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Synthesis of 2,2-diaryl-1,1-difluoroethenes via Pd-catalyzed

dehydrosulfonylative cross-coupling of

α-[difluoro(phenylsulfonyl)methyl]benzyl tosylates with arylboronic acids

Rui Zhang, Chuanfa Ni, Yanchuan Zhao, and Jinbo Hu*

Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Ling-Ling Road, Shanghai 200032, China

*Corresponding author. Tel.: +86 21 54925174; Fax: +86 21 64166128; E-mail: jinbohu@sioc.ac.cn.

<u>Dedicated to the memory of Sir Derek Barton for the 100th anniversary (1918-2018)</u> <u>of his birth.</u>

Graphical Abstract



Abstract

By using $PhSO_2CF_2H$ as the difluoromethylidene equivalent, a novel method for connecting aromatic aldehydes and arylboronic acids via consecutive reactions was developed to obtain structurally diverse 2,2-diaryl-1,1-difluoroethenes. The key step is the palladium-catalyzed dehydrosulfonylative cross-coupling of tosylates that are prepared from $PhSO_2CF_2H$, aromatic aldehydes and tosyl chloride. Mechanistic investigations showed that the reaction proceeds mainly through base-mediated dehydrosulfonylation followed by palladium-catalyzed $C(sp^2)-C(sp^2)$ cross-coupling reaction.

Keywords

1,1-Difluoroalkenes, Sulfone, Benzyl tosylate, Cross-coupling reaction, Palladium catalysis.

1. Introduction

1,1-Difluoroalkenes have attracted much attention in organic synthesis^{1,2} as well as in pharmaceutical and agrochemical research^{3,4} due to their unique chemical and biological properties.⁵ On one hand, 1.1-difluoroalkenes have been used as versatile building blocks to deliver structurally diverse functionalized molecules, most of which are otherwise difficult to efficiently prepare. On the other hand, the difluoromethylidene group (= CF_2) is regarded as the bioisostere of carbonyl group and has been applied in the improvement of enzyme inhibitors.⁶ In these contexts, many methods, including the difluoromethylidenation reactions, have been developed to synthesize 1,1-difluoroalkenes.¹ However, the methods that can deliver 1,1-diaryl-2,2-difluoroethenes are rare and usually suffer from limitations. The Wittig-type gem-difluoroolefination of diaryl ketones⁷ and Barton-Kellogg-type gem-difluoroolefination diaryl thioketones⁸ are of low efficiency and were demonstrated with only very few examples. The Julia-Kocienski-type gem-difluoroolefination of diaryl ketones⁹ and gem-difluoroolefination of diaryl diazo compounds¹⁰ are synthetically useful, but the availability of the diaryl compounds can impose restriction on their wide application. The metal-catalyzed cross-coupling reactions of 2,2-difluoro-1-arylvinylstannane reagents,¹¹ 2,2-difluoro-1-arylvinylzinc reagents, ¹² α -halo- β , β -difluorostyrenes¹² and 2,2-difluoro-1-arylvinyl tosylates, ¹³ also involve the use of not readily-available coupling partners. Furthermore, the recently disclosed Rh(I)-catalyzed defluorinative cross-coupling of trifluoromethylketone N-tosylhydrazones and arylboronates affords 1,1-diaryl-2,2-difluoroethenes in moderate yields.¹⁴

In the past decade, a series of fluorinated sulfones have been developed as general fluoroalkylation reagents and widely used for the incorporation of various fluoroalkyl groups into organic molecules by us and others.^{8,15,16} Difluoromethyl sulfones are among the most versatile fluorinated sulfones and are capable of incorporating difluoromethyl (-CF₂H), difluoromethylene (-CF₂-), difluoromethylidene group (=CF₂), as well as difluoro(sulfinato)methyl (-CF₂SO₂M)

groups.^{15b,e} The reaction of two molecules with difluoromethyl sulfones via consecutive reactions is a unique synthetic method, which allows easy access to many unsymmetrical *gem*-difluorinated compounds (Scheme 1a). This strategy has been used for the synthesis of difluoromethylene-containing compounds (Scheme 1a, path a);¹⁵ however, the synthesis of difluoromethylidiene-containing compounds, namely, 1,1-difluoroalkenes, by using similar strategy is still underdeveloped (Scheme 1a, path b).





b) Dehydrosulfonylation of PhSO₂CF₂-benzyl benzoates



c) Coupling reaction with gem-difluorovinyl tosylates



d) Coupling reaction with PhSO₂CF₂-benzyl tosylates (This work)



Scheme 1. The transformation of difluoromethyl sulfones and the synthesis of 1,1-difluoroalkenes.

Inspired by our previous work on the preparation of 2,2-difluoro-1-arylvinyl benzoates from α -[difluoro(phenylsulfonyl)methyl]benzyl benzoates (Scheme 1b)¹⁷

and Jeong's work on the Suzuki- and Stille-type cross-coupling reactions of 1c).¹³ (Scheme 2,2-difluoro-1-arylvinyl tosylates we envisioned that α -[difluoro(phenylsulfonyl)methyl]benzyl tosylates could be used as alternative 2,2-difluoro-1-arylvinyl precursors of tosylates to prepare 2,2-diaryl-1,1-difluoroethenes. palladium-catalyzed Herein, we report a dehydrosulfonylative cross-coupling reaction of readily available α -[difluoro(phenylsulfonyl)methyl]benzyl tosylates with arylboronic acids (Scheme 1d). Since the base-mediated dehydrosulfonylative elimination reaction and the subsequent palladium-catalyzed cross-coupling can proceed smoothly in one pot without the isolation of the 2,2-difluoro-1-arylvinyl tosylate intermediates, this synthetic method provides a very convenient approach to obtain structurally diverse 2,2-diaryl-1,1-difluoroethenes.

