Tetrahedron 65 (2009) 478–483

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Free radical (phenylsulfonyl)difluoromethylation of alkynes with $PhSO_2CF_2I$ reagent: stereoselective preparation of $PhSO_2CF_2$- and CF_2H-substituted alkenes

Ya Li, Huaifeng Li, Jinbo Hu *

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

ARTICLE INFO

Article history:
Received 6 September 2008
Received in revised form 4 November 2008
Accepted 6 November 2008
Available online 12 November 2008

Keywords:
Fluorine
Radical fluoroalkylation
(Phenylsulfonyl)difluoromethylation
Difluoromethyl

ABSTRACT

Stereoselective free radical (phenylsulfonyl)difluoromethylation of terminal alkynes with iododifluoromethyl phenyl sulfone ($PhSO_2CF_2I$) has been accomplished by using Et_3B/air as an initiator. The obtained $PhSO_2CF_2$-substituted vinyl iodides, which can be further subjected to Suzuki coupling and Sonogashira coupling reactions, are useful precursors for the preparation of many structurally diverse $PhSO_2CF_2$- and CF_2H-substituted alkenes.

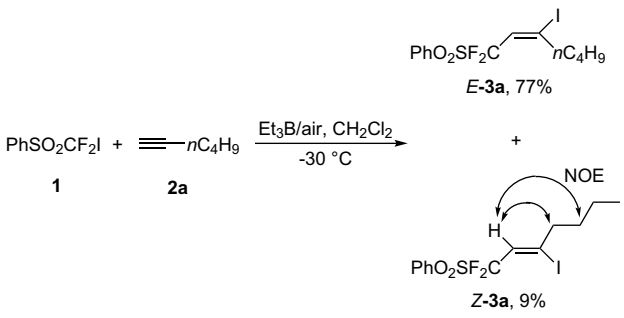
1. Introduction

Partially fluorinated organic compounds often exhibit an increase in oxidative, hydrolytic, and thermal stabilities as compared with their non-fluorinated counterparts, which can be attributed to the high electronegativity, low polarizability, and the relative small size of the fluorine atom.[1–6] As a consequence, much effort has been devoted to the studies on efficient synthesis of fluorinated bioactive compounds. Among various fluorinated compounds, CF_2H-containing compounds are of particular interest, given the fact that by the year 2005, thirty-nine difluoromethylated compounds had been registered to be in the different developmental phases of the drug discovery process.[7]

Fluorination and fluoroalkylation are the two major methods to prepare CF_2H-containing compounds.[3,4] Fluorination reagents, such as SF_4, DAST, TBAF, and BrF_3, are frequently used to transform aldehydes or their derivatives into CF_2H-containing compounds. In the fluoroalkylation arena, chlorodifluoromethane and dibromodifluoromethane, both of which are ozone depleting substances, are often employed to construct the CF_2H moiety. In our continuing effort to develop difluoromethylation methodologies, we found that $PhSO_2CF_2H$, $PhSO_2CF_2SiMe_3$, and $PhSO_2CF_2Br$ compounds are robust nucleophilic difluoromethylation reagents.[8] Recently, we disclosed a highly efficient radical (phenylsulfonyl)difluoromethylation of terminal alkenes with iododifluoromethyl phenyl sulfone ($PhSO_2CF_2I$, **1**) by using Et_3B/air as an initiator.[9] In this paper, we wish to report our extended study on radical (phenylsulfonyl)-difluoromethylation of alkynes using $PhSO_2CF_2I$ reagent, which serves as a good method for the stereoselective preparation of both $PhSO_2CF_2$- and CF_2H-substituted alkenes.

2. Results and discussion

Firstly, we used 1-hexyne (**2a**) as a model compound to examine the radical addition reaction between iododifluoromethyl phenyl sulfone (**1**) and an alkyne. As expected, the atom transfer reaction

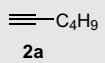
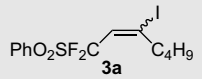
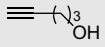
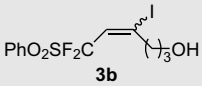
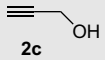
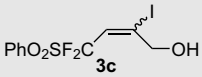
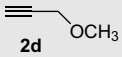
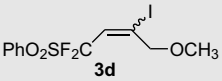
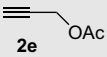
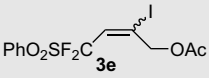
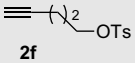
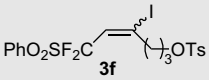
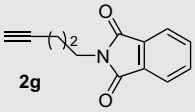
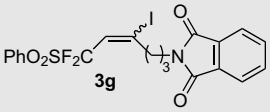


Scheme 1.

* Corresponding author. Tel.: +86 21 54925174; fax: +86 21 64166128.
E-mail address: jinbohu@mail.sioc.ac.cn (J. Hu).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.11.011

Table 1
Et_3B-initiated radical (phenylsulfonyl)difluoromethylation of terminal alkynes

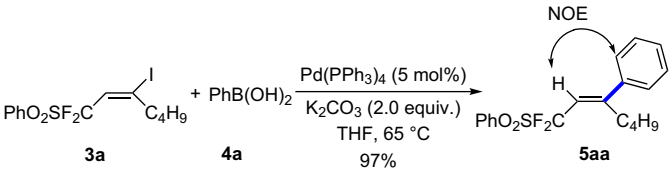
Entry	Alkyne **2**	Product **3**	Isomeric ratio (*E*/*Z*)	Yield[a] (%)
1	 **2a**	 **3a**	9:1	85
2	 **2b**	 **3b**	9:1	67[b]
3	 **2c**	 **3c**	2:1	62[b]
4	 **2d**	 **3d**	3:1	62
5	 **2e**	 **3e**	3:1	61
6	 **2f**	 **3f**	8:1	55
7	 **2g**	 **3g**	8:1	64[b]

