F_2N_2O_3SK$ (M + K): 405.0481. Found: 389.0734 (M + Na), 405.0473 (M + K).

*Methyl 4-(2-Cyano-2,2-difluoro-1-{[(4-methylphenyl)sulfonyl]amino}ethyl)benzoate (**8c**).* 179 mg, 91% yield. Colorless crystals: mp 175−176 °C (hexanes/EtOAc 10:1); R_f 0.37 (hexanes/EtOAc 1:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.92 (s, 3H), 5.06 (dt, 1H, J = 13.0, 10.2), 6.69 (d, 1H J = 10.2), 7.13 (d, 2H, J = 8.3), 7.30 (d, 2H, J = 8.3), 7.62 (d, 2H, J = 8.3), 7.91 (d, 2H, J = 8.3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3, 52.4, 61.3 (t, J = 25.6), 109.2 (t, J = 251.2), 110.7 (t, J = 44.7), 126.9, 128.3, 129.7, 130.1, 131.4, 134.8,

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136.3, 144.4, 166.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.2 (dd, 1F, J = 288.2, 10.2), −99.5 (dd, 1F, J = 288.2, 14.8). Calcd for $C_{18}H_{16}F_2N_2O_4S$ (394.39): C, 54.82; H, 4.09; N, 7.10. Found: C, 54.72; H, 4.07; N, 7.16.

*N-[2-Cyano-2,2-difluoro-1-(2-furyl)ethyl]-4-methylbenzenesulfonamide (**8d**).* 134 mg, 82% yield. Colorless crystals: mp 147−150 °C (hexanes/EtOAc 10:1); R_f 0.25 (hexanes/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 5.12 (q, 1H, J = 10.3), 6.00 (d, 1H, J = 10.3), 6.27 (br, 1H), 6,31−6.37 (m, 1H), 7.23 (d, 2H, J = 8.1), 7.31 (br, 1H), 7.69 (d, 2H, J = 8.1); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.5, 55.7 (t, J = 27.7), 108.4 (t, J = 252.0), 110.9, 111.6, 127.0, 129.7, 136.5, 143.0, 144.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.7 (dd, 1F, J = 286.1, 10.3), −99.0 (dd, 1F, J = 286.1, 10.3). Calcd for $C_{14}H_{12}F_2N_2O_3S$ (326.32): C, 51.53; H, 3.71; N, 8.58. Found: C, 51.38; H, 3.80; N, 8.50.

*N-(1-Cyano-1,1-difluoro-3,3-dimethylbutan-2-yl)-4-methylbenzenesulfonamide (**8e**).* 120 mg, 76% yield. Colorless crystals: mp 157−159 °C (hexanes); R_f 0.27 (hexanes/EtOAc 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 9H), 2.43 (s, 3H), 3.86 (dt, 1H, J = 13.2, 9.5), 5.24−5.39 (m, 1H), 7.30 (d, 2H, J = 8.3), 7.78 (d, 2H, J = 8.3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 27.4, 34.5, 65.0 (t, J = 23.6), 111.0 (t, J = 251.6), 112.0 (t, J = 44.9), 126.9, 129.6, 138.0, 143.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −89.4 (dd, 1F, J = 292.5, 13.2), −92.5 (dd, 1F, J = 292.5, 10.1). Calcd for $C_{14}H_{18}F_2N_2O_2S$ (316.37): C, 53.15; H, 5.73; N, 8.85. Found: C, 53.14; H, 5.74; N, 8.79.

Reaction of Silane 1 with Imines 9. General Procedure. Trifluoroacetic acid (48 μL, 0.625 mmol) was added to a mixture of imine **9** (0.5 mmol) and KHF_2 (29 mg, 0.375 mmol) in acetonitrile (1.5 mL) at 0 °C, and the suspension was stirred for 5 min. Silane **1** (112 mg, 0.75 mmol) was added, the cooling bath was removed, and the mixture was stirred for 18 h at room temperature. For the workup, saturated aqueous Na_2CO_3 (1 mL) was added dropwise, and the mixture was stirred for an additional 2 min, diluted with water (7 mL), and extracted with ether/hexane (1:1, 3 × 4 mL). The combined organic phase was filtered through Na_2SO_4 and concentrated, and the residue was purified by chromatography.