2. Results and discussion

Our investigation began with the preparation of α -[difluoro(phenylsulfonyl)methyl]benzyl tosylate (1a) by an aldol-type reaction of commercially available PhSO₂CF₂H and benzaldehyde followed by treatment with tosyl chloride (Scheme 2). As previously described,¹⁸ the addition of PhSO₂CF₂H to benzaldehyde could readily take place in THF in the presence of lithium hexamethyldisilazide (LiHMDS) as the base and hexamethylphosphoric triamide (HMPA) as an additive at -78 °C. We found that the further addition of tosyl chloride to the reaction mixture at the same temperature could afford the desired benzyl tosylate **1a** in 85% yield. The same procedures are also applicable for the preparation of other tosylates (1b-1i) from the corresponding aromatic aldehydes in good to excellent isolated yields (Table 1). The electronic nature and steric hindrance of the aryl substituent possess little influence on the reaction. Note that all the so-obtained tosylates are crystalline solids and thus can be easily isolated and purified by recrystallization. Compared with our previous observation that the reaction of

 α -[fluorobis(phenylsulfonyl)methyl]benzyl alcoholates with tosyl chloride failed to give the desired tosylates,¹⁹ the ready tosylation of α -[difluoro(phenylsulfonyl)methyl]benzyl alcoholates by tosyl chloride should be attributed to their lower steric hindrance and higher thermal stability.



Scheme 2. Development of one-pot procedures for the synthesis of α -[difluoro(phenylsulfonyl)methyl]benzyl tosylate **1a**.





^a Isolated yields after recrystallization.

With α -[difluoro(phenylsulfonyl)methyl]benzyl tosylates **1** in hand, we investigated their dehydrosulfonylative cross-coupling reaction with arylboronic acids under palladium catalysis to prepare 2,2-diaryl-1,1-difluoroethenes. The reaction between tosylate 1a and phenylboronic acid (2a) was chosen as a model reaction to test and then optimize the coupling reaction (Table 2). Typically, the reaction was carried out with a loading of 4 mol% Pd₂(dba)₃ at 80 °C for 8 hours, a base was added to promote the formation of the intermediate, 2,2-difluoro-1-phenylvinyl tosylate, and the molar ratio of 1a, 2a, and the base was 1.5/1.0/3.0. When Cs₂CO₃ was used as the base and $Pd_2(dba)_3$ was used as the catalyst, the reaction conducted in 1,2-dimethoxyethane (DME) afforded the desired coupling product **3a** in 68% yield (by ¹⁹F NMR). Screening of solvents showed that other solvents are inferior to DME (Table 1, entries 2–5). The base effect is also significant: K_2CO_3 and t-BuOLi were found to be less effective due to their weaker basicity than Cs₂CO₃, thus retarding the dehydrosulfonylative elimination of 1a (Table 1, entries 6 and 7). The reaction temperature also showed some influence on the reaction: the yield of 3a was decreased to some extent when running the reaction at 100 °C or 60 °C (Table 1, entries 8 and 9). Importantly, it was found that the use of a phosphine ligand could further improve the reaction, with $P(o-tol)_3$ giving **3a** in the highest yield (75%) (Table 1, entries 10 and 11). Eventually, screening of the reactant ratio and catalyst loading established the optimal reaction conditions as follows: 1.2 equiv of 1a, 1.0 equiv of 2a, 3.0 equiv of Cs₂CO₃, 4 mol% Pd₂(dba)₃ catalyst, 8 mol% P(o-tol)₃ ligand, DME solvent, 80 °C reaction temperature, and 8 h reaction time under N2 atmosphere (Table 1, entry 12).

CF ₂ SO ₂ Ph OTs +		B(OH) ₂	Pd ₂ (dba) ₃ (4 mol%)/Ligand			
			Base (3 equiv), S Temp, 8 h	Solvent		
	1a	2a			3a	
Entry	Ligand (mol%)	Base	Solvent	Temp. (°C)	Yield (%)	
1	—	Cs_2CO_3	DME	80	68	
2		Cs_2CO_3	DMF	80	34	
3		Cs_2CO_3	DMSO	80	b	
4		Cs_2CO_3	1,4-dioxane	80	16	
5	_	Cs_2CO_3	NMP	80	19	
6		K ₂ CO ₃	DME	80	8	
7	_	t-BuOLi	DME	80	0	
8		Cs_2CO_3	DME	100	60	
9	_	Cs_2CO_3	DME	60	48	
10	P(o-tol) ₃ (18)	Cs_2CO_3	DME	80	75	
11	sPhos (18)	Cs_2CO_3	DME	80	70	
12 ^c	$P(o-tol)_3(8)$	Cs ₂ CO ₃	DME	80	75 (72)	

Table 2Screening of cross-coupling conditions ^a.

^a Unless otherwise noted, all reactions were conducted according to the following conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), base (0.6 mmol), $Pd_2(dba)_3$ (0.008 mmol), ligand (0.036 mmol) in solvent (2.0 mL) at 60, 80, or 100 °C for 8 h. Yields were determined by ¹⁹F NMR spectroscopy analysis with PhSO₂CF₂H as an internal standard. Isolated yield was given in the parentheses.