[a] The overall yield of *Z*- and *E*-isomer.
[b] The *Z*- and *E*-isomer could not be separated by flash chromatography.

between **1** and **2a** proceeded smoothly under the same conditions for radical (phenylsulfonyl)difluoromethylation of terminal alkenes with **1**,[9] that is, Et_3B in hexane (1.0 mol/L) was added to a mixture of 1-hexyne (**2a**), $PhSO_2CF_2I$ (**1**), and CH_2Cl_2 solvent at −30 °C, and *E*-**3a** and *Z*-**3a** product isomers were isolated in 77% and 9% yields, respectively. The stereochemistry of the products was determined on the basis of the relative strong NOEs between the proton on the double bond and protons on aliphatic *n*-butyl group in product *Z*-**3a** (Scheme 1).

By using this standard reaction condition, we extended this Et_3B/air-initiated radical (phenylsulfonyl)difluoromethylation reaction to a variety of structurally diverse terminal alkynes **1b**–**1g**. As shown in Table 1, the free radical (phenylsulfonyl)difluoromethylation reaction can tolerate many functional groups on the substrates **1b**–**1g**, such as hydroxyl, methoxy, acetyl, sulfonyl, and amide groups, giving satisfactory chemical yields of products. The *E*/*Z* isomeric ratio of the products **3a**–**3g** ranges from 2:1 to 9:1. It is worthwhile to mention that the two isomers in entries 1, 4, 5, and 6 could be easily separated by flash chromatography, while products **3b**, **3c**, and **3g** (entries 2, 3, and 7) were obtained in *Z*- and *E*-isomer mixtures due to their similar polarities.

Products **3** can further undergo coupling reactions with nucleophilic reagents because of the existence of vinyl iodide functionality. Using compound *E*-**3a** as a model compound, we first tested its Suzuki coupling reaction with boronic acids (Scheme 2). To our delight, the coupling reaction of **3a** with phenyl boronic acid (**4a**) proceeded smoothly under typical coupling reaction conditions, and the coupling product **5aa** was isolated in 97% yield. Obvious NOEs between the proton on the double bond and protons on the substituted phenyl group indicated that the configuration of the double bond was maintained intact during this coupling reaction.

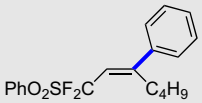
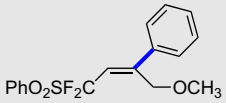
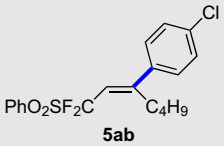
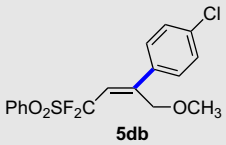
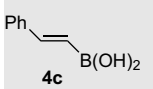
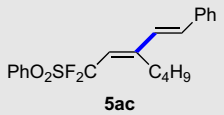
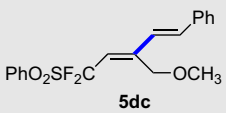


Scheme 2.

Using this optimized reaction condition, we studied the scope of the coupling reaction of compound **3** with **4a**, 4-chlorophenyl boronic acid (**4b**), and α,β-unsaturated boronic acid (**4c**), respectively. As shown in Table 2, the coupling reaction proceeded smoothly in all cases, and the products **5** were obtained in good to excellent yields. By using this method, we thus can obtain a variety of structurally diverse $PhSO_2CF_2$-sustituted alkenes.

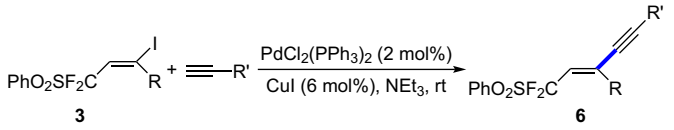
We also studied the Sonogashira coupling reaction between compound **3** and terminal alkynes. Using NEt_3 as both the base and the solvent, we found that the Sonogashira coupling reaction proceeded readily, giving almost quantitative yield of products **6** (Table 3). We therefore extended this reaction to several functionalized terminal alkynes. As shown in Table 3, it is apparent that the coupling products **6** could be isolated in excellent yields in all cases.

Table 2
The Suzuki coupling reactions between compound **3** and boronic acids

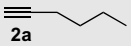
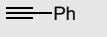
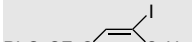
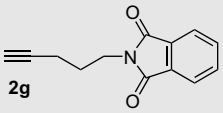
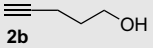
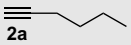
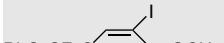
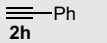
Boronic acid	Product **5**	Yield[a] (%)	Product **5**	Yield[a] (%)
$PhB(OH)_2$ **4a**	 **5aa**	97	 **5da**	75
p-$ClC_6H_4B(OH)_2$ **4b**	 **5ab**	85	 **5db**	85
 **4c**	 **5ac**	75	 **5dc**	79

[a] Isolated yield.

