An Efficient Synthesis of *N*′-(Fluoroalkylsulfonyl) Amidines by a Copper(I)-Catalyzed One-Pot Three-Component Reaction

Wanting Xiong, Yong Xin, Jingwei Zhao, Shizheng Zhu*

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. of China
Fax +86(21)64166128; E-mail: zhusz@sioc.ac.cn

Received 5 January 2011; revised 17 January 2011

Abstract: Fluoroalkylsulfonyl azides were successfully employed as an efficient reacting partner in copper(I)-catalyzed three-component couplings with terminal alkynes and amines to afford the corresponding *N*′-(fluoroalkylsulfonyl) amidines in good yields. Possible reaction pathways are proposed.

Key words: multicomponent reactions, fluoroalkylsulfonyl azides, 1-alkynes, amines, amidines

Since the introduction of sulfonyl azides by Curtius and co-workers,[1] extensive investigations on those compounds have been carried out to develop synthetically important transformations such as the nitrene reaction,[2] cycloaddition,[3] the Schmidt reaction[4] and others.[5] In particular, the copper(I)-catalyzed cycloaddition of the azides with 1-alkynes has dramatically broadened the scope and utility of such azides.[6]

For the three-component coupling of a sulfonyl azide, an alkyne and an amine, the reaction is believed to proceed via three steps, i.e. formation of a triazole intermediate via 1,3-dipolar cycloaddition between the azide and the alkyne, release of nitrogen to give the cuprated ketenimine species, and subsequent addition of the amine, leading to the corresponding *N*-sulfonimino products.[7]

Compared with their hydrocarbon analogues, fluoroalkylsulfonyl azides ($R_fSO_2N_3$) have been studied rarely. During the course of investigating the chemical transformations of fluoroalkylsulfonyl azides, we have reported their reactions with various compounds, including alkenes, amines, pyridine, benzene and triphenylphosphine, etc.[8] Recently, we also investigated the one-pot reaction of fluoroalkylsulfonyl azides with 1-alkynes and phosphorous amides, which gave *N*-(fluoroalkylsulfonyl) phosphorus amidines. As an extension of the exploration on the utility of fluoroalkylsulfonyl azides in organic synthesis, we recently studied the copper(I)-catalyzed three-component reaction of fluoroalkylsulfonyl azides with 1-alkynes and amines, which afforded a series of *N*′-(fluoroalkylsulfonyl) amidine products in good yield. Herein, we wish to report these results.

Initially, a template reaction of (nonafluorobutyl)sulfonyl azide (**1a**, 1.2 mmol), phenylacetylene (**2a**) and diisopropylamine (**3a**, 1.2 mmol) was carried out in tetrahydrofuran at room temperature in the presence of 10 mol% copper(I) iodide. After the mixture was stirred for 30 minutes, both the ^{19}F NMR spectrum and TLC analysis showed that the reaction had finished and only one product was formed. General workup and purification by column chromatography gave a white solid, *N*,*N*-diisopropyl-*N*′-[(nonafluorobutyl)sulfonyl]-2-phenylacetamidine (**4aaa**), in 85% yield (Table 1, entry 1).

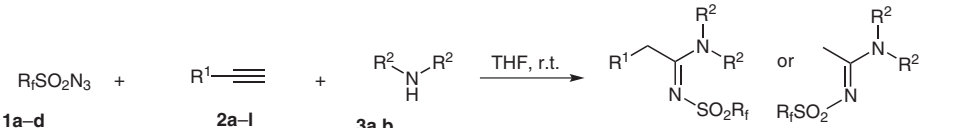
It was found that other copper ion sources, such as copper(I) bromide and copper(I) acetate, were almost equally effective in this reaction. Increasing the amount of copper(I) iodide (up to 20 mol%) did not further increase the product yield. Tetrahydrofuran was the best solvent among those examined, which included dioxane, dichloromethane, tetrahydrofuran and benzene. High reaction temperature (reflux in THF) led to the formation of the byproduct nonafluorobutane-1-sulfonamide ($C_4F_9SO_2NH_2$). Under the optimized conditions, a wide range of 1-alkynes, azides and amines smoothly reacted to afford the corresponding amidine products **4** in good yields. These results are summarized in Table 1. The structures of the amidines **4** were unambiguously confirmed by spectroscopic methods and elemental analysis.

It is noteworthy that both aliphatic alkynes and aromatic alkynes afforded the desired products in the same good yields. Not only simple aliphatic alkynes but also substrates bearing particular functional groups readily participated in the reaction. In addition, alkynes directly conjugated with a double bond or a carbonyl group were all suitable for this reaction. Electronic variation on the aromatic moiety caused no appreciable change in the efficiency of the coupling. Other fluoroalkylsulfonyl azides **1b–d** were also effectively employed and gave satisfactory results (Table 1, entries 1–10). It is noteworthy that in the case of (trimethylsilyl)acetylene (**2l**), the reaction with **1a** and **3a** under the same reaction conditions did not give corresponding product, rather the desilylated product **5** (Table 1, entry 20). This structure was characterized by spectroscopic methods and further confirmed by a single-crystal X-ray diffraction analysis; the product **5** showed the *E* form of the generated C=N double bond (Figure 1).

According to several literature works and combining our previous work on fluorinated azides, probable pathways of the reaction are proposed (see Scheme 1).

