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Nucleophilic difluoromethylation and difluoromethylenation using bromodifluoromethyl phenyl sulfone

G.K. Surya Prakash^{a,*}, Ying Wang^a, Jinbo Hu^{a,b}, George A. Olah^a

^a Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, CA 90089-1661, USA

^b Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Feng-Lin Road, Shanghai 200032, China

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Abstract

Tetrakis(dimethylamino)ethylene (TDAE) was found to be an effective electron-transfer agent that promoted the reactions of bromodifluoromethyl phenyl sulfone with aldehydes to give structurally diverse (benzenesulfonyl)difluoromethylated alcohols in good yield, which can be further transformed into difluoromethyl alcohols and 1,1-difluoro-1-alkenes via reductive desulfonylation and Julia olefination, respectively.

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1. Introduction

gem-Difluorinated compounds, such as difluoromethyl alcohols and 1,1-difluoro-1-alkenes, are highly useful for pharmaceutical or agrochemical applications, since the diffuoromethylene functionality (CF_2) is known to be an isostere and isopolar to an oxygen atom [1]. Difluoromethyl group (CF₂H) can act as both a liphophilic isostere of hydroxyl group (OH) and a hydrogen donor through hydrogen bonding [2], while gem-difluorovinyl functionality can act as a bioisostere for aldehydes and ketones [3] with a different reactivity pattern. Many functionalized difluoromethyl compounds and 1,1-difluoro-1-alkenes are used as enzyme inhibitors [4], pesticides [5], among others. Moreover, 1,1-difluoro-1-alkenes can be further converted into different fluorinated compounds and polymers [6]. Thus, the development of effective ways for the preparation of these two classes of gem-difluorinated compounds is of great significance. Recently, we have reported methods [7] to

introduce difluoromethyl and difluoromethylene functionalities using a difluoromethyl phenyl sulfone as a synthon under highly basic conditions.

Bromodifluoromethyl phenyl sulfone (PhSO₂CF₂Br) was first synthesized by Burton and coworkers in 1981 [8], however, its synthetic application has rarely been explored. Recently, we have reported the use of bromodifluromethyl phenyl sulfone for the preparation of fluroalkylsilanes [9]. Tetrakis(dimethylamino)ethylene (TDAE), as an efficient reductant to generate substituted difluoromethylated carbanions from halo-difluoromethyl precursors, has been reported by Dolbier and coworkers [10]. However, the reaction between TDAE and bromodifluoromethyl phenyl sulfone to generate (benzenesulfonyl)difluoromethyl anion $(PhSO_2CF_2^{-})$, has not been reported. In this paper, we describe the efficient TDAE-mediated nucleophilic reactions between bromodifluoromethyl phenyl sulfone (1) and aldehydes (2). The resulting (benzensulfonyl)difluoromethyl alcohols (3) can be further transformed into diffuoromethyl alcohols (4) and 1,1-diffuoro-1-alkenes (6) via reductive desulfonylation and Julia olefination, respectively (Scheme 1) [11].

^{*} Corresponding author. Fax: +1 213 740 6270.

E-mail address: gprakash@usc.edu (G.K. Surya Prakash).

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Scheme 1. Difluoromethylation of aldehydes using 1.

2. Results and discussion

Nucleophilic addition reactions between 1 and 2 were carried out according to the following procedure: under an argon atmosphere, the TDAE was added dropwise to the mixture of 1 and 2 in DMF solution under 60 W sun lamp irradiation. The reaction conditions were carefully optimized by using different reactant ratios, reaction temperatures and light intensities, and we found the best product yields can be obtained with the following reaction conditions: 2.2 equivalents of TDAE, 2.2 equivalents of sulfone (1) and 1.0 equivalents of aldehyde (2) in DMF were stirred under the sun lamp at -30 °C for 1 h and then at room temperature for 6 h. A variety of (benzenesulfonyl)difluoromethylated alcohols (3) were prepared in moderate to good yields as shown in Table 1. However, the reactions of 1/TDAE system with ketones gave very poor yields of products (10-30%) because of steric constrains.

The mechanism of this reaction is proposed in Scheme 2, which is similar to the early reports [10]. Initially, an orange–red charge-transfer complex is formed between 1 and TDAE. Then two electrons from TDAE is transferred to bromodifluoromethyl phenyl sulfone to generate (benzene-sulfonyl)difluoromethyl anion (PhSO₂CF₂⁻) and Br⁻. (Benzenesulfonyl)difluoromethyl anion undergoes further addition into aldehydes to give (benzenesulfonyl)difluoromethyl alcohols 3. Here, the sun lamp irradiation is necessary for inducing the electron transfer from TDAE to 1.