Table 3
The coupling reaction of compound **3** with terminal alkynes

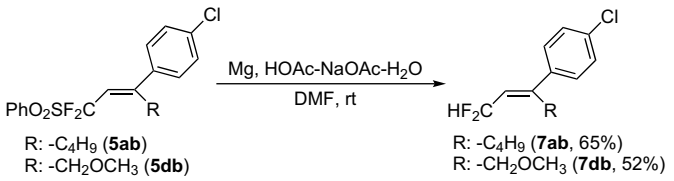


3 6

Compound **3**	Alkyne **2**	Product **6**	Yield[a] (%)
	 **2a**	**6aa**	97
	 **2h**	**6ab**	98
 **3a**	 **2g**	**6ac**	91
	 **2b**	**6ad**	96
	 **2a**	**6da**	93
 **3d**	 **2h**	**6db**	94

[a] Isolated yield.

Next, we attempted the reductive desulfonylation reaction of compound **5** and **6** to obtain CF_2H-substituted alkenes. Using an environmentally friendly Mg/HOAc/NaOAc desulfonylation system that was previously developed by our group,[10] compounds **5ab** and **5db** can be easily transformed into CF_2H-substituted alkenes (Scheme 3). However, compounds **6** were totally destroyed when subjected to the same conditions. It is worth noting that CF_2H-sustituted alkenes are useful precursors for synthesis of biologically interesting compounds,[11–15] and currently very few general methods are available for their efficient synthesis.



Scheme 3.

3. Conclusion

In conclusion, we have successfully developed an efficient and stereoselective radical (phenylsulfonyl)difluoromethylation of terminal alkynes. By using Et_3B/air as radical initiator, $PhSO_2CF_2I$ can add to a variety of alkynes to afford the corresponding products in good yields and with moderate to good *Z*/*E* stereoselectivity. These obtained $PhSO_2CF_2$-containing compounds, which can further undergo Suzuki or Sonogashira coupling reactions, are highly useful precursors for preparation of $PhSO_2CF_2$- and CF_2H-substituted alkenes.

4. Experiment sections

4.1. General

Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received. $PhSO_2CF_2I$ reagent was prepared according to the previously reported procedures.[9,16] ^1H NMR spectra were recorded on Bruker 300 or Mercury 300 spectrometers with Me_4Si as internal standard. ^{19}F NMR spectra were recorded on Bruker 300 or Mercury 300 spectrometers with $CFCl_3$ as external standard. ^{13}C NMR spectra were recorded on Avance 500 or DPX-400 spectrometers. Mass spectra were obtained on a HP5989A spectrometer. High-resolution mass data were recorded on a high-resolution mass spectrometer in the EI or MALDI mode.

4.2. Typical procedure of the radical addition of iododifluoromethyl phenyl sulfone (1) with alkynes

Et_3B (1.0 mL, 1.0 mol in hexane) was added into a 10-mL Schlenk flask containing iododifluoromethyl phenyl sulfone (**1**) (318 mg, 1.0 mmol) and 1-hexyne (**2a**) (164 mg, 2.0 mmol) in 4.0 mL of CH_2Cl_2 at −30 °C. Then a balloon filled with 100 mL of air was connected to the reaction flask. The reaction mixture was stirred at this temperature for 0.5 h. After removing of volatile solvents under vacuum, the crude product was further purified by silica gel column chromatography with ethyl acetate/petroleum ether (1: 10) to give products *E*-**3a** (solid, 306 mg, 77% yield) and *Z*-**3a** (oil, 34 mg, 9% yield).

*4.2.1. (E)-(1,1-Difluoro-3-iodohept-2-enylsulfonyl)benzene (E-**3a**)*

White solid; mp 43–44 °C; IR (film): 2928, 1625, 1581, 1450, 1344, 1158, 1089, 997 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, *J*=7.8 Hz, 2H), 7.75–7.80 (m, 1H), 7.60–7.65 (m, 2H), 6.42 (t, *J*=14.1 Hz, 1H), 2.65 (t, *J*=7.5 Hz, 2H), 1.53–1.58 (m, 2H), 1.25–1.29 (m, 2H), 0.89 (t, *J*=6.6 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.8 (d, *J*=15.2 Hz, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.5, 132.7, 130.8, 129.4, 125.4 (t, *J*=6.4 Hz), 125.1 (t, *J*=23.4 Hz), 120.1 (t, *J*=285.0 Hz), 41.2 (t, *J*=2.8 Hz), 32.3, 21.7, 13.8; ESI (*m*/*z*): 418 ($M+NH_4^+$). Anal. Calcd for $C_{13}H_{15}F_2IO_2S$: C, 39.01; H, 3.78. Found: C, 39.25; H, 3.76.

*4.2.2. (Z)-(1,1-Difluoro-3-iodohept-2-enylsulfonyl)benzene (Z-**3a**)*

Oily liquid; IR (film): 2959, 2933, 1633, 1584, 1449, 1346, 1166, 1091, 997 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, *J*=8.1 Hz, 2H), 7.74–7.77 (m, 1H), 7.62 (t, *J*=7.8 Hz, 2H), 6.40 (t, *J*=13.2 Hz, 1H), 2.69 (t, *J*=7.2 Hz, 2H), 1.52–1.60 (m, 2H), 1.31–1.38 (m, 2H), 0.94 (t, *J*=7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −98.6 (d, *J*=13.0 Hz, 2F); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.4, 132.7, 130.9, 129.3, 120.4 (t, *J*=18.1 Hz), 119.0, 118.9 (t, *J*=286.2 Hz), 48.4, 31.2, 21.2, 13.7; ESI (*m*/*z*): 418 ($M+NH_4^+$); HRMS (FTMS) calcd for $C_{13}H_{15}F_2IO_2SNa^+$ ($M+Na^+$): 422.9703, found: 422.9698.