^b Intractable mixture.

^c **1a** (0.24 mmol) and P(o-tol)₃ (0.016 mmol) were used.

With the optimized conditions in hand, we first examined the substrate scope by reacting tosylate **1a** with different arylboronic acids **2** (Table 3). For ease of isolation of the desired product, all reactions were performed on 0.5-mmol scale. Generally, both electron-rich and electron-deficient arylboronic acids reacted smoothly to give *gem*-difluoroolefins **3a-3i** in moderate to good isolated yields (50–76%). The oxidative homo-coupling was the major side reaction of arylboronic acids. Besides, it was found that vigorous stirring was needed to promote the formation of products **3** due to the low solubility of Cs_2CO_3 in DME.



Table 3Scope of arylboronic acids ^a.

^a Reaction conditions: **1a** (0.6 mmol), **2** (0.5 mmol), Cs_2CO_3 (1.5 mmol), $Pd_2(dba)_3$ (0.02 mmol), $P(o-tol)_3$ (0.04 mmol) in DME (5.0 mL) at 80 °C for 8 h. Isolated yields.

We then examined the reactions of various tosylates **1b-1i** with phenylboronic acid (**2a**). As shown in Table 4, the reaction is compatible with simple alkyl groups, such as methyl, isopropyl, and *tert*-butyl, trifluoromethyl group, trifluoromethoxy group, even 2-naphthyl substituent. However, both the arene substitution pattern and the electron-donating ability of the substituent could significantly influence the formation of the coupling products. In the cases of alkyl-substituted benzyl tosylates,

the *meta-* and *para-*substituted ones could smoothly undergo the reaction to afford the coupling products in moderate yields (Table 4, **3c**, **3k**, and **3l**), while the *ortho-*substituted ones failed to participate in the reaction due to the difficulty in dehydrosulfonylation caused by the steric hindrance (Table 4, **3j**). In the case where methoxy-substituted benzyl tosylate was used, the cross-coupling reaction was unsuccessful (Table 4, **3d**). The failure of this reaction presumably arises from the strong electron-donating destabilization of the carbanion of benzyl tosylate **1f**, which renders the deprotonation of **1f** much more difficult.

Table 4 Scope of α -[difluoro(phenylsulfonyl)methyl]benzyl tosylates.

^a Reaction conditions: **1** (0.6 mmol), **2a** (0.5 mmol), Cs_2CO_3 (1.5 mmol), $Pd_2(dba)_3$ (0.02 mmol), $P(o-tol)_3$ (0.04 mmol) in DME (5.0 mL) at 80 °C for 8 h. Isolated yields. ^b Yields were determined by ¹⁹F NMR spectroscopy analysis with PhOCF₃ as an internal standard.

To gain further insights into this palladium-catalyzed dehydrosulfonylative cross-coupling reaction, we conducted the control experiment in the absence of the palladium and monitored the progress of the reactions after 1 h with ¹⁹F NMR spectroscopy (Scheme 3). In the absence of $Pd_2(dba)_3/P(o-tol)_3$, the consumption of tosylate **1a** led to the formation 2,2-difluoro-1-phenylvinyl tosylate (**4a**) as the major product (Scheme 3a); whereas in the presence of $Pd_2(dba)_3/P(o-tol)_3$, in addition to the coupling product **3a**, the intermediate **4a** was also observed in substantial amount (Scheme 3b). Theses results suggested that **4a** is a possible intermediate for the generation of **3a**. Moreover, tosylate **1a** was consumed at the similar rate with or without the catalyst, indicating that the dehydrosulfonylation of **1a** to form **4a** should be a major pathway. In combination with previously reported coupling reaction of isolated 2,2-difluoro-1-arylvinyl tosylates **4** with arylboronic acids,^{13b} a proposed

a) Dehydrosulfonylation of 1a to form 4a without palladium catalyst a

 $\begin{array}{c} CF_2SO_2Ph \\ Ph & OTs \\ 1a (0.6 \text{ mmol}) \\ (95\% \text{ conv.}) \end{array} + Ph-B(OH)_2 \\ \begin{array}{c} Cs_2CO_3 (3.0 \text{ equiv}) \\ DME, 80 \ ^\circ C, 1 \text{ h} \end{array} + Ph-B(OH)_2 \\ \begin{array}{c} Cs_2CO_3 (3.0 \text{ equiv}) \\ DME, 80 \ ^\circ C, 1 \text{ h} \end{array} + Ph-OTs \\ \begin{array}{c} 4a, 44\% \\ 4a, 44\% \end{array}$

b) Observation of intermediate 4a in the cross-coupling reaction ^a

 $\begin{array}{ccccc} & & Pd_2(dba)_3 \ (4 \ mol\%) \\ Pd_2(dba)_3 \ (4 \ mol\%) \\ P(o-tol)_3 \ (8 \ mol\%) \\ P(o-tol)_3 \ (8 \ mol\%) \\ \hline CF_2 \\ Cs_2CO_3 \ (3.0 \ equiv) \\ \hline DME, \ 80 \ ^oC, \ 1 \ h \\ \hline 4a, \ 34\% \\ \hline 3a, \ 29\% \\ \end{array}$

c) Proposed reaction pathway

Scheme 3. Mechanism considerations. ^a Conversions and yields were determined by ¹⁹F NMR spectroscopy analysis with PhOCF₃ as an internal standard.

mechanism of our present reaction is given in Scheme 3c, path a. First, Cs_2CO_3 -promoted dehydrosulfonylation of tosylate **1** gave 2,2-difluoro-1-arylvinyl tosylate **4**. Second, the palladium-catalyzed cross-coupling of **4** with arylboronic acids affords 2,2-diaryl-1,1-difluoroethenes **3**. Although the involvement of palladium-catalyzed $C(sp^3)-C(sp^2)$ coupling²⁰ of **1** with arylboronic acids **2** to give intermediate **5** followed by dehydrosulfonylation (Scheme 3c, path b) cannot be fully ruled out at this stage, this pathway should not be the major one, if any, as we observed that the dehydrosulfonylation of **1a** was faster than the formation of **3a**.