SYNTHESIS 2011, No. 7, pp 1142–1148
Advanced online publication: 01.03.2011
DOI: 10.1055/s-0030-1258450; Art ID: H09211SS

Table 1 Results of the Three-Component Reaction[a]



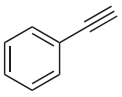
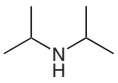
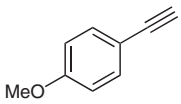
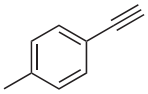
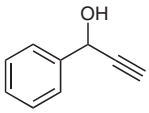
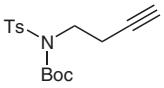
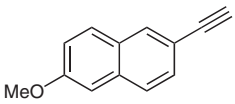
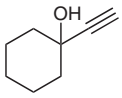
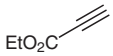
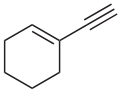
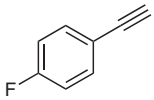
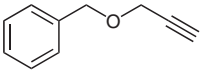
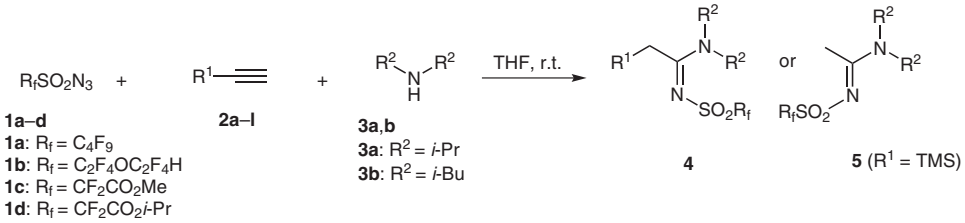
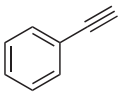
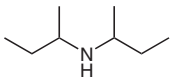
Entry	Azide	1-Alkyne	Amine	Product	Mp (°C)	Yield (%)
1	**1a**	 **2a**	 **3a**	**4aaa**	68–70	85
2	**1b**			**4baa**	60–62	79
3	**1c**			**4caa**	137–139	83
4	**1d**			**4daa**	117–118	81
5	**1a**	 **2b**	**3a**	**4aba**	yellow oil	81
6	**1b**			**4bba**	yellow oil	78
7	**1c**			**4cba**	145–147	78
8	**1a**	 **2c**	**3a**	**4aca**	83–85	80
9	**1b**			**4bca**	71–73	70
10	**1c**			**4cca**	147–149	80
11	**1a**	 **2d**	**3a**	**4ada**	117–119	88
12	**1a**	 **2e**	**3a**	**4aea**	98–100	68
13	**1a**	 **2f**	**3a**	**4afa**	115–117	70
14	**1a**	 **2g**	**3a**	**4aga**	135–137	73
15	**1a**	 **2h**	**3a**	**4aha**	81–83	76
16	**1a**	 **2i**	**3a**	**4aia**	43–45	72
17	**1a**	 **2j**	**3a**	**4aja**	67–69	80
18	**1a**	 **2k**	**3a**	**4aka**	62–64	81

Table 1 Results of the Three-Component Reaction[a] (continued)



Entry	Azide	1-Alkyne	Amine	Product	Mp (°C)	Yield (%)
19	**1a**	 **2a**	 **3b**	**4aab**	65–67	79
20	**1a**	TMS— **2l**	**3a**	**5**	79–81	40

[a] The reactions were carried out in the presence of 10 mol% CuI in THF at r.t., with a molar ratio **1/2/3** of 1.2:1:1.2.

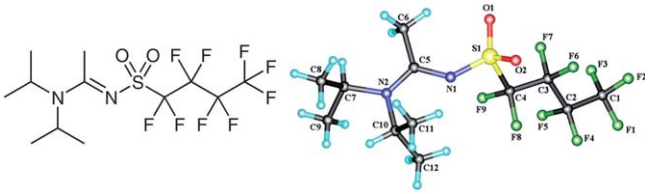
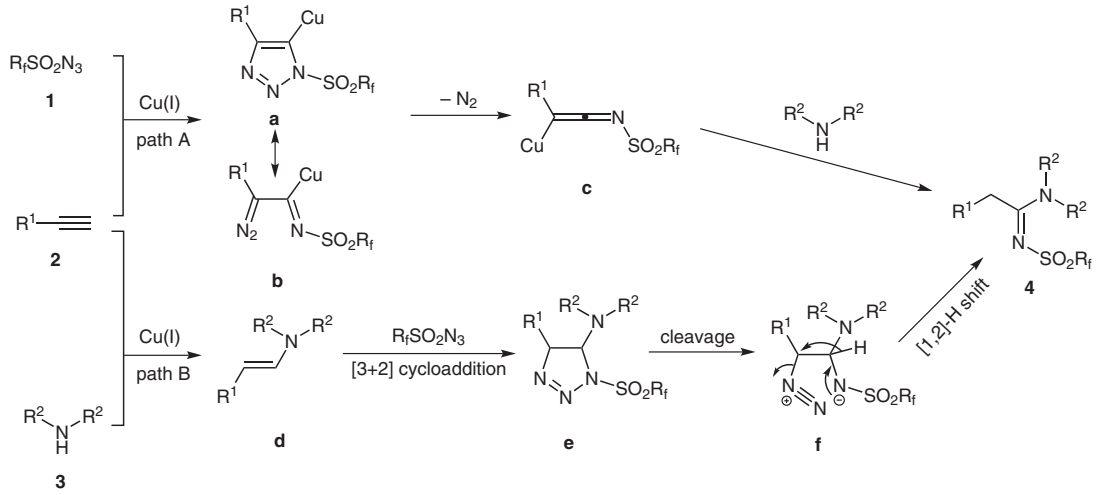


Figure 1 The molecular structure of product **5**

In pathway A, a [3+2] cycloaddition proceeds in the presence of copper(I) iodide and affords a pair of resonance components **a** and **b**, which both could form the intermediate **c** by releasing nitrogen.[9] Then, nucleophilic addition of amine **3** gives the product **4**. On the other hand, pathway B consists of [3+2] cycloaddition, cleavage and a hydride shift along with nitrogen release,[10] which could also give the product **4**.