*4.2.3. (E)-6,6-Difluoro-4-iodo-6-(phenylsulfonyl)hex-4-en-1-ol (**3b**)*

White solid; mp 72–74 °C (for a sample with isomeric ratio *E*/*Z*=9:1); IR (film): 3251, 1626, 1583, 1449, 1337, 1160, 1074, 1011 cm^{-1}. For *E*-isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 7.99 (d, *J*=7.8 Hz, 2H), 7.76–7.81 (m, 1H), 7.61–7.66 (m, 2H), 6.47 (t, *J*=14.4 Hz, 1H), 3.69 (t, *J*=6.0 Hz, 2H), 2.82 (t, *J*=7.5 Hz, 2H), 1.83–1.92 (m, 2H), 1.65 (t, *J*=5.6 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.6 (d, *J*=15.2 Hz, 2F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.5, 132.4, 130.7, 129.4, 125.7 (t, *J*=24.4 Hz), 124.5 (t, *J*=6.7 Hz), 120.0 (t, *J*=285.5 Hz), 61.0, 37.6 (d, *J*=2.7 Hz), 33.2; ESI (*m*/*z*): 403 (M^++1), 425 ($M+Na^+$). Anal. Calcd for $C_{12}H_{13}F_2IO_3S$: C, 35.84; H, 3.26. Found: C, 35.92; H, 3.30.

*4.2.4. (E)-4,4-Difluoro-2-iodo-4-(phenylsulfonyl)but-2-en-1-ol (**3c**)*

White solid; mp 67–70 °C (for a sample with isomeric ratio *E*/*Z*=2:1); IR (film): 3420, 1631, 1581, 1451, 1330, 1163, 1009, 682 cm^{-1}. For *E*-isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 7.99 (d, *J*=8.4 Hz, 2H), 7.77–7.84 (m, 1H), 7.64–7.68 (m, 2H), 6.56 (t, *J*=13.8 Hz, 1H), 4.45 (s, 2H), 2.65 (s, 1H); ^{19}F NMR (282 MHz, $CDCl_3$):

δ −95.2 (d, *J*=13.5 Hz, 2F); ESI (*m*/*z*): 392 ($M+NH_4^+$). Anal. Calcd for $C_{10}H_9F_2IO_3S$: C, 32.10; H, 2.42. Found: C, 32.15; H, 2.42.

*4.2.5. (E)-(1,1-Difluoro-3-iodo-4-methoxybut-2-enylsulfonyl)benzene (**3d**)*

Oily liquid; IR (film): 2932, 1624, 1583, 1449, 1345, 1166, 1100, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, *J*=7.8 Hz, 2H), 7.78–7.83 (m, 1H), 7.62–7.68 (m, 2H), 6.69 (t, *J*=14.1 Hz, 1H), 4.20 (s, 2H), 3.34 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −96.0 (d, *J*=13.3 Hz, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.7, 132.3, 1130.8, 129.5, 127.6 (t, *J*=24.6 Hz), 123.1 (t, *J*=6.6 Hz), 119.9 (t, *J*=285.0 Hz); ESI (*m*/*z*): 389 (M^++1); HRMS (MALDI) calcd for $C_{11}H_{11}F_2IO_3SNa^+$ ($M+Na^+$): 410.9328, found: 410.9334.

*4.2.6. (E)-4,4-Difluoro-2-iodo-4-(phenylsulfonyl)but-2-enyl acetate (**3e**)*

White solid; mp 69–70 °C; IR (film): 3100, 2933, 1732, 1630, 1452, 1337, 1241, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, *J*=7.5 Hz, 2H), 7.80 (t, *J*=7.2 Hz, 1H), 7.62–7.67 (m, 2H), 6.69 (t, *J*=14.1 Hz, 1H), 4.93 (s, 2H), 2.16 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −96.5 (d, *J*=15.0 Hz, 2F); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.6, 135.7, 132.2, 130.9, 129.5, 128.3 (t, *J*=24.7 Hz), 119.8 (t, *J*=285.2 Hz), 116.0 (t, *J*=6.5 Hz), 65.4 (t, *J*=4.2 Hz), 20.8; ESI (*m*/*z*): 417 (M^++1), 434 ($M+NH_4^+$). Anal. Calcd for $C_{12}H_{11}F_2IO_4S$: C, 34.63; H, 2.66. Found: C, 34.82; H, 2.48.

*4.2.7. (E)-6,6-Difluoro-4-iodo-6-(phenylsulfonyl)hex-4-enyl 4-methylbenzenesulfonate (**3f**)*

White solid; mp 73–74 °C; IR (film): 3070, 1625, 1581, 1447, 1362, 1343, 1176, 1164, 1077 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, *J*=7.5 Hz, 2H), 7.78 (d, *J*=8.4 Hz, 3H), 7.61–7.66 (m, 2H), 7.33 (d, *J*=8.1 Hz, 2H), 6.44 (t, *J*=13.8 Hz, 1H), 4.07 (t, *J*=6.0 Hz, 2H), 2.74 (t, *J*=7.5 Hz, 2H), 2.43 (s, 3H), 1.89–1.98 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −96.4 (d, *J*=14.1 Hz, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.9, 135.7, 132.9, 132.4, 130.8, 129.9 129.5, 127.8 (d, *J*=8.1 Hz), 126.5 (t, *J*=25.3 Hz), 122.0 (t, *J*=7.1 Hz), 119.9 (t, *J*=287.5 Hz), 68.7, 37.7 (d, *J*=2.3 Hz), 29.5, 21.6; ESI (*m*/*z*): 557 (M^++1), 574 ($M+NH_4^+$). Anal. Calcd for $C_{19}H_{19}F_2IO_5S_2$: C, 41.02; H, 3.44. Found: C, 41.21; H, 3.59.