The resulting (benzenesulfonyl)difluoromethyl alcohols are very useful intermediates, which can be further converted into various fluorinated materials [12]. Two types of reactions of the difluoromethyl alcohols were carried out to demonstrate the utility of alcohols: the reductive desulfonylation to give difluoromethyl compounds **4** and the Julia olefination to give 1,1-difluoro-1-alkenes **6**. The results are outlined in Scheme 3.

Reductive desulfonylations of **3** were completed to give difluoromethyl alcohols **4** in good yields by using 5 equivalents 10% Na(Hg) amalgam and 5 equivalents of

 Na_2HPO_4 in methanol at -20 to -10 °C over 1 h. The results of desulfonylations are shown in Table 2.

Julia-type olefination of **3** were also successfully achieved to give 1,1-difluoro-1-alkenes 6 in good yields. First, the alcohols were converted into the mesylates by using 2 equivalents of MsCl, 4 equivalents of Et₃N, and catalytic amount of 4-dimethylaminopyridine (DMAP) in CH₂Cl₂ at 0 °C over 2 h. Then the mesylates underwent the reductive elimination to give 1,1-difluoro-1-alkenes 5 by treatment with 6 equivalents of 10% Na(Hg), 4 equivalents of Na₂HPO₄ in CH₃OH at -40 to 0 °C for 1 h. The Julia olefinations of (benzenesufonyl)difluoromethyl alcohols (3) are more difficult than that of the alcohols without fluorine atoms because the high electronegativity of fluorine atoms in the carbanion intermediate make it easier to undergo the protonation to form diffuoromethyl compounds 4. From the ¹⁹F NMR spectrum of the reaction mixture, we can see that both the 1,1-difluoro-1-alkenes and the difluoromethyl alcohols are formed. Thus, the choice of the right leaving group becomes very important for the elimination of these (benzenesulfonyl)difluoromethyl alcohol derivatives. We explored acetate (Ac), tosylate (Ts), triflate, and mesylate groups as the protecting groups for the alcohol, and found that the mesylates were the best for the further reductive elimination to give 1,1-difluoro-1-alkenes 6. This suggests that neither the good leaving groups such as the triflate $(-OSO_2CF_3)$ and tosylate $(-OSO_2C_6H_4CH_3)$ nor the relatively stable leaving group such as acetate (OAc) were suitable for this olefination protocol. This can be surmised by considering that reactive leaving groups can be easily displaced before the desulfonylation step and making further reductive elimination difficult, while the stable leaving group is difficult to be removed in the reductive elimination of the carbanion intermediate, resulting in the formation of difluoromethyl compounds. Considering the protonation side-reaction, we also tried SmI_2 as the reducing agent [11] in the reductive elimination step to avoid using the protic solvent MeOH, which is necessary in Na(Hg) reduction. However, the result was not ideal and other products were Table 1 Nucleophilic (benzenesulfonyl)difluoromethylation of aldehydes using PhSO₂CF₂Br/TDAE in DMF at -30 °C \sim RT under sun-lamp irradiation

Entry	Aldehyde 2	Product 3	Yield ^a (%)
a	O Ph H	$\begin{array}{c} OH \\ Ph \\ Ph \\ H \end{array} CF_2SO_2Ph \\ H \end{array}$	74
b	Ph H	HO CF ₂ SO ₂ Ph Ph H	40
c	Ph H	HO CF ₂ SO ₂ Ph Ph H	53
d	p-CIC ₆ H ₄ H	OH CF ₂ SO ₂ Ph p-CIC ₆ H ₄ H	65
e	<i>p</i> -BrC ₆ H₄ H	OH p-BrC ₆ H ₄ H	55
f	СНО	HO HO H	70
g	СНО	HO HO H	82
h	CHO CI	HO HO H CI	57
i	СНО	HO CF ₂ SO ₂ Ph	80

^a Isolated yields.

formed rather than the expected alkenes. Finally, we optimized the Julia olefination reaction of (benzenesulfonyl)difluoromethyl alcohols with the OMs group as the leaving group and the Na(Hg) as the reducing reagent for the elimination step. The results are listed in Table 3.

$$PhSO_{2}CF_{2}Br + TDAE \xrightarrow{sun lamp} PhSO_{2}CF_{2}^{-} + Br^{-} + TDAE^{2+}$$

$$PhSO_{2}CF_{2}^{-} + RCHO \longrightarrow \stackrel{O}{R} \stackrel{CF_{2}SO_{2}Ph}{H}$$

$$\stackrel{O}{R} \stackrel{CF_{2}SO_{2}Ph}{H} + H^{+} \longrightarrow \stackrel{HO}{R} \stackrel{CF_{2}SO_{2}Ph}{H}$$

Scheme 2. Mechanism of nucleophilic reaction of aldehydes with $PhSO_2CF_2Br/TDAE$ reagent.