3. Conclusions

In summary, we report a new *gem*-difluoroolefination protocol for the synthesis of 2,2-diaryl-1,1-difluoroethenes from readily available PhSO₂CF₂H, aromatic aldehydes, and arylboronic acids. The key step is the palladium-catalyzed dehydrosulfonylative cross-coupling of α -[difluoro(phenylsulfonyl)methyl]benzyl tosylates that are derived from PhSO₂CF₂H, aromatic aldehydes, and tosyl chloride. The dehydrosulfonylation and coupling reaction are operated in one pot without the separation of the intermediates, 2,2-difluoro-1-arylvinyl tosylates. This protocol not only represents a novel synthetic application of PhSO₂CF₂H,¹⁵ it also provides an efficient approach to prepare a series of 2,2-diaryl-1,1-difluoroethenes with varying structures from simple starting materials.

4. Experimental section

4.1. General

Unless otherwise mentioned, solvents and reagents were purchased from commercial

sources and used as received. The solvents MeCN and DMF were distilled over CaH₂. The solvents THF and toluene were distilled over sodium. Difluoromethyl phenyl sulfone (PhSO₂CF₂H) was either prepared according to reported procedures²¹ or purchased from J&K Scientific. All the melting points were uncorrected. ¹H, ¹⁹F and ¹³C NMR spectra were recorded on a Bruker AM-300 NMR, VarianMercury-300, or Agilent MR-400 NMR spectrometer. ¹H NMR chemical shifts were determined relative to internal (CH₃)₄Si (TMS) at δ 0.0 or to the signal of a residual protonated solvent CDCl₃ at δ 7.26. ¹⁹F NMR chemical shifts were determined relative to external CFCl₃ at δ 0.0. MS (EI-MS) were obtained on an Agilent 5975C gas chromatography and HP5989A mass spectrometer. MS (ESI) were obtained on an AGILENT1100 mass spectrometer. High-resolution mass data were recorded on a Thermo Scientific LTQ FTICR mass spectrometer in the ESI mode.

4.2. Typical experimental procedures for the synthesis of a -[difluoro(phenylsulfonyl)methyl]benzyl tosylates **1a–1i**

Into a 250-mL three-necked round bottom flask equipped with a magnetic stir bar were added benzaldehyde (7.959 g, 75.0 mmol, 1.5 equiv), difluoromethyl phenyl sulfone (9.61 g, 50.0 mmol, 1.0 equiv), hexamethylphosphoramide (HMPA) (12.0 mL), and THF (120.0 mL). The mixture was cooled to -78 °C with a dry ice-acetone cold bath, and stirred at this temperature for 10 min. A solution of lithium bis(trimethylsilyl)amide (1.0 M in THF, 75.0 mL, 75.0 mmol, 1.5 equiv) was added dropwise at -78 °C. The mixture was stirred at -78 °C for 2 hours, after which *p*-toluenesulfonyl chloride (14.3 g, 75.0 mmol, 1.5 equiv) was added and then the mixture was stirred at -78 °C for another 1 hour. The reaction was quenched by the addition of a saturated aqueous solution of NH₄Cl (40 mL). Ethyl acetate (EtOAc) (50 mL) were added to the reaction and the organic phase was separated. The aqueous phase was extracted with EtOAc (2×50 mL) and the combined organic phases were dried with MgSO₄, filtered, and evaporated under vacuum. The residue was purified by recrystallization from petroleum ether (PE)/EtOAc to afford the desired product **1a**

as a white solid (19.194 g, 85% yield).

4.2.1. 2,2-Difluoro-1-phenyl-2-(phenylsulfonyl)ethyl 4-methylbenzenesulfonate (1a) Performed on 50-mmol scale, 19.194 g, 85% yield. White solid, m.p. 112–114 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.90 (d, *J* = 7.8 Hz, 2H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.56 (t, *J* = 7.8 Hz, 2H), 7.34 – 7.32 (m, 3H), 7.27 – 7.23 (m, 3H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.17 (dd, *J* = 14.1, 9.5 Hz, 1H), 2.37 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 145.16 (s), 135.53 (s), 133.20 (s), 132.94 (s), 130.78 (s), 130.27 (s), 129.51 (s), 129.29 (s), 129.01 (s), 128.46 (s), 128.18 (s), 119.01 (dd, *J* = 298.8, 290.0 Hz), 77.37 (d, *J* = 20.2 Hz), 77.47 – 77.20 (m), 77.24 (d, *J* = 7.3 Hz), 21.62 (s); ¹⁹F NMR (376 MHz, CDCl₃) δ –107.54 (dd, *J* = 240.9, 9.4 Hz, 1F), –110.38 (dd, *J* = 240.9, 14.1 Hz, 1F); MS (ESI, m/z, %): 474.90 (M+Na⁺, 100.00); HRMS (ESI): Calcd. For C₂₁H₁₈F₂O₅S₂Na⁺: 475.0456; Found: 475.0452.