*4.2.8. (E)-2-(6,6-Difluoro-4-iodo-6-(phenylsulfonyl)hex-4-enyl)isoindoline-1,3-dione (**3g**)*

White solid; mp 127–129 °C (for a sample with isomeric ratio *E*/*Z*=8:1). IR (film): 3059, 1769, 1712, 1622, 1451, 1397, 1336, 1161 cm^{-1}. For *E*-isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 7.84–7.88 (m, 4H), 7.72–7.77 (m, 3H), 7.26–7.60 (m, 2H), 6.45 (t, *J*=14.1 Hz, 1H), 3.74 (t, *J*=6.9 Hz, 2H), 2.74–2.79 (m, 2H), 1.99–2.01 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.7 (d, *J*=13.8 Hz, 2F); ESI (*m*/*z*): 532 (M^++1), 549 ($M+NH_4^+$); HRMS (MALDI) calcd for $C_{20}H_{16}F_2INO_4SNa^+$ ($M+Na^+$): 553.9700, found: 553.9705.

4.3. Typical procedure of the Suzuki reactions of compounds (3) with boronic acids

A mixture of *E*-**3a** (160 mg, 0.4 mmol), phenyl boronic acid (**4a**) (60 mg, 0.48 mmol), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol), and K_2CO_3 (111 mg, 0.8 mmol) was stirred in THF at 65 °C under N_2 atmosphere for 8 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with ethyl acetate/petroleum ether (1:30) to afford **5aa** (136 mg, 97%).

*4.3.1. (E)-(1,1-Difluor-1-(phenylsulfonyl)hept-2-en-3-yl)benzene (**5aa**)*

Oily liquid; IR (film): 2959, 1636, 1584, 1448, 1342, 1220, 1166, 1076 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, *J*=7.2 Hz, 2H), 7.73–7.78 (m, 1H), 7.60–7.65 (m, 2H), 7.37 (s, 5H), 5.75 (t, *J*=15.6 Hz, 1H), 2.73 (s, 2H), 1.29–1.30 (m, 4H), 0.83–0.85 (m, 3H); ^{19}F NMR (282 MHz, $CDCl_3$); δ −95.3 (d, *J*=15.5 Hz, 2F); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 140.7, 135.1, 133.4, 130.8, 129.2, 128.9, 128.5, 126.6, 121.8 (t, *J*=282.2 Hz), 112.1 (t, *J*=22.2 Hz), 31.2, 31.0, 22.6, 53.7; ESI (*m*/*z*): 368 ($M+NH_4^+$); HRMS (EI) calcd for $C_{13}H_{15}F_2^+$ (M^+-PhSO_2): 209.1142, found: 209.1154.

*4.3.2. (E)-1-Chloro-4-(1,1-difluoro-1-(phenylsulfonyl)hept-2-en-3-yl)benzene (**5ab**)*

White solid; mp 69–71 °C; IR (film): 2963, 1906, 1636, 1591, 1492, 1449, 1334, 1214, 1161, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, *J*=7.5 Hz, 2H), 7.74–7.79 (m, 1H), 7.60–7.65 (m, 2H), 7.34 (s, 4H), 5.75 (t, *J*=15.3 Hz, 1H), 2.73 (s, 2H), 1.29 (s, 4H), 0.83 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.4 (d, *J*=16.3 Hz, 2F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9 (t, *J*=5.7 Hz), 139.1, 135.1, 135.0, 133.2, 130.7, 129.2, 128.7, 128.0, 121.7 (t, *J*=282.3 Hz), 112.6 (t, *J*=22.4 Hz), 31.2, 30.9, 22.6, 13.7; ESI (*m*/*z*): 385 (M^++1), 402 ($M+NH_4^+$). Anal Calcd for $C_{19}H_{19}ClF_2O_2S$: C, 59.29; H, 4.98. Found: C, 59.31; H, 4.94.

*4.3.3. ((1E,3E)-3-(2,2-Difluoro-2-(phenylsulfonyl)ethylidene)hept-1-enyl)benzene (**5ac**)*

White solid; mp 90–91 °C; IR (film): 1609, 1448, 1338, 1217, 1160, 1077, 995 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, *J*=7.2 Hz, 2H), 7.73–7.78 (m, 1H), 7.60–7.65 (m, 2H), 7.42–7.48 (m, 2H), 7.27–7.39 (m, 3H), 6.87 (t, *J*=16.5 Hz, 1H), 6.73 (d, *J*=16.5 Hz, 1H), 5.70 (t, *J*=16.2 Hz, 1H), 2.54–2.59 (m, 2H), 1.37–1.54 (m, 4H), 0.93 (t, *J*=7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −94.4 (d, *J*=16.3 Hz, 2F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9 (t, *J*=5.4 Hz), 136.1, 135.0, 133.4, 130.7, 129.8, 129.2, 128.7, 127.0, 122.1 (t, *J*=282.0 Hz), 113.0 (t, *J*=22.1 Hz), 32.3, 28.1, 23.0, 13.8; ESI (*m*/*z*): 399 ($M+Na^+$). Anal. Calcd for $C_{21}H_{22}F_2O_2S$: C, 67.00; H, 5.89. Found: C, 66.93; H, 5.85.