*2,2-Difluoro-3-(methylamino)-3-phenylpropanenitrile (**11a**).* 65 mg, 66% yield. Colorless oil: R_f 0.32 (hexanes/EtOAc 20:1); bp 111−125 °C (bath temp.)/9 Torr; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67−1.81 (br, 1H), 2.47 (s, 3H), 4.05 (t, 1H, J = 9.7), 7.42−7.48 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.6, 68.6 (t, J = 23.9), 111.88 (t, J = 44.9), 111.91 (t, J = 248.5), 128.6, 128.9, 129.7, 132.7 (d, J = 3.5); ^{19}F NMR (282 MHz, $CDCl_3$) δ −95.4 (dd, 1F, J = 288.2, 9.7), −99.0 (dd, 1F, J = 288.2, 9.7). Calcd for $C_{10}H_{10}F_2N_2$ (196.20): C, 61.22; H, 5.14; N, 14.28. Found: C, 61.03; H, 5.03; N, 14.05.

*2,2-Difluoro-3-[(4-methoxyphenyl)amino]-3-phenylpropanenitrile (**11b**).* 98 mg, 68% yield. Colorless oil: R_f 0.35 (hexanes/EtOAc 10:1); bp 140−145 °C (bath temp.)/0.109 Torr; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 3H), 4.17 (d, 1H, J = 8.5), 4.89 (dt, 1H, J = 13.2, 8.5), 6.70−6.78 (m, 2H), 6.78−6.85 (m, 2H), 7.41−7.55 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.5, 64.1 (t, J = 24.5), 111.0 (t, J = 251.2), 111.9 (t, J = 45.2), 114.8, 116.7, 128.1, 129.0, 129.6, 132.6, 138.7, 153.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ −96.0 (dd, 1F, J = 287.5, 8.5), −100.5 (dd, 1F, J = 287.5, 13.2). Calcd for $C_{16}H_{14}F_2N_2O$ (288.29): C, 66.66; H, 4.89; N, 9.72. Found: C, 66.85; H, 4.82; N, 9.72.

*3-(Cyclopropylamino)-2,2-difluoro-3-thien-2-ylpropanenitrile (**11c**).* 89 mg, 78% yield. Colorless oil: R_f 0.33 (hexanes/EtOAc 40:1); bp 98−105 °C (bath temp.)/0.67 Torr; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.47−0.66 (m, 4H), 2.17−2.41 (m, 2H), 4.51 (ddd, 1H, J = 16.7, 9.5, 7.5), 7.10 (dd, 1H, J = 5.1, 3.8), 7.19 (d, 1H, J = 3.8), 7.41 (d, 1H, J = 5.1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.9, 7.1, 29.3, 62.7 (t, J = 25.6), 110.8 (t, J = 249.6), 112.0 (t, J = 44.9), 126.7, 127.3, 127.6, 136.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ −94.8 (dd, 1F, J = 286.1, 7.5), −102.1 (dd, 1F, J = 284.0, 16.7). Calcd for $C_{10}H_{10}F_2N_2S$ (228.26): C, 52.62; H, 4.42; N, 12.27. Found: C, 52.54; H, 4.46; N, 12.17.

Reaction of Silane 1 with Enamines 10. General Procedure. Trifluoroacetic acid (48 μL, 0.625 mmol) was added to a mixture of enamine **10** (0.5 mmol) and KHF_2 (29 mg, 0.375 mmol) in acetonitrile (1.5 mL) at −30 °C, and the suspension was stirred for 5 min. Silane **1** (112 mg, 0.75 mmol) was added, the cooling bath was replaced by ice/water bath, and the mixture was stirred for 1 h at 0 °C and then for an additional hour at room temperature. For the workup, saturated aqueous Na_2CO_3 (1 mL) was added dropwise, and the mixture was stirred for an additional 2 min, diluted with water (7 mL), and extracted with ether/hexane (1:1, 3 × 4 mL). The combined organic phase was filtered through Na_2SO_4 and concentrated to give the crude material, which was purified by chromatography.

*Difluoro(1-morpholin-4-ylcyclohexyl)acetonitrile (**12a**).* 116 mg, 95% yield. Colorless oil: R_f 0.43 (hexanes/EtOAc 20:1); bp 95−103 °C (bath temp.)/0.106 Torr; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20−1.93 (m, 8H), 2.01−2.18 (m, 2H, J = 9.2), 2.88−3.09 (br, 4H), 3.60−3.84 (br, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 25.4, 27.3, 46.6, 62.6 (t, J = 19.0), 68.3, 112.7 (t, J = 45.5), 116.1 (t, J = 258.1); ^{19}F NMR (282 MHz, $CDCl_3$) δ −98.1 (s, 2F). Calcd for $C_{12}H_{18}F_2N_2O$ (244.28): C, 59.00; H, 7.43; N, 11.47. Found: C, 58.93; H, 7.53; N, 11.34.