Scheme 3. Reductive desulfonylation and Julia olefination of 3.

3. Conclusions

The nucleophilic reactions of bromodifluoromethyl phenyl sulfone with aldehydes in the presence of TDAE were completed successfully. The resulting difluoromethyl alcohols are very useful intermediates, which can undergo both reductive desulfonylation to give difluoromethyl alcohols and via Julia olefination to give 1,1-difluoro-1-alkenes in good yields. The methodology provides convenient and efficient ways to introduce the difluoromethyl group and 1,1-difluorovinyl functionality into the organic compounds.

4. Experimental

4.1. General

Materials and Instrumentation. Unless otherwise mentioned, all chemicals were purchased from commercial sources. Bromodifluoromethyl phenyl sulfone 1 was prepared using known procedures [8]. CH₂Cl₂ was distilled over calcium hydride. Silica gel column chromatography was used to isolate the products using 60-200 mesh silica gel. ¹H, ¹³C, and ¹⁹F NMR spectra were recorded on either a 400 MHz or 360 MHz NMR spectrometer. ¹H NMR chemical shifts were determined relative to the signal of residual proton in CDCl₃ δ 7.26 or Acetone-d₆ δ 2.04. ¹³C NMR chemical shifts were determined relative to the ¹³C signal of sovent: CDCl₃ δ 77.0 or Acetone-d₆ δ 29.8. ¹⁹F NMR chemical shifts were determined relative to internal CFCl₃ at δ 0.0. High-resolution mass data of low boiling compounds were recorded on a GC chromatograph with micromass GCT (time of flight) mass spectrometer. Other high-resolution mass data were recorded on a highresolution mass spectrometer in the EI mode.

4.2. Typical procedure for nucleophilic reactions of **1** with aldehydes

Under an argon atmosphere, bromodifluoromethyl phenyl sulfone 1 (600 mg, 2.2 mmol), 5 mL DMF, and benzaldehyde (106.1 mg, 1 mmol) were added into a dry Schlenk flask and contents were cooled to -30 °C. After

Table 2

$\begin{array}{c} HO \qquad CF_2SO_2Ph \\ R \qquad H \qquad 3 \\ \qquad 1 \ eq. \end{array}$	+ 10% Na(Hg) 7 eq. Na ₂ HPO ₄ MeOH 7 eq20 °C ~ -10 °C 1 hr	► HO R H 4	
Entry	Carbinol 3	Product 4	Yield ^a (%)
a	OH CF ₂ SO ₂ Ph Ph H	OH Ph H CF ₂ H	79
b	HO CF ₂ SO ₂ Ph Ph H	HO CF ₂ H	84
c	HO CF ₂ SO ₂ Ph Ph H	HO CF ₂ H Ph H	86

Desulfonvlation of	(benzenesulfonvl	Ddifluoromethyl	alcohols 3	using Na(Hg)	amalgam
Destinon junion of	(benzenebunon)	() ann aor onneur y r	uncomons e	aoning i au(iig)	unnungunn

^a Isolated yields.

stirring the mixture for 15 min, TDAE (440 mg, 2.2 mmol) was added in dropwise. Under the irradiation of sun lamp, the reaction mixture was stirred at -30 °C for 1 h and then at room temperature for 6 h. The completion of the reaction was monitored by ¹⁹F NMR. The resulting orange-red solution was filtered and the solid was washed with 100 mL ether. After the ether layer was separated from the DMF layer, the DMF layer was hydrolyzed with 50 mL brine and extracted by ether (20 mL \times 3). Then the combined ether layer was washed by brine five times and dried over magnesium sulfate. After removing the solvent by a rotary evaporator, the crude product was further purified by silica gel column chromatography (first hexane: ethyl acetate = 7:1, then hexane:ethyl acetate = 1:1) to give pure 2benzenesulfonyl-2,2-difluoro-1-phenylethanol (3a) (221 mg, 74% yield) as a colorless crystal. ¹H NMR (CDCl₃): δ 3.92 (d, J = 4.4 Hz, 1H); 5.60 (dd, J = 21 Hz, 3 Hz, 1H); 7.36 (m, 1)3H); 7.48 (m, 2H); 7.56 (t, J = 8 Hz, 2H); 7.70 (t, J = 8 Hz, 1H); 7.98 (d, J = 8 Hz, 2H). ¹⁹F NMR (CDCl₃): $\delta - 104.4$ (dd, *J* = 238 Hz, 3 