*4.3.4. (Z)-(4,4-Difluoro-1-methoxy-4-(phenylsulfonyl)but-2-en-2-yl)benzene (**5da**)*

White solid; mp 45–47 °C; IR (film): 1643, 1447, 1374, 1342, 1211, 1166, 1087, 1012 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.04 (d, *J*=7.8 Hz, 2H), 7.76–7.81 (m, 1H), 7.62–7.67 (m, 2H), 7.49–7.51 (m, 2H), 7.38–7.40 (m, 3H), 5.98 (t, *J*=15.6 Hz, 1H), 4.60 (s, 2H), 3.21 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −94.3 (d, *J*=15.8 Hz, 2F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2 (t, *J*=5.8 Hz), 138.3, 135.3, 133.0, 130.8, 129.4, 129.3, 128.5, 127.1, 121.3 (t, *J*=282.1 Hz), 68.3 (t, *J*=3.6 Hz), 58.0; ESI (*m*/*z*): 356 ($M+NH_4^+$), 361 ($M+Na^+$). Anal. Calcd for $C_{17}H_{16}F_2O_3S$: C, 60.34; H, 4.77. Found: C, 60.35; H, 4.71.

*4.3.5. (Z)-1-Chloro-4-(4,4-difluoro-1-methoxy-4-(phenylsulfonyl)-but-2-en-2-yl)benzene (**5db**)*

White solid; mp 68–69 °C; IR (film): 1644, 1491, 1448, 1372, 1345, 1214, 1165, 1086 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, *J*=7.5 Hz, 2H), 7.76–7.81 (m, 1H), 7.62–7.68 (m, 2H), 7.35–7.45 (m, 4H), 5.97 (t, *J*=15.6 Hz, 1H), 4.58 (s, 2H), 3.27 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −94.3 (d, *J*=16.3 Hz, 2F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3 (t, *J*=5.8 Hz), 136.7, 135.5, 135.4, 132.9, 130.8, 129.3, 128.7, 128.5, 121.2 (t, *J*=282.3 Hz), 115.4 (t, *J*=23.8 Hz), 68.2 (t, *J*=3.7 Hz), 58.0; EI (*m*/*z* %): 231 (M^+-PhSO_2). Anal. Calcd for $C_{17}H_{15}ClF_2O_3S$: C, 54.77; H, 4.06. Found: C, 54.74; H, 4.04.

*4.3.6. ((1E,3Z)-5,5-Difluoro-3-(methoxymethyl)-5-(phenylsulfonyl)penta-1,3-dienyl)benzene (**5dc**)*

White solid; mp 111–113 °C; IR (film): 1628, 1450, 1336, 1216, 1160, 1086, 993 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, *J*=7.2 Hz, 2H), 7.75–7.80 (m, 1H), 7.61–7.66 (m, 2H), 7.46–7.50 (m, 2H), 7.25–7.39 (m, 3H), 7.16 (d, *J*=15.6 Hz, 1H), 6.79 (d, *J*=15.6 Hz, 1H), 5.90 (t, *J*=15.9 Hz, 1H), 4.45 (s, 2H), 3.36 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −93.5 (d, *J*=16.6 Hz, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.3 (t, *J*=6.1 Hz), 136.2, 135.6 (t, *J*=1.6 Hz), 135.4, 133.0,

130.8, 129.4, 128.88, 128.80, 127.5 (d, J=1.5 Hz), 127.2, 121.6 (t, J=283.4 Hz), 115.3 (t, J=23.1 Hz), 67.0 (t, J=3.4 Hz), 57.9; ESI (m/z): 382 ($M+NH_4^+$). Anal. Calcd for $C_{19}H_{18}F_2O_3S$: C, 62.64; H, 4.98. Found: C, 62.60; H, 5.18.

4.4. Typical procedure of the Sonogashira coupling reactions of compounds (3) with alkynes

Under N_2 atmosphere, a mixture of *E*-**3a** (120 mg, 0.3 mmol), 1-hexyne (**2a**) (30 mg, 0.36 mmol), $PdCl_2(PPh_3)_2$ (4 mg, 0.006 mmol), and NEt_3 (2.0 mL) was stirred at room temperature for about 10 min. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with ethyl acetate/petroleum ether (1:30) to afford **6aa** (103 mg, 97%).

*4.4.1. (E)-(3-Butyl-1,1-difluoronon-2-en-4-ynylsulfonyl)benzene (**6aa**)*

Oily liquid; IR (film): 2959, 2223, 1620, 1449, 1345, 1217, 1166, 1092, 998 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, J=7.5 Hz, 2H), 7.76 (t, J=7.5 Hz, 1H), 7.59–7.64 (m, 2H), 5.80 (t, J=15.6 Hz, 1H), 2.36 (t, J=7.2 Hz, 4H), 1.25–1.60 (m, 8H), 0.86–0.97 (m, 6H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.5 (d, J=16.1 Hz, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1 (t, J=6.1 Hz), 135.1, 133.3, 130.8, 129.2, 121.4 (t, J=283.4 Hz), 117.5 (t, J=22.8 Hz), 96.4 (t, J=1.3 Hz), 80.7 (d, J=2.1 Hz), 32.8 (t, J=2.5 Hz), 30.7 (t, J=2.5 Hz), 30.4, 22.3, 21.9, 19.1, 13.8, 13.5; ESI (m/z): 355 (M^++1), 372 ($M+NH_4^+$). Anal. Calcd for $C_{19}H_{24}F_2O_2S$: C, 64.38; H, 6.82. Found: C, 64.62; H, 6.80.