4.2.2. 2,2-Difluoro-2-(phenylsulfonyl)-1-(m-tolyl)ethyl 4-methylbenzenesulfonate (**1b**) Performed on 50-mmol scale, 19.246 g, 82% yield. White solid, m.p. 115–118 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.90 (d, *J* = 7.9 Hz, 2H), 7.72 (t, *J* = 7.9 Hz, 1H), 7.61 – 7.54 (m, 4H), 7.16 – 7.11 (m, 5H), 7.04 (s, 1H), 6.12 (dd, *J* = 14.6, 9.1 Hz, 1H), 2.37 (s, 3H), 2.22 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 145.20 (s), 138.21 (s), 135.64 (s), 133.26 (s), 132.94 (s), 131.06 (s), 130.70 (s), 129.50 (s), 129.46 (s), 129.34 (s), 129.18 (s), 128.39 (s), 128.09 (s), 126.28 (s), 119.10 (dd, *J* = 298.7, 289.6 Hz), 77.52 (dd, *J* = 28.0, 20.3 Hz). 21.53 (s), 21.10 (s); ¹⁹F NMR (376 MHz, CDCl₃) δ –107.28 (dd, *J* = 241.3, 9.1 Hz, 1F), –110.66 (dd, *J* = 241.3, 14.6 Hz, 1F); MS (ESI, m/z, %): 488.90 (M+Na⁺, 100.00); HRMS (ESI): Calcd. For C₂₂H₁₀F₂O₅S₂Na⁺: 489.0612; Found: 489.0619.

4.2.3. 2,2-Difluoro-2-(phenylsulfonyl)-1-(o-tolyl)ethyl 4-methylbenzenesulfonate (**1**c) Performed on 50-mmol scale, 21.255 g, 91% yield. White solid, m.p. 138–139 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.94 (d, *J* = 7.9 Hz, 2H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.9 Hz, 4H), 7.25 (d, J = 6.6 Hz, 1H), 7.21 – 7.10 (m, 4H), 6.99 (t, J = 7.6 Hz, 1H), 6.53 (dd, J = 16.5, 6.9 Hz, 1H), 2.44 (s, 2H), 2.36 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 145.17 (s), 137.42 (s), 135.63 (s), 133.24 (s), 132.85 (s), 130.79 (s), 130.54 (s), 130.06 (s), 129.48 (s), 129.36 (s), 129.01 (s), 128.09 (s), 127.98 (s), 126.20 (s), 119.36 (dd, J = 299.9, 287.5 Hz), 73.12 (dd, J = 24.6, 15.1 Hz), 21.59 (s), 19.28 (s); ¹⁹F NMR (376 MHz, CDCl₃) δ –106.89 (d, J = 247.2 Hz, 1F), –111.72 (d, J = 244.1Hz, 1F) ; MS (ESI, m/z, %): 488.95 (M+Na⁺, 100.00); HRMS (ESI): Calcd. For C₂₂H₁₀F₂O₅S₂Na⁺: 489.0612; Found: 489.0617.

4.2.4.2,2-Difluoro-1-(4-isopropylphenyl)-2-(phenylsulfonyl)ethyl4-methylbenzenesulfonate (1d)

Performed on 20-mmol scale, 8.482 g, 86% yield. White solid, m.p. 130–131 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.90 (d, J = 7.7 Hz, 2H), 7.71 (dd, J = 10.7, 4.3 Hz, 1H), 7.55 (t, J = 8.0 Hz, 4H), 7.19 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 7.05 (d, J = 8.2 Hz, 2H), 6.14 (dd, J = 14.6, 9.3 Hz, 1H), 2.84 (hept, J = 7.0 Hz, 1H), 2.34 (s, 3H), 1.19 (d, J = 6.9 Hz, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 151.29 (s), 144.94 (s), 135.58 (s), 133.38 (s), 133.00 (s), 130.70 (s), 129.42 (s), 129.31 (s), 129.11 (s), 128.07 (s), 126.51 (s), 119.16 (dd, J = 298.8, 289.5 Hz), 77.8 – 77.32 (m), 33.87 (s), 23.81 (s), 23.78 (s), 21.55 (s); ¹⁹F NMR (376 MHz, CDCl₃) δ –107.31 (dd, J = 241.3, 9.3 Hz, 1F), -110.64 (dd, J = 241.4, 14.5 Hz, 1F); MS (ESI, m/z, %): 516.95 (M+Na⁺, 100.00); HRMS (ESI): Calcd. For C₂₄H₂₄F₂O₅S₂Na⁺: 517.0925; Found: 517.0920.