In summary, fluoroalkylsulfonyl azides can now be listed as new and efficient reacting partners in copper(I)-catalyzed three-component coupling reactions with 1-alkynes and amines. The fruitful utility of the fluoroalkylsulfonyl azides has allowed us to demonstrate the synthetic usefulness of such compounds, and expanding the scope of the multicomponent reaction to prepare additional fluoroalkylsulfonyl-substituted compounds is now under further investigation in our laboratory.

Melting points were measured on a Mel-Temp apparatus and are uncorrected. ^{1}H (300 MHz) and ^{19}F (282 MHz) NMR spectra were recorded on a Bruker AM-300 UltraShield, 300-MHz, high-performance digital FT-NMR spectrometer with TMS and $CFCl_3$ as the internal and external standards, respectively. FT-IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Low-resolution mass spectra (LRMS) and high-resolution mass spectra (HRMS) were obtained on Finnigan GC-MS 4021 and MAT-8430 instruments using the electron-impact ionization technique (70 eV) or electrospray ionization. Elemental analyses were performed by the Shanghai Institute of Organic Chemistry. Single-crystal X-ray structure analysis was performed on a Bruker AXS D8 instrument. All solvents and reagents were used as obtained without further purification, unless otherwise stated.



Scheme 1 Proposed reaction pathways

N′-(Fluoroalkylsulfonyl) Amidines by the Copper(I)-Catalyzed One-Pot Three-Component Reaction of Fluoroalkylsulfonyl Azides, Terminal Alkynes and Amines; General Procedure

Under N_2 atmosphere and at r.t., a terminal alkyne **2** (1.0 mmol), a fluoroalkylsulfonyl azide **1** (1.2 mmol) and an amine **3** (1.2 mmol) were added to a single-necked flask containing CuI (20 mg, 0.1 mmol) and anhyd THF (10 mL). The mixture was stirred until the reaction was finished (ca. 30 min), as monitored by TLC analysis and ^{19}F NMR spectra. Then, the reaction was quenched with sat. aq NH_4Cl. The CuI residue was removed by filtration, and the filtrate was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed with brine (30 mL), then dried ($MgSO_4$). The solvent was removed and the product was purified by column chromatography (petroleum ether–EtOAc, 10:1 v:v).

N,*N*-Diisopropyl-*N*′-[(nonafluorobutyl)sulfonyl]-2-phenylacetamidine (4aaa)

White solid; 425 mg (85%).

IR (KBr): 2977, 2938, 1556, 1440, 1352, 1322, 1213, 1138, 1058 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.32 (m, 2 H), 7.28–7.20 (m, 3 H), 4.33 (s, 2 H, CH_2), 4.14–4.10 (m, 1 H, NCH), 3.59 (br s, 1 H, NCH), 1.50 (d, *J* = 6.9 Hz, 6 H, 2 CH_3), 0.95 (d, *J* = 6.9 Hz, 6 H, 2 CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.7 (t, *J* = 9.6 Hz, 3 F, CF_3), –112.6 (m, 2 F, CF_2S), –120.8 (m, 2 F, CF_2), –125.9 (t, *J* = 15.5 Hz, 2 F, CF_2).

MS (ESI): *m*/*z* = 501.1 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{21}F_9N_2O_2SNa$: 523.1072; found: 523.1054.

Anal. Calcd for $C_{18}H_{21}F_9N_2O_2S$: C, 43.20; H, 4.23; N, 5.60. Found: C, 43.58; H, 4.36; N, 5.43.

N,*N*-Diisopropyl-*N*′-[(1,1,2,2,4,4,5,5-octafluoro-3-oxapentyl)sulfonyl]-2-phenylacetamidine (4baa)

Yellow solid; 393 mg (79%).

IR (KBr): 2977, 2389, 1558, 1447, 1379, 1316, 1209, 1135, 1053 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.31 (m, 2 H), 7.28–7.21 (m, 3 H), 5.86 (tt, *J* = 3.6, 52.5 Hz, 1 H, HCF_2), 4.32 (s, 2 H, CH_2), 4.11 (q, *J* = 6.6 Hz, 1 H, NCH), 3.60 (br s, 1 H, NCH), 1.51 (d, *J* = 6.6 Hz, 6 H, 2 CH_3), 0.95 (d, *J* = 6.6 Hz, 6 H, 2 CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.6 (t, *J* = 12.5 Hz, 2 F, CF_2O), –88.8 (m, 2 F, OCF_2), –116.3 (s, 2 F, CF_2S), –137.4 (td, *J* = 5.5, 52.2 Hz, 2 F, CF_2H).

MS (ESI): *m*/*z* = 499.2 $[M + H]^+$, 521.1 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{23}F_8N_2O_3S$: 499.1296; found: 499.1305.