*4.4.2. (E)-(3-(2,2-Difluoro-2(phenylsulfonyl)ethylidene)hept-1-ynyl)benzene (**6ab**)*

Oily liquid; IR (film): 2211, 1618, 1490, 1449, 1338, 1164, 1097, 998, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, J=7.8 Hz, 2H), 7.74–7.79 (m, 1H), 7.60–7.65 (m, 2H), 7.46 (s, 2H), 7.36 (s, 3H), 6.00 (t, J=15.0 Hz, 1H), 2.46–2.49 (m, 2H), 1.59–1.68 (m, 2H), 1.35–1.43 (m, 2H), 0.94 (t, J=6.9 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.7 (d, J=16.6 Hz, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.4, 135.4, 133.3, 131.9, 130.9, 129.4, 129.2, 128.5, 122.2, 121.4 (t, J=283.9 Hz), 118.8 (t, J=23.6 Hz), 94.5, 89.1 (d, J=3.0 Hz), 32.6 (t, J=2.7 Hz), 30.9, 22.5, 14.0; ESI (m/z): 392 ($M+NH_4^+$). Anal. Calcd for $C_{21}H_{20}F_2O_2S$: C, 67.36; H, 5.38. Found: C, 67.33; H, 5.45.

*4.4.3. (E)-2-(6-(2,2-Difluoro-2-(phenylsulfonyl)ethylidene)dec-4-ynyl)isoindoline-1,3-dione (**6ac**)*

White solid; mp 70–72 °C; IR (film): 2933, 1771, 1709, 1623, 1398, 1337, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, J=7.8 Hz, 2H), 7.81–7.85 (m, 2H), 7.69–7.78 (m, 3H), 7.59–7.64 (m, 2H), 5.68 (t, J=15.3 Hz, 1H), 3.78–3.83 (m, 2H), 2.45 (t, J=6.6 Hz, 2H), 2.69 (t, J=6.6 Hz, 2H), 1.95–2.02 (m, 2H), 1.43–1.50 (m, 2H), 1.27–1.34 (m, 2H), 0.89 (t, J=7.5 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.2 (d, J=15.5 Hz, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3, 141.6 (t, J=5.8 Hz), 135.2, 134.0, 133.2, 132.0, 130.7, 129.2, 123.2, 121.2 (t, J=285.0 Hz), 118.0 (t, J=22.5 Hz), 94.5, 81.2 (d, J=3.8 Hz), 37.2, 32.6, 30.6, 27.1, 22.3, 17.3, 13.8; ESI (m/z): 508 ($M+Na^+$). Anal. Calcd for $C_{26}H_{25}F_2NO_4S$: C, 64.32; H, 5.17; N, 2.88. Found: C, 64.31; H, 5.26; N, 2.76.

*4.4.4. (E)-6-(2,2-Difluoro-2-(phenylsulfonyl)ethylidene)dec-4-yn-1-ol (**6ad**)*

Oily liquid; IR (film): 3396, 2957, 2223, 1620, 1449, 1337, 1165, 1091, 999 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, J=7.8 Hz, 2H), 7.73–7.78 (m, 1H), 7.62 (t, J=7.8 Hz, 2H), 5.82 (t, J=15.6 Hz, 1H), 3.76 (t, J=6.0 Hz, 2H), 2.47–2.51 (m, 2H), 2.33–2.38 (m, 2H), 1.77–1.86 (m, 2H), 1.67 (d, J=3.6 Hz, 1H), 1.48–1.58 (m, 2H), 1.25–1.39 (m, 2H), 0.90 (t, J=7.5 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.2 (d, J=15.2 Hz, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.9 (t, J=6.3 Hz), 135.2, 133.1, 130.7, 129.2, 121.3 (t, J=283.3 Hz), 117.9 (t, J=23.5 Hz), 95.2, 81.1 (d, J=3.3 Hz), 61.4, 32.7 (t, J=2.6 Hz), 31.1, 30.7, 22.3, 15.9, 13.8; ESI (m/z): 357 (M^++1), 374 ($M+NH_4^+$), 379 ($M+Na^+$). Anal. Calcd for $C_{18}H_{22}F_2O_3S$: C, 60.47; H, 6.41. Found: C, 60.47; H, 6.42.

*4.4.5. (Z)-(1,1-Difluoro-3-(methoxymethyl)non-2-en-4-ynylsulfonyl)benzene (**6da**)*

Oily liquid; IR (film): 2961, 2222, 1622, 1450, 1345, 1166, 1097, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, J=8.1 Hz, 2H), 7.74–7.79 (m, 1H), 6.28 (t, J=7.5 Hz, 2H), 5.97 (t, J=14.4 Hz, 1H), 4.19 (s, 2H), 3.37 (s, 3H), 2.39 (t, J=6.9 Hz, 2H), 1.39–1.65 (m, 4H), 0.92 (t, J=7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.8 (d, J=16.1 Hz, 2F); ESI (m/z): 365 (M^++Na); HRMS (FTMS) calcd for $C_{17}H_{20}F_2O_3SNa^+$ (M^++Na): 365.0993, found: 365.1002.