4.2.5. 1-(4-(tert-Butyl)phenyl)-2,2-difluoro-2-(phenylsulfonyl)ethyl 4-methylbenzenesulfonate (1e)

Performed on 20-mmol scale, 8.397 g, 83% yield. White solid, m.p. 151-153 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.91 (d, J = 7.6 Hz, 2H), 7.73 – 7.69 (m, 1H), 7.57 – 7.53 (m, 4H), 7.19 (s, 4H), 7.10 (d, J = 8.1 Hz, 2H), 6.14 (dd, J = 14.8, 9.1 Hz, 1H), 2.34 (s, 3H), 1.26 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 153.51 (s), 144.85 (s), 135.55 (s), 133.42 (s), 133.03 (s), 130.72 (s), 129.39 (s), 129.30 (s), 128.83 (s), 128.08 (s),

125.35 (s), 119.16 (dd, J = 298.8, 289.2 Hz), 77.77 – 77.29 (m), 34.67 (s), 31.17 (s), 21.57 (s); ¹⁹F NMR (376 MHz, CDCl₃) δ –107.12 (dd, J = 241.6, 9.1 Hz, 1F), –110.82 (dd, J = 241.7, 14.8 Hz, 1F); MS (ESI, m/z, %): 530.95 (M+Na⁺, 100.00); HRMS (ESI): Calcd. For C₂₅H₂₆F₂O₅S₂Na⁺: 531.1082; Found: 531.1079.

4.2.6. 2,2-Difluoro-1-(4-methoxyphenyl)-2-(phenylsulfonyl)ethyl
4-methylbenzenesulfonate (1f)

Performed on 20-mmol scale, 8.403 g, 87% yield. White solid, m.p. 95–98 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, J = 7.7 Hz, 2H), 7.72 – 7.70 (m, 1H), 7.66 – 7.64 (m, 2H), 7.59 – 7.55 (m, 2H), 7.31 – 7.24 (m, 2H), 7.15 (d, J = 8.1 Hz, 2H), 6.83 – 6.77 (m, 3H), 3.83 (s, 3H), 2.36 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 145.06 (s), 135.45 (s), 133.19 (s), 133.03 (s), 131.40 (s), 130.83 (s), 129.63 (s), 129.33 (s), 129.25 (s), 128.22 (s), 120.62 (s), 119.22 (dd, J = 298.8, 288.6 Hz), 118.38 (s), 110.70 (s), 70.29 (dd, J = 29.8, 20.2 Hz), 55.83 (s), 21.59 (s); ¹⁹F NMR (376 MHz, CDCl₃) δ –107.09 (dd, J = 243.2, 7.3 Hz, 1F), –111.54 (dd, J = 243.2, 16.1 Hz, 1F) ; MS (ESI, m/z, %): 504.95 (M+Na⁺, 100.00); HRMS (ESI): Calcd. For C₂₂H₂₀F₂O₆S₂Na⁺: 505.0562; Found: 505.0526.

4.2.7. 2,2-Difluoro-2-(phenylsulfonyl)-1-(4-(trifluoromethyl)phenyl)ethyl 4-methylbenzenesulfonate (1g)

Performed on 20-mmol scale, 7.721 g, 74% yield. White solid, m.p. 140–143 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.91 (d, J = 7.6 Hz, 2H), 7.77 – 7.73 (m, 1H), 7.62 – 7.57 (m, 4H), 7.48 (q, J = 8.4 Hz, 4H), 7.16 (d, J = 8.1 Hz, 2H), 6.21 (dd, J = 13.7, 9.4 Hz, 1H), 2.37 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 145.63 (s), 135.78 (s), 133.55 (s), 132.86 (s), 132.83 (q, J = 32.89 Hz), 132.61 (s), 130.80 (s), 129.62 (s), 129.47 (s), 129.41 (s), 128.18 (s), 125.39 (q, J = 3.7 Hz), 123.56 (q, J = 272.4 Hz), 118.75 (dd, J = 299.3, 290.3 Hz), 76.39 (dd, J = 27.6, 20.9 Hz), 21.53 (s); ¹⁹F NMR (376 MHz, CDCl₃) δ –63.06 (s, 3F), –107.85 (dd, J = 241.7, 9.4 Hz, 1F), –110.39 (dd, J = 241.7, 13.7 Hz, 1F) ; MS (ESI, m/z, %): 542.90 (M+Na⁺, 100.00); HRMS (ESI): Calcd. For

 $C_{22}H_{17}F_5O_5S_2Na^+$: 543.0330; Found: 543.0342.

4.2.8. 2,2-Difluoro-2-(phenylsulfonyl)-1-(4-(trifluoromethoxy)phenyl)ethyl 4-methylbenzenesulfonate (1h)

Performed on 20-mmol scale, 8.797 g, 83% yield. White solid, m.p. 105–108 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.91 (d, J = 7.6 Hz, 2H), 7.75 (t, J = 7.5 Hz, 1H), 7.58 (t, J = 8.1 Hz, 4H), 7.36 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 6.18 (dd, J = 13.6, 9.7 Hz, 1H), 2.36 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 150.48 (s), 145.55 (s), 135.73 (s), 133.05 (s), 132.71 (s), 130.78 (s), 130.71 (s), 129.57 (s), 129.38 (s), 128.23 (d, J = 2.1 Hz), 128.11 (s), 120.74 (s), 120.26 (q, J = 258.0 Hz), 118.82 (dd, J = 298.6, 290.5 Hz), 76.42 (dd, J = 27.5, 20.7 Hz), 21.50 (s); ¹⁹F NMR (376 MHz, CDCl₃) δ –58.34 (s, 3F), –108.54 (dd, J = 241.2, 9.6 Hz, 1F), – 110.88 (dd, J = 241.4, 13.6 Hz, 1F) ; MS (ESI, m/z, %): 558.90 (M+Na⁺, 100.00); HRMS (ESI): Calcd. For C₂₂H₁₇F₅O₆S₂Na⁺: 559.0279; Found: 559.0264.