*2,2-Difluoro-4-methyl-3-pyrrolidin-1-ylpentanenitrile (**12b**).* 83 mg, 82% yield. Colorless oil: R_f 0.64 (hexanes/EtOAc 20:1); bp 90−100 °C (bath temp.)/9 Torr; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97−1.16 (m, 6H), 1.72−1.90 (m, 4H), 2.12−2.29 (m, 1H), 2.86−3.10 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6 (dd, J = 2.3, 4.6), 21.1, 24.8, 26.9, 49.0, 68.3 (t, J = 22.2), 113.5 (t, J = 44.9), 114.4 (dd, J = 255.7, 258.0); ^{19}F NMR (282 MHz, $CDCl_3$) δ −85.8 (d, 1F, J = 288.2), −98.2 (dd, 1F, J = 288.2, 19.1). Calcd for $C_{10}H_{16}F_2N_2$ (202.24): C, 59.39; H, 7.97; N, 13.85. Found: C, 59.14; H, 7.75; N, 13.72.

*3-Amino-2,2-difluoro-1-(1-naphthyl)propan-1-ol Hydrochloride (**13**).* A solution of nitrile **5f** (117 mg, 0.5 mmol) in Et_2O (1 mL) was added dropwise to a solution of $LiAlH_4$ (34 mg, 0.85 mmol) in Et_2O (1 mL) at 0 °C, and the mixture was stirred for 2 h at room temperature. The mixture was cooled to 0 °C, and water (40 μL), NaOH (30 μL of 20% aq solution), and water (140 μL) were successively added. The solid material was filtered and washed with ether (3 × 1 mL), and the filtrate was treated with HCl (314 μL, 1.74 M in dioxane, 0.55 mmol). The precipitate was filtered, washed with ether (1 mL), and dried under vacuum. Yield 130 mg (95%). Colorless crystals: mp 216−220 °C (dec); ^{1}H NMR (300 MHz, CD_3OD) δ 3.58−3.87 (m, 2H), 4.72−5.35 (br, 3H), 6.00 (dd, 1H, J = 14.6, 7.0), 7.45−7.60 (m, 3H), 7.85−7.95 (m, 3H), 8.23 (d, 1H, J = 8.4); ^{13}C NMR (75 MHz, CD_3OD) δ 42.5 (t, J = 26.2), 70.6 (dd, J = 29.4, 25.3), 121.6 (dd, J = 250.5, 247.0), 124.7 (t, J = 2.3), 126.1, 126.6, 127.2, 127.3, 129.7, 130.3, 132.9, 133.8 (d, J = 2.3), 135.0; ^{19}F NMR (282 MHz, CD_3OD) δ −111.5 (ddt, 1F, J = 252.2, 23.3, 7.0), −117.4 (dddd, 1F, J = 252.2, 23.3, 14.6, 8.5). Calcd for $C_{13}H_{14}ClF_2NO$ (273.71): C, 57.05; H, 5.16; N, 5.12. Found: C, 57.10; H, 5.20; N, 5.13.

*2,2-Difluoro-3-{[(4-methylphenyl)sulfonyl]amino}-3-phenylpropanamide (**14**).* A solution of nitrile **8a** (168 mg, 0.5 mmol) and phenol (94 mg, 1 mmol) in 33% HBr/AcOH (1.5 g) was stirred for 18 h at room temperature. The mixture was poured into Et_2O (10 mL), and the precipitate was filtered. The collected solid was dissolved in minimal amount of refluxing methanol (ca. 5 mL) and cooled to room temperature followed by dropwise addition of Et_2O (ca. 10 mL). The precipitate was filtered and dried. Yield 149 mg (84%). Colorless crystals: mp 260−265 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.21 (s, 3H), 3.77−3.85 (br, 3H), 5.05 (t, 1H, J = 14.7), 7.04−7.23 (m, 7H), 7.43 (d, 2H, J = 8.1); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.8, 58.5 (t, J = 24.6), 115.1 (t, J = 258.5), 126.3, 127.9, 128.2, 128.6, 129.0, 132.7, 137.9, 142.5, 164.1 (t, J = 27.9); ^{19}F NMR (282 MHz, DMSO-d_6) δ −112.1 (m, 2F). Calcd for $C_{16}H_{16}F_2N_2O_3S$ (354.37): C, 54.23; H, 4.55; N, 7.91. Found: C, 54.18; H, 4.57; N, 7.83.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra for all compounds and free induction decay (FID) files for the mixture of compounds **4a** + **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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AUTHOR INFORMATION

Corresponding Author
*E-mail: adil25@mail.ru.

Notes
The authors declare no competing financial interest.

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DEDICATION

This paper is dedicated to Professor Vladimir Tartakovsky on the occasion of his 80th birthday.

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(15) The immediate precursor, Me_3SiCF_2Br, is commercially available from several companies.