Anal. Calcd for $C_{18}H_{22}F_8N_2O_3S$: C, 43.37; H, 4.45; N, 5.62. Found: C, 43.53; H, 4.56; N, 5.44.

N′-{[Difluoro(methoxycarbonyl)methyl]sulfonyl}-*N*,*N*-diisopropyl-2-phenylacetamidine (4caa)

White solid; 323 mg (83%).

IR (KBr): 3031, 2977, 1766, 1586, 1478, 1277, 1207 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.33 (m, 2 H), 7.29–7.24 (m, 3 H), 4.34 (s, 2 H, CH_2), 4.11 (q, *J* = 6.6 Hz, 1 H, NCH), 4.00 (s, 3 H, OCH_3), 3.59 (br s, 1 H, NCH), 1.51 (d, *J* = 6.9 Hz, 6 H, 2 CH_3), 0.95 (d, *J* = 6.9 Hz, 6 H, 2 CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –109.2 (s, CF_2S).

MS (ESI): *m*/*z* = 390.9 $[M + H]^+$, 412.9 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{24}F_2N_2O_4S$: C, 52.29; H, 6.20; N, 7.17. Found: C, 52.33; H, 6.12; N, 7.18.

N′-{[Difluoro(isopropoxycarbonyl)methyl]sulfonyl}-*N*,*N*-diisopropyl-2-phenylacetamidine (4daa)

Yellow solid; 339 mg (81%).

IR (KBr): 2989, 2971, 1760, 1553, 1446, 1377, 1315, 1299, 1134 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.31 (m, 2 H), 7.25–7.22 (m, 3 H), 5.24 (q, *J* = 6.6 Hz, 1 H, OCH), 4.32 (s, 2 H, CH_2), 4.09 (q, *J* = 6.6 Hz, 1 H, NCH), 3.57 (br s, 1 H, NCH), 1.51 (d, *J* = 6.6 Hz, 6 H, 2 CH_3), 1.38 (d, *J* = 6.0 Hz, 6 H, 2 CH_3), 0.93 (d, *J* = 6.6 Hz, 6 H, 2 CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –109.2 (s, CF_2S).

MS (ESI): *m*/*z* = 419.2 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{29}F_2N_2O_4S$: 419.1811; found: 419.1801.

Anal. Calcd for $C_{19}H_{28}F_2N_2O_4S$: C, 54.53; H, 6.74; N, 6.69. Found: C, 54.80; H, 6.67; N, 6.55.

N,*N*-Diisopropyl-2-(4-methoxyphenyl)-*N*′-[(nonafluorobutyl)sulfonyl]acetamidine (4aba)

Yellow oil; 430 mg (81%).

IR (KBr): 2976, 2940, 1613, 1555, 1514, 1445, 1377, 1330, 1210, 1139 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 9.0 Hz, 2 H), 6.87 (d, *J* = 9.0 Hz, 2 H), 4.25 (s, 2 H, CH_2), 4.13 (q, *J* = 6.6 Hz, 1 H, NCH), 3.79 (s, 3 H, OCH_3), 3.59 (br s, 1 H, NCH), 1.49 (d, *J* = 6.6 Hz, 6 H, 2 CH_3), 0.97 (d, *J* = 6.6 Hz, 6 H, 2 CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –81.1 (t, *J* = 10.3 Hz, 3 F, CF_3), –113.1 (t, *J* = 13.8 Hz, 2 F, CF_2S), –121.2 (m, 2 F, CF_2), –126.4 (dt, *J* = 5.6, 14.1 Hz, 2 F, CF_2).

MS (ESI): *m*/*z* = 531.0 $[M + H]^+$.

Anal. Calcd for $C_{19}H_{23}F_9N_2O_3S$: C, 43.02; H, 4.37; N, 5.28. Found: C, 43.08; H, 4.55; N, 5.21.

N,*N*-Diisopropyl-2-(4-methoxyphenyl)-*N*′-[(1,1,2,2,4,4,5,5-octafluoro-3-oxapentyl)sulfonyl]acetamidine (4bba)

Yellow oil; 412 mg (78%).

IR (KBr): 2977, 2940, 2841, 1614, 1557, 1515, 1486, 1377, 1326, 1252 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 8.4 Hz, 2 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 5.86 (tt, *J* = 3.6, 52.8 Hz, 1 H, HCF_2), 4.23 (s, 2 H, CH_2), 4.12 (q, *J* = 6.6 Hz, 1 H, NCH), 3.79 (s, 3 H, OCH_3), 3.59 (br s, 1 H, NCH), 1.49 (d, *J* = 6.9 Hz, 6 H, 2 CH_3), 0.96 (d, *J* = 6.9 Hz, 6 H, 2 CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –81.1 (t, *J* = 12.4 Hz, 2 F, CF_2O), –89.2 (m, 2 F, OCF_2), –116.8 (s, 2 F, CF_2S), –137.8 (td, *J* = 5.9, 53.3 Hz, 2 F, CF_2H).

MS (ESI): *m*/*z* = 529.0 $[M + H]^+$.

Anal. Calcd for $C_{19}H_{24}F_8N_2O_4S$: C, 43.18; H, 4.58; N, 5.30. Found: C, 42.99; H, 4.82; N, 5.36.

N′-{[Difluoro(methoxycarbonyl)methyl]sulfonyl}-*N*,*N*-diisopropyl-2-(4-methoxyphenyl)acetamidine (4cba)

White solid; 328 mg (78%).

