



Free radical (phenylsulfonyl)difluoromethylation of alkynes with $\text{PhSO}_2\text{CF}_2\text{I}$ reagent: stereoselective preparation of PhSO_2CF_2 - and CF_2H -substituted alkenes

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ABSTRACT

Stereoselective free radical (phenylsulfonyl)difluoromethylation of terminal alkynes with iododifluoromethyl phenyl sulfone ($\text{PhSO}_2\text{CF}_2\text{I}$) has been accomplished by using $\text{Et}_3\text{B}/\text{air}$ 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.

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1. Introduction

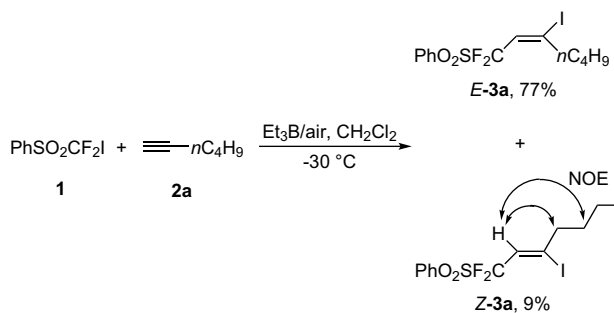
Partially fluorinated organic compounds often exhibit an increase in oxidative, hydrolytic, and thermal stabilities as compared with their non-fluorinated counterparts, which can be attributed to the high electronegativity, low polarizability, and the relative small size of the fluorine atom.^{1–6} As 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 $\text{PhSO}_2\text{CF}_2\text{H}$, $\text{PhSO}_2\text{CF}_2\text{SiMe}_3$, and $\text{PhSO}_2\text{CF}_2\text{Br}$ compounds are robust nucleophilic difluoromethylation reagents.⁸ Recently, we disclosed

a highly efficient radical (phenylsulfonyl)difluoromethylation of terminal alkenes with iododifluoromethyl phenyl sulfone ($\text{PhSO}_2\text{CF}_2\text{I}$, **1**) by using $\text{Et}_3\text{B}/\text{air}$ as an initiator.⁹ In this paper, we wish to report our extended study on radical (phenylsulfonyl)difluoromethylation of alkynes using $\text{PhSO}_2\text{CF}_2\text{I}$ 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.

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Table 1
Et₃B-initiated radical (phenylsulfonyl)difluoromethylation of terminal alkynes

Entry	Alkyne 2	Product 3	Isomeric ratio (<i>E/Z</i>)	Yield ^a (%)
1			9:1	85
2			9:1	67 ^b
3			2:1	62 ^b
4			3:1	62
5			3:1	61
6			8:1	55
7			8:1	64 ^b

^a The overall yield of *Z*- and *E*-isomer.

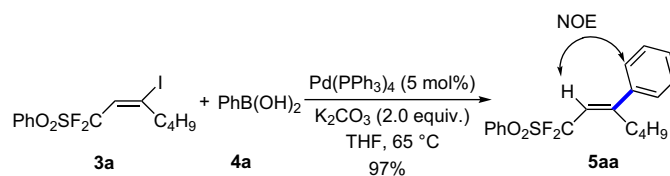
^b The *Z*- and *E*-isomer could not be separated by flash chromatography.

between **1** and **2a** proceeded smoothly under the same conditions for radical (phenylsulfonyl)difluoromethylation of terminal alkenes with **1**,⁹ that is, Et₃B in hexane (1.0 mol/L) was added to a mixture of 1-hexyne (**2a**), PhSO₂CF₂I (**1**), and CH₂Cl₂ 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 Et₃B/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 PhSO₂CF₂-substituted alkenes.

We also studied the Sonogashira coupling reaction between compound **3** and terminal alkynes. Using NEt₃ 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

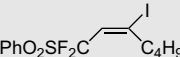
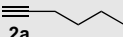
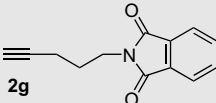
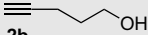
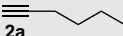
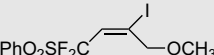
Boronic acid	Product 5	Yield ^a (%)	Product 5	Yield ^a (%)
PhB(OH) ₂ 4a		97		75
<i>p</i> -ClC ₆ H ₄ B(OH) ₂ 4b		85		85
Ph-CH=CH-B(OH) ₂ 4c		75		79

^a Isolated yield.

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

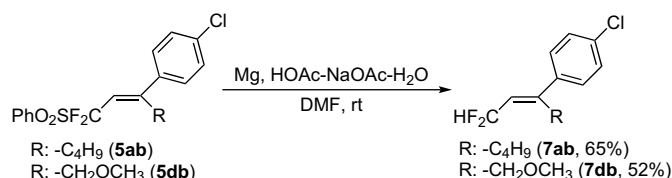
PhO2SF2C-CH=CH-I + C#C-R'
 $\xrightarrow[\text{Cul (6 mol\%), NEt}_3, \text{rt}]{\text{PdCl}_2(\text{PPh}_3)_2 \text{ (2 mol\%)}}$
PhO2SF2C-CH=CH-C#C-R'

3 **6**

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

^a Isolated yield.

Next, we attempted the reductive desulfonation reaction of compound **5** and **6** to obtain CF₂H-substituted alkenes. Using an environmentally friendly Mg/HOAc/NaOAc desulfonation system that was previously developed by our group,¹⁰ compounds **5ab** and **5db** can be easily transformed into CF₂H-substituted alkenes (Scheme 3). However, compounds **6** were totally destroyed when subjected to the same conditions. It is worth noting that CF₂H-substituted 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 Et₃B/air as radical initiator, PhSO₂CF₂I 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 PhSO₂CF₂-containing compounds, which can further undergo Suzuki or Sonogashira coupling reactions, are highly useful precursors for preparation of PhSO₂CF₂- and CF₂H-substituted alkenes.

4. Experiment sections

4.1. General

Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received. PhSO₂CF₂I

reagent was prepared according to the previously reported procedures.^{9,16} ¹H NMR spectra were recorded on Bruker 300 or Mercury 300 spectrometers with Me₄Si as internal standard. ¹⁹F NMR spectra were recorded on Bruker 300 or Mercury 300 spectrometers with CFCl₃ as external standard. ¹³C 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

Et₃B (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 CH₂Cl₂ 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, CDCl₃): 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); ¹⁹F NMR (282 MHz, CDCl₃): δ -95.8 (d, *J*=15.2 Hz, 2F); ¹³C NMR (75 MHz, CDCl₃): 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+NH₄⁺). Anal. Calcd for C₁₃H₁₅F₂IO₂S: 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, CDCl₃): 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); ¹⁹F NMR (282 MHz, CDCl₃): δ -98.6 (d, *J*=13.0 Hz, 2F); ¹³C NMR (125 MHz, CDCl₃): 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+NH₄⁺); HRMS (FTMS) calcd for C₁₃H₁₅F₂IO₂Sn⁺ (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, CDCl₃): 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); ¹⁹F NMR (282 MHz, CDCl₃): δ -95.6 (d, *J*=15.2 Hz, 2F); ¹³C NMR (100 MHz, CDCl₃): 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 C₁₂H₁₃F₂IO₃S: 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, CDCl₃): 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); ¹⁹F NMR (282 MHz, CDCl₃):

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-Difluoro-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. ((1*E*,3*E*)-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. ((1*E*,3*Z*)-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 $\times$ 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.

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Supplementary data

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

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