*4.4.6. (Z)-(5,5-Difluoro-3-(methoxymethyl)-5-(phenylsulfonyl)-pent-3-en-1-ynyl)benzene (**6db**)*

White solid; mp 62–64 °C; IR (film): 1693, 1596, 1356, 1265, 1168, 1029, 924, 858 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, J=7.8 Hz, 2H), 7.75–7.80 (m, 1H), 7.61–7.69 (m, 2H), 7.49–7.52 (m, 2H), 7.33–7.36 (m, 3H), 6.16 (t, J=15.6 Hz, 1H), 4.32 (s, 2H), 3.43 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.5 (d, J=15.2 Hz, 2F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3 (t, J=6.2 Hz), 135.4, 132.8, 132.0, 130.8, 129.39, 129.30, 128.3, 121.9, 120.98 (t, J=282.3 Hz), 120.91 (t, J=24.1 Hz), 96.0, 87.1, 69.3 (t, J=4.0 Hz), 58.5; ESI (m/z): 363 (M^++1), 380 ($M+NH_4^+$). Anal. Calcd for $C_{19}H_{16}F_2O_3S$: C, 62.97; H, 4.45. Found: C, 63.18; H, 4.39.

4.5. Typical procedure for magnesium-mediated desulfonylation

Into a 10-mL flask containing compound **5aa** (196 mg, 0.51 mmol) in 8.0 mL DMF at room temperature was added 4 mL of HOAc/NaOAc (1:1) buffer solution (8 mol/L). Magnesium turnings (184 mg, 7.6 mmol) were added in portions. The reaction mixture was stirred at room temperature for 5 h followed by adding 15 mL of water. The solution mixture was extracted with Et_2O (20 mL×3), and the combined organic phase was dried over $MgSO_4$. After the removal of ethyl ether, the crude product was purified by silica gel column chromatography using petroleum as eluent to give product **7aa** (liquid, 81 mg, 65%).

*4.5.1. (E)-1-Chloro-4-(1,1-difluorohept-2-en-3-yl)benzene (**7ab**)*

Liquid; IR (film): 2960, 1654, 1593, 1493, 1405, 1380, 1141, 1070, 1014 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.28–7.35 (m, 4H), 6.48 (td, J=56.1, 6.9 Hz, 1H), 5.71–5.80 (m, 1H), 2.53–2.58 (m, 2H), 1.25–1.36 (m, 4H), 0.86 (t, J=7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −109.2 (dd, J=55.2, 9.6 Hz, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.4 (t, J=12.5 Hz), 138.8, 134.3, 128.7, 127.8, 120.9 (t, J=26.0 Hz), 112.4 (t, J=230.7 Hz), 30.7, 30.2, 22.4, 13.7; EI (m/z %): 244 (M^+, 2.7), 202 (100.0). Anal. Calcd for $C_{13}H_{15}ClF_2$: C, 63.81; H, 6.18. Found: C, 63.97; H, 6.28.

*4.5.2. (Z)-1-Chloro-4-(4,4-difluoro-1-methoxybut-2-en-2-yl)-benzene (**7db**)*

Liquid; IR (film): 2963, 1657, 1594, 1493, 1410, 1261, 1094, 1015, 800 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.38 (m, 4H), 6.71 (td, J=56.4, 6.9 Hz, 1H), 5.91–5.99 (m, 1H), 4.38 (s, 2H), 3.37 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −109.8 (dd, J=56.1, 9.8 Hz, 2F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4 (t, J=12.0 Hz), 137.1, 134.8, 128.7, 127.9, 123.9 (t, J=26.6 Hz), 111.7 (t, J=230.1 Hz), 69.9, 58.3; EI (m/z %): 232 (M^+, 4.3), 202 (36.4), 45 (100.0); HRMS (EI) calcd for $C_{11}H_{11}F_2ClO$: 232.0466, found: 232.0461.

Acknowledgements

We thank the National Natural Science Foundation of China (20502029, 20772144, 20825209), Shanghai Rising-Star Program

(06QA14063), and the Chinese Academy of Sciences (Hundreds-Talent Program and Knowledge Innovation Program) for financial support.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.11.011.

References and notes

1. *Organofluorine Compounds in Medicinal Chemistry and Biomedicinal Applications*; Filler, R., Kobayashi, Y., Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, 1993.
2. *Fluorine in Bioorganic Chemistry*; Welch, J. T., Eswarakrishnan, S., Eds.; Wiley: New York, NY, 1991.
3. Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, 2006.
4. Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, 2004.
5. Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell: Oxford, 2004.
6. Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757–786.
7. Prakash, G. K. S.; Weber, C.; Chacko, S.; Olah, G. A. *J. Comb. Chem.* **2007**, *9*, 920–923.
8. Prakash, G. K. S.; Hu, J. *Acc. Chem. Res.* **2007**, *40*, 921–930 and the references cited therein.
9. Li, Y.; Liu, J.; Zhang, L.; Zhu, L.; Hu, J. *J. Org. Chem.* **2007**, *72*, 5824–5827.
10. Ni, C.; Hu, J. *Tetrahedron Lett.* **2005**, *46*, 8273–8277.
11. Konno, T.; Kitazume, T. *Chem. Commun.* **1996**, 2227–2228.
12. Tellier, F.; Sauvetre, R. *J. Fluorine Chem.* **1996**, *76*, 181–185.
13. Furuya, T.; Fukuhara, T.; Hara, S. *J. Fluorine Chem.* **2005**, *126*, 721–725.
14. Xiao, L.; Kitazume, T. *Tetrahedron: Asymmetry* **1997**, *8*, 3597–3601.
15. Konno, T.; Ishihara, T.; Yamanaka, H. *Tetrahedron Lett.* **2000**, *41*, 8467–8472.
16. Prakash, G. K. S.; Hu, J.; Olah, G. A. *Org. Lett.* **2004**, *6*, 4315–4317.