IR (KBr): 2976, 1764, 1557, 1516, 1448, 1375, 1316, 1175, 1145, 1059 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 8.7 Hz, 2 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 4.24 (s, 2 H, CH_2), 4.10 (q, *J* = 6.6 Hz, 1 H, NCH),

3.98 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.56 (br s, 1 H, NCH), 1.47 (d, J = 6.6 Hz, 6 H, 2 CH_3), 0.94 (d, J = 6.6 Hz, 6 H, 2 CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –109.8 (s, CF_2S).

MS (ESI): m/z = 421.2 $[M + H]^+$.

Anal. Calcd for $C_{18}H_{26}F_2N_2O_5S$: C, 51.42; H, 6.23; N, 6.66. Found: C, 51.24; H, 6.24; N, 6.62.

_N_,_N_-Diisopropyl-_N′_-[(nonafluorobutyl)sulfonyl]-2-(4-tolyl)acetamidine (4aca)
White solid; 411 mg (80%).

IR (KBr): 2978, 2938, 1626, 1553, 1446, 1377, 1331, 1211, 1139, 1056 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15 (d, J = 8.1 Hz, 2 H), 7.10 (d, J = 8.1 Hz, 2 H), 4.29 (s, 2 H, CH_2), 4.14 (q, J = 6.6 Hz, 1 H, NCH), 3.61 (br s, 1 H, NCH), 2.33 (s, 3 H, $ArCH_3$), 1.51 (d, J = 6.6 Hz, 6 H, 2 CH_3), 0.98 (d, J = 6.6 Hz, 6 H, 2 CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.7 (t, J = 9.9 Hz, 3 F, CF_3), –112.7 (t, J = 13.1 Hz, 2 F, CF_2S), –120.8 (m, 2 F, CF_2), –126.0 (m, 2 F, CF_2).

MS (ESI): m/z = 515.0 $[M + H]^+$, 537.0 $[M + Na]^+$.

Anal. Calcd for $C_{19}H_{23}F_9N_2O_2S$: C, 44.36; H, 4.51; N, 5.45. Found: C, 44.53; H, 4.63; N, 5.42.

_N_,_N_-Diisopropyl-_N′_-[(1,1,2,2,4,4,5,5-octafluoro-3-oxapentyl)sulfonyl]-2-(4-tolyl)acetamidine (4bca)
White solid; 358 mg (70%).

IR (KBr): 2981, 2939, 1627, 1561, 1450, 1381, 1315, 1120, 1054 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15 (d, J = 7.5 Hz, 2 H), 7.10 (d, J = 7.5 Hz, 2 H), 5.86 (t, J = 52.5 Hz, 1 H, HCF_2), 4.27 (s, 2 H, CH_2), 4.10 (q, J = 6.6 Hz, 1 H, NCH), 3.60 (br s, 1 H, NCH), 2.32 (s, 3 H, $ArCH_3$), 1.50 (d, J = 6.0 Hz, 6 H, 2 CH_3), 0.97 (d, J = 6.0 Hz, 6 H, 2 CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.6 (t, J = 12.0 Hz, 2 F, CF_2O), –88.8 (m, 2 F, OCF_2), –116.3 (s, 2 F, CF_2S), –137.4 (td, J = 5.6, 52.5 Hz, 2 F, CF_2H).

MS (ESI): m/z = 513.0 $[M + H]^+$, 535.0 $[M + Na]^+$.

Anal. Calcd for $C_{19}H_{24}F_8N_2O_3S$: C, 44.53; H, 4.72; N, 5.47. Found: C, 44.72; H, 5.02; N, 5.43.

_N′_-{[Difluoro(methoxycarbonyl)methyl]sulfonyl}-_N_,_N_-diisopropyl-2-(4-tolyl)acetamidine (4cca)
White solid; 323 mg (80%).

IR (KBr): 2976, 1766, 1558, 1448, 1376, 1301, 1146, 1059 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.11 (br s, 4 H), 4.26 (s, 2 H, CH_2), 4.10 (q, J = 6.3 Hz, 1 H, NCH), 3.98 (s, 3 H, OCH_3), 3.57 (br s, 1 H, NCH), 2.31 (s, 3 H, $ArCH_3$), 1.48 (d, J = 6.3 Hz, 6 H, 2 CH_3), 0.94 (d, J = 6.3 Hz, 6 H, 2 CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –109.8 (s, CF_2S).

MS (ESI): m/z = 405.2 $[M + H]^+$.

Anal. Calcd for $C_{18}H_{26}F_2N_2O_4S$: C, 53.45; H, 6.48; N, 6.93. Found: C, 53.11; H, 6.45; N, 6.79.

3-Hydroxy-_N_,_N_-diisopropyl-_N′_-[(nonafluorobutyl)sulfonyl]-3-phenylpropanamidine (4ada)
White solid; 466 mg (88%).

IR (KBr): 3502, 2983, 1558, 1435, 1301, 1236, 1145, 1116 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.47 (m, 2 H), 7.41–7.31 (m, 3 H), 5.38–5.36 (m, 1 H, OCH), 4.49 (br s, 1 H, NCH), 3.73 (br s, 1 H, NCH), 3.35 (dd, J = 3.9, 14.4 Hz, 1 H, CH), 3.25–3.17 (m, 1 H, CH), 2.54 (br s, 1 H, OH), 1.48 (t, J = 8.1 Hz, 6 H, 2 CH_3), 1.32 (d, J = 5.7 Hz, 3 H, CH_3), 1.18 (br s, 3 H, CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –81.1 (t, J = 9.9 Hz, 3 F, CF_3), –113.0 (s, 2 F, CF_2S), –121.3 (s, 2 F, CF_2), –126.4 (t, J = 11.8 Hz, 2 F, CF_2).