4.2.9. 2,2-Difluoro-1-(naphthalen-2-yl)-2-(phenylsulfonyl)ethyl
4-methylbenzenesulfonate (1i)

Performed on 20-mmol scale, 8.332 g, 83% yield. White solid, m.p. 145–147 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.90 (d, J = 7.5 Hz, 2H), 7.80 – 7.64 (m, 5H), 7.60 – 7.46 (m, 6H), 7.37 (d, J = 8.6 Hz, 1H), 6.99 (d, J = 8.2 Hz, 2H), 6.32 (dd, J = 14.1, 9.6 Hz, 1H), 2.18 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 145.24 (s), 135.56 (s), 133.89 (s), 133.21 (s), 132.91 (s), 132.47 (s), 130.76 (s), 129.87 (s), 129.38 (s), 129.28 (s), 128.48 (s), 128.35 (s), 128.10 (s), 127.64 (s), 127.42 (s), 126.64 (s), 125.01 (s), 119.23 (dd, J = 298.8, 290.2 Hz), 77.68 (d, J = 20.4, 7.2 Hz), 21.39 (s); ¹⁹F NMR (376 MHz, CDCl₃) δ –107.51 (dd, J = 241.2, 9.6 Hz, 1F), –110.19 (dd, J = 241.2, 14.1 Hz, 1F) ; MS (ESI, m/z, %): 524.90 (M+Na⁺, 100.00); HRMS (ESI): Calcd. For C₂₅H₁₀F₂O₅S₂Na⁺: 525.0612; Found: 525.0603.

4.3. Typical experimental procedures for the synthesis of

2,2-diaryl-1,1-difluoroethenes 3a-3l

Under the N₂ atmosphere, DME (5.0 mL) was added into an oven-dried 20-mL Schlenk tube containing tosylate **1a** (270.2 mg, 0.6 mmol, 1.0 equiv), phenylboronic acid (**2a**) (60.9 mg, 0.5 mmol, 1.0 equiv), tris(dibenzylideneacetone)dipalladium(0) (Pd₂(dba)₃) (18.4 mg, 0.02 mmol, 4 mol%), tri(*o*-tolyl)phosphine (12.2 mg, 0.04 mmol, 8 mol%), Cs₂CO₃ (489.0 mg, 1.5 mmol, 3.0 equiv) and a magnetic stir bar. The mixture were heated to 80 °C and stirred vigorously for 8 hours. After the addition of petroleum ether (PE) (10 mL), the mixture was filtered through Celite layer. The filtrate was concentrated under vacuum and purified by flash column chromatography (silica gel; petroleum ether/diethyl ether, 5:1, v/v) to give the desired product **3a** as colorless oil (77.6 mg, 72% yield).

4.3.1. (2,2-Difluoroethene-1,1-diyl)dibenzene (**3a**)

Prepared from **1a** (0.6 mmol) and phenylboronic acid (**2a**) (0.5 mmol), 77.6 mg, 72% yield. Colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.26 (m, 9H); ¹⁹F NMR (376 MHz, CDCl₃) δ –87.80 (s, 2F); MS (ESI, m/z, %): 238.95 (M+Na⁺, 100.00). The characterization data are in consistence with previous report.¹⁴

4.3.2. 1-(2,2-Difluoro-1-phenylvinyl)-4-methylbenzene (3b)

Prepared from **1a** (0.6 mmol) and *p*-tolylboronic acid (**2b**) (0.5 mmol), 74.5 mg, 76% yield. Colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.22 (m, 9H), 7.15 (s, 4H), 2.36 (s, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ –88.10 (d, *J* = 34.0 Hz, 1F), –88.30 (d, *J* = 34.1 Hz, 1F); MS (ESI, m/z, %): 253.00 (M+Na⁺, 100.00). The characterization data are in consistence with previous report.¹⁴

4.3.3. 1-(2,2-Difluoro-1-phenylvinyl)-3-methylbenzene (3c)

Method A, prepared from **1a** (0.6 mmol) and *m*-tolylboronic acid (**2c**) (0.5 mmol), 53.7 mg, 61% yield; Method B, prepared from **1b** (0.6 mmol) and phenylboronic acid (**2a**) (0.5 mmol), 62.5 mg, 71% yield. Colorless oil; ¹H NMR (400 MHz, CDCl₃) δ

7.39 – 7.19 (m, 6H), 7.15 – 7.03 (m, 3H), 2.33 (s, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ –87.79 (d, *J* = 32.9 Hz, 1F), –88.14 (d, *J* = 32.8 Hz, 1F); MS (ESI, m/z, %): 253.0 (M+Na⁺, 100.00). The characterization data are in consistence with previous report.¹⁴

4.3.4. 1-(2,2-Difluoro-1-phenylvinyl)-4-methoxybenzene (3d)

Prepared from **1a** (0.6 mmol) and 4-methoxyphenylboronic acid (**2d**) (0.5 mmol), 67.8 mg, 64% yield. Colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.22 (m, 5H), 7.18 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 1H), 3.81 (s, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ –88.73 (d, *J* = 34.9 Hz, 1F), –88.91 (d, *J* = 34.9 Hz, 1F); MS (ESI, m/z, %): 269.0 (M+Na⁺, 100.00). The characterization data are in consistence with previous report.¹⁴

4.3.5. (4-(2,2-Difluoro-1-phenylvinyl)phenyl)(methyl)sulfane (3e)