MS (ESI): m/z = 531.2 $[M + H]^+$.

Anal. Calcd for $C_{19}H_{23}F_9N_2O_3S$: C, 43.02; H, 4.37; N, 5.28. Found: C, 42.91; H, 4.45; N, 5.35.

4-[(_tert_-Butoxycarbonyl)(tosyl)amino]-_N_,_N_-diisopropyl-_N′_-[(nonafluorobutyl)sulfonyl]butanamidine (4aea)
Yellow solid; 490 mg (68%).

IR (KBr): 2981, 1724, 1554, 1375, 1235, 1138 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, J = 8.7 Hz, 2 H), 7.31 (d, J = 8.7 Hz, 2 H), 4.21 (br s, 1 H, NCH), 3.94 (t, J = 6.6 Hz, 2 H, NCH_2), 3.61 (br s, 1 H, NCH), 2.92 (t, J = 8.3 Hz, 2 H, CH_2), 2.44 (s, 3 H, $ArCH_3$), 2.17–2.12 (m, 2 H, CH_2), 1.44 (m, 6 H, 2 CH_3), 1.36–1.33 (m, 15 H, 5 CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –81.2 (t, J = 9.9 Hz, 3 F, CF_3), –113.3 (m, 2 F, CF_2S), –121.3 (m, 2 F, CF_2), –126.5 (t, J = 12.8 Hz, 2 F, CF_2).

MS (EI): m/z (%) = 452 (48) $[M – TsNBoc + 1]^+$, 424 (47) $[M – C_4F_9SO_2N]^+$, 325 (35) $[M – N(i\text{-}Pr)_2 – C_4F_9SO_2N – H]^+$, 297 (100) $[C_4F_9SO_2N^+]$.

Anal. Calcd for $C_{26}H_{36}F_9N_3O_6S_2$: C, 43.27; H, 5.03; N, 5.82. Found: C, 43.12; H, 4.90; N, 5.84.

_N_,_N_-Diisopropyl-2-(6-methoxy-2-naphthyl)-_N′_-[(nonafluorobutyl)sulfonyl]acetamidine (4afa)
White solid; 406 mg (70%).

IR (KBr): 2982, 2936, 1606, 1556, 1445, 1378, 1323, 1209, 1137 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.67 (m, 2 H), 7.56 (s, 1 H), 7.31 (dd, J = 1.8, 8.4 Hz, 1 H), 7.15 (dd, J = 1.8, 8.4 Hz, 1 H), 7.11 (s, 1 H), 4.45 (s, 2 H, CH_2), 4.21 (q, J = 6.6 Hz, 1 H, NCH), 3.91 (s, 3 H, OCH_3), 3.60 (br s, 1 H, NCH), 1.53 (d, J = 6.6 Hz, 6 H, 2 CH_3), 0.92 (d, J = 6.6 Hz, 6 H, 2 CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –81.1 (t, J = 9.6 Hz, 3 F, CF_3), –113.1 (t, J = 14.1 Hz, 2 F, CF_2S), –121.3 (s, 2 F, CF_2), –126.4 (m, 2 F, CF_2).

MS (ESI): m/z = 581.2 $[M + H]^+$.

Anal. Calcd for $C_{23}H_{25}F_9N_2O_3S$: C, 47.59; H, 4.34; N, 4.83. Found: C, 47.45; H, 4.28; N, 4.96.

2-(1-Hydroxycyclohexyl)-_N_,_N_-diisopropyl-_N′_-[(nonafluorobutyl)sulfonyl]acetamidine (4aga)
White solid; 381 mg (73%).

IR (KBr): 3528, 2935, 1562, 1426, 1313, 1115 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.64 (q, J = 6.6 Hz, 1 H, NCH), 3.74 (br s, 1 H, NCH), 3.15 (br s, 2 H, CH_2), 2.39 (br s, 1 H, OH), 1.67–1.59 (m, 10 H, 5 CH_2), 1.48 (d, J = 6.6 Hz, 6 H, 2 CH_3), 1.27 (d, J = 6.6 Hz, 6 H, 2 CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –81.2 (t, J = 9.9 Hz, 3 F, CF_3), –112.9 (m, 2 F, CF_2S), –121.4 (t, J = 5.2 Hz, 2 F, CF_2), –126.4 (m, 2 F, CF_2).

MS (ESI): m/z = 523.2 $[M + H]^+$.

Anal. Calcd for $C_{18}H_{27}F_9N_2O_3S$: C, 41.38; H, 5.21; N, 5.36. Found: C, 41.34; H, 5.36; N, 5.43.

2-(Ethoxycarbonyl)-*N*,*N*-diisopropyl-*N*′-[(nonafluorobutyl)sulfonyl]acetamidine (4aha)
White solid; 377 mg (76%).

IR (KBr): 2988, 1740, 1568, 1318, 1236, 1210, 1137 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.23 (q, *J* = 6.9 Hz, 2 H, OCH_2), 4.07–4.02 (m, 3 H), 3.75 (br s, 1 H, NCH), 1.49 (d, *J* = 6.3 Hz, 6 H, 2 CH_3), 1.32–1.29 (m, 9 H, 3 CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –81.2 (t, *J* = 9.4 Hz, 3 F, CF_3), –113.3 (m, 2 F, CF_2S), –121.5 (t, *J* = 4.8 Hz, 2 F, CF_2), –126.5 (m, 2 F, CF_2).

MS (ESI): *m*/*z* = 497.0 $[M + H]^+$.

Anal. Calcd for $C_{15}H_{21}F_9N_2O_4S$: C, 36.29; H, 4.26; N, 5.64. Found: C, 36.32; H, 4.32; N, 5.80.

2-(1-Cyclohexen-1-yl)-*N*,*N*-diisopropyl-*N*′-[(nonafluorobutyl)sulfonyl]acetamidine (4aia)
White solid; 363 mg (72%).

IR (KBr): 2976, 2938, 1556, 1446, 1377, 1349, 1120 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.44 (s, 1 H, =CH), 4.09 (q, *J* = 6.6 Hz, 1 H, NCH), 3.65 (br s, 1 H, NCH), 3.53 (s, 2 H, CH_2), 2.02–2.00 (m, 4 H, 2 CH_2), 1.67–1.64 (m, 2 H, CH_2), 1.57–1.54 (m, 2 H, CH_2), 1.48 (d, *J* = 6.6 Hz, 6 H, 2 CH_3), 1.23 (d, *J* = 6.6 Hz, 6 H, 2 CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –81.2 (t, *J* = 10.2 Hz, 3 F, CF_3), –113.3 (s, 2 F, CF_2S), –121.4 (m, 2 F, CF_2), –126.5 (dt, *J* = 5.9, 13.8 Hz, 2 F, CF_2).

MS (ESI): *m*/*z* = 505.2 $[M + H]^+$.

Anal. Calcd for $C_{18}H_{25}F_9N_2O_2S$: C, 42.86; H, 5.00; N, 5.55. Found: C, 42.44; H, 4.76; N, 5.67.

2-(4-Fluorophenyl)-*N*,*N*-diisopropyl-*N*′-[(nonafluorobutyl)sulfonyl]acetamidine (4aja)
White solid; 414 mg (80%).

IR (KBr): 2982, 1560, 1514, 1449, 1378, 1117 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.19 (m, 2 H), 7.05 (t, *J* = 8.4 Hz, 2 H), 4.29 (s, 2 H, CH_2), 4.08 (q, *J* = 6.6 Hz, 1 H, NCH), 3.61 (br s, 1 H, NCH), 1.50 (d, *J* = 6.9 Hz, 6 H, 2 CH_3), 0.99 (d, *J* = 6.9 Hz, 6 H, 2 CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –81.1 (t, *J* = 10.0 Hz, 3 F, CF_3), –113.2 (m, 2 F, CF_2S), –115.0 (s, 1 F, ArF), –121.3 (t, *J* = 4.7 Hz, 2 F, CF_2), –126.5 (m, 2 F, CF_2).

MS (ESI): *m*/*z* = 519.0 $[M + H]^+$.

Anal. Calcd for $C_{18}H_{20}F_{10}N_2O_2S$: C, 41.70; H, 3.89; N, 5.40. Found: C, 41.52; H, 3.90; N, 5.48.

3-(Benzyloxy)-*N*,*N*-diisopropyl-*N*′-[(nonafluorobutyl)sulfonyl]propanamidine (4aka)
White solid; 441 mg (81%).

IR (KBr): 2975, 2939, 2875, 1556, 1446, 1376, 1205, 1117 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5 H), 4.49–4.43 (m, 3 H), 3.91 (t, *J* = 6.3 Hz, 2 H, OCH_2), 3.65 (br s, 1 H, NCH), 3.21 (t, *J* = 6.3 Hz, 2 H, CH_2), 1.43 (d, *J* = 6.3 Hz, 6 H, 2 CH_3), 1.14 (d, *J* = 5.4 Hz, 6 H, 2 CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –81.1 (t, *J* = 10.9 Hz, 3 F, CF_3), –113.2 (s, 2 F, CF_2S), –121.4 (s, 2 F, CF_2), –126.5 (m, 2 F, CF_2).

MS (EI): *m*/*z* (%) = 544 (0.6) $[M^+]$, 261 (24) $[M^+ – R_fSO_2]$, 100 (99) $[N(i\text{-}Pr)_2^+]$, 91 (100) $[PhCH_2^+]$.

Anal. Calcd for $C_{20}H_{25}F_9N_2O_3S$: C, 44.12; H, 4.63; N, 5.15. Found: C, 44.02; H, 4.45; N, 5.24.

***N*,*N*-Diisobutyl-*N*′-[(nonafluorobutyl)sulfonyl]-2-phenylacetamidine (4aab)**
White solid; 417 mg (79%).

IR (KBr): 2973, 2940, 1555, 1443, 1314, 1200, 1139 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.32 (m, 2 H), 7.28–7.23 (m, 3 H), 4.48–4.39 (m, 1 H), 4.26–4.18 (m, 1 H), 3.84 (q, *J* = 6.6 Hz, 1 H), 3.15 (br s, 1 H), 2.36–2.26 (m, 1 H), 1.74–1.65 (m, 1 H), 1.47 (d, *J* = 6.6 Hz, 3 H, CH_3), 1.41–1.24 (m, 2 H), 0.91–0.85 (m, 6 H, 2 CH_3), 0.73–0.67 (m, 3 H, CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –81.1 (t, *J* = 9.9 Hz, 3 F, CF_3), –113.1 (t, *J* = 14.1 Hz, 2 F, CF_2S), –121.3 (m, 2 F, CF_2), –126.4 (m, 2 F, CF_2).