Prepared from **1a** (0.6 mmol) and 4-(methylthio)phenylboronic acid (**2e**) (0.5 mmol), 66.1 mg, 58% yield. Colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 7.36 – 7.21 (m, 7H), 7.17 (d, *J* = 8.4 Hz, 2H), 2.48 (s, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ –87.67 (d, *J* = 32.4 Hz, 1F), –87.77 (d, *J* = 32.4 Hz, 1F); MS (ESI, m/z, %): 284.95 (M+Na⁺, 100.00). The characterization data are in consistence with previous report.^{8b}

4.3.6. 1-(2,2-Difluoro-1-phenylvinyl)-3-methoxybenzene (3f)

Prepared from **1a** (0.6 mmol) and 3-methoxyphenylboronic acid (**2f**) (0.5 mmol), 58.3 mg, 55% yield. Colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 7.36 – 7.24 (m, 6H), 6.86 – 6.81 (m, 3H), 3.77 (s, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ –87.09 (d, *J* = 31.8 Hz, 1F), -87.56 (d, *J* = 31.7 Hz, 1F); MS (ESI, m/z, %): 268.95 (M+Na⁺, 100.00). The characterization data are in consistence with previous report.^{8b}

4.3.7. 1-(2,2-Difluoro-1-phenylvinyl)-4-(trifluoromethyl)benzene (3g)

Method A, prepared from **1a** (0.6 mmol) and 4-(trifluoromethyl)phenylboronic acid (**2g**) (0.5 mmol), 62.4 mg, 50% yield; Method B, prepared from **1g** (0.6 mmol) and

phenylboronic acid (**2a**) (0.5 mmol), 91.1 mg, 73% yield. Colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, J = 8.1 Hz, 2H), 7.38 – 7.29 (m, 5H),7.23 (dd, J = 8.1, 7.0 Hz, 2H); ¹⁹F NMR (376 MHz, CDCl₃) δ –62.74 (s, 3F), –85.74 (d, J = 28.1 Hz, 1F), -86.47 (d, J = 28.1 Hz, 1F); MS (ESI, m/z, %): 322.95 (M+Na⁺, 100.00). The characterization data are in consistence with previous report.^{9a}

4.3.8. 1-(2,2-Difluoro-1-phenylvinyl)-4-(trifluoromethoxy)benzene (3h)

Method A, prepared from **1a** (0.6 mmol) and 4-(trifluoromethoxy)phenylboronic acid (**2h**) (0.5 mmol), 85.1 mg, 64% yield; Method B, prepared from **1h** (0.6 mmol) and phenylboronic acid (**2a**) (0.5 mmol), 86.2 mg, 65% yield. Colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.24 (m, 7H), 7.19 (d, *J* = 8.1 Hz, 2H); ¹⁹F NMR (376 MHz, CDCl₃) δ –57.86 (s), –86.88 (d, *J* = 30.7 Hz, 1F), –87.33 (d, *J* = 30.7 Hz, 1F); MS (ESI, m/z, %): 322.95 (M+Na⁺, 100.00). The characterization data are in consistence with previous report.^{9a}

4.3.9. 2-(2,2-Difluoro-1-phenylvinyl)naphthalene (3i)

Method A, prepared from **1a** (0.6 mmol) and 2-naphthylboronic acid (**2i**) (0.5 mmol), 81.2 mg, 70% yield; Method B, prepared from **1i** (0.6 mmol) and phenylboronic acid (**2a**) (0.5 mmol), 84.7 mg, 73% yield. Colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 7.83 – 7.72 (m, 4H), 7.48 – 7.46 (m, 2H), 7.34 – 7.29 (m, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ –87.35 (d, *J* = 31.5 Hz, 1F), –87.56 (d, *J* = 31.5 Hz, 1F); MS (ESI, m/z, %): 289.0 (M+Na⁺, 100.00). The characterization data are in consistence with previous report.^{9a}

4.3.10. 1-(2,2-Difluoro-1-phenylvinyl)-4-isopropylbenzene (3k)

Prepared from **1d** (0.6 mmol) and phenylboronic acid (**2a**) (0.5 mmol), 83.8 mg, 65% yield. Colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 7.36 – 7.26 (m, 5H), 7.21 – 7.16 (m, 4H), 2.91 (hept, J = 6.9 Hz, 1H), 1.26 (d, J = 6.9 Hz, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ –88.23 (d, J = 2.8 Hz, 2F); MS (ESI, m/z, %): 281.0 (M+Na⁺, 100.00). The

characterization data are in consistence with previous report.9a

4.3.11. 1-(tert-Butyl)-4-(2,2-difluoro-1-phenylvinyl)benzene (3l)

Prepared from **1e** (0.6 mmol) and phenylboronic acid (**2a**) (0.5 mmol), 84.3 mg, 62% yield. Colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 7.36 – 7.32 (m, 4H), 7.30 – 7.26 (m, 3H), 7.19 (d, *J* = 8.1 Hz, 2H), 1.32 (s, 2H); ¹⁹F NMR (376 MHz, CDCl₃) δ –88.02 (d, *J* = 33.4 Hz, 1F), –88.20 (d, *J* = 33.4 Hz, 1F); MS (ESI, m/z, %): 295.0 (M+Na⁺, 100.00). The characterization data are in consistence with previous report.¹⁴

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <u>https://doi.org/10.1016/j.tet.2018.xx.xxx</u>.

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