MS (ESI): *m*/*z* = 529.2 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{25}F_9N_2O_2S$: C, 45.45; H, 4.77; N, 5.30. Found: C, 45.54; H, 4.86; N, 5.39.

(*E*)-*N*,*N*-Diisopropyl-*N*′-[(nonafluorobutyl)sulfonyl]acetamidine (5)
White solid; 170 mg (40%).

IR (KBr): 2978, 2941, 2346, 1560, 1430, 1326, 1237, 1138 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.12 (br s, 2 H), 2.58 (s, 3 H, CH_3), 1.39 (d, *J* = 6.3 Hz, 6 H, 2 CH_3), 1.33 (d, *J* = 6.3 Hz, 6 H, 2 CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.1 (t, *J* = 11.7 Hz, 3 F, CF_3), –112.5 (br s, 2 F, CF_2S), –120.4 (s, 2 F, CF_2), –125.4 (t, *J* = 14.1 Hz, 2 F, CF_2).

MS (ESI): *m*/*z* = 425.2 $[M + H]^+$, 447.0 $[M + Na]^+$.

Anal. Calcd for $C_{12}H_{17}F_9N_2O_2S$: C, 33.97; H, 4.04; N, 6.60. Found: C, 34.16; H, 3.93; N, 6.38.

X-ray Crystallography of Compound 5
Crystal data for $C_{12}H_{17}F_9N_2O_2S$: *M* = 424.34, monoclinic, space group *P*2(1)/*c*, *a* = 14.1721(5) Å, *b* = 10.5562(3) Å, *c* = 12.4206(4) Å, β = 94.666(2)°, *V* = 1852.01(10) $Å^3$, *Z* = 4, D_c = 1.522 mg/m^3, F(000) = 864, crystal dimension 0.32 × 0.28 × 0.22 mm, Mo Kα radiation (λ = 0.711 Å), 4.82 ≤ 2θ ≤ 51.00; intensity data were collected at 298 K with a Bruker AXS D8 diffractometer, employing the ω/2θ scanning technique, in the range of 17 ≤ *h* ≤ 16, 12 ≤ *k* ≤ 12, 14 ≤ *l* ≤ 15. The structure was solved by a direct method; all non-hydrogen atoms were positioned and anisotropic thermal parameters refined from 3442 observed reflections with R_{int} = 0.0288 by a full-matrix least-squares technique converged to *R* = 0.0925 and *Rw* = 0.1972. Full crystallographic parameters have been deposited with the Cambridge Crystallographic Data Centre under the reference number CCDC 802157. These data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk.

Acknowledgment

This work was financially supported by the National Nature Foundation of China (Nos. 20972178 and 21032006).

References

(1) Curtius, T.; Rissom, J.; Kraemer, G.; Vorbach, C.; Meier, H.; Bottler, H.; Hasse, G.; Raudenbusch, W.; Tüxen, R.; Derlon, H. *J. Prakt. Chem.* **1930**, *125*, 303.
(2) Horner, L.; Christmann, A. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 599.
(3) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565.
(4) Aube, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965.

(5) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem. Int. Ed.* **2005**, *44*, 5188.
(6) (a) Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038. (b) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046. (c) Cui, S. L.; Lin, X. F.; Wang, Y. G. *Org. Lett.* **2006**, *8*, 4517. (d) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (e) Jin, Y.; Fu, H.; Yin, Y. W.; Jiang, Y. Y.; Zhao, Y. F. *Synlett* **2007**, 901. (f) Ji, Y. K.; Seok, H. K.; Chang, S. *Tetrahedron Lett.* **2008**, *49*, 1745.
(7) (a) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2006**, *45*, 3154. (b) Yoo, E. J.; Ahlquist, M.; Kim, S. H.; Bae, I.; Fokin, V. V.; Sharpless, K. B.; Chang, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 1730.
(8) (a) Xu, Y.; Xu, G. L.; Zhu, S. Z.; Zhu, G. Y.; Jia, Y. S.; Huang, Q. C. *J. Fluorine Chem.* **1999**, *96*, 79. (b) Xu, Y.; Zhu, S. Z. *Tetrahedron* **2001**, *57*, 669. (c) Xu, Y.; Zhu, S. Z. *Tetrahedron* **2001**, *57*, 3909. (d) Xu, Y.; Zhu, S. Z. *Synthesis* **2001**, 690. (e) Xu, Y.; Zhu, S. Z. *Tetrahedron* **1999**, *48*, 13725. (f) Zhu, S. Z.; He, P. *Tetrahedron* **2005**, *61*, 5679. (g) Zhu, S. Z. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2077.
(9) Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193.
(10) (a) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104. (b) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 3368. (c) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673. (d) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (e) Odom, A. L. *Dalton Trans.* **2005**, 225. (f) Croce, P. D.; Stradi, R. *Tetrahedron* **1977**, *33*, 865. (g) Fioravanti, S.; Pellacani, L.; Ricci, D.; Tardella, P. A. *Tetrahedron: Asymmetry* **1997**, *8*, 2261. (h) Xu, Y.; Wang, Y.; Zhu, S. *Synthesis* **2000**, 513. (i) Xu, Y.; Zhu, S. *Tetrahedron* **2001**, *57*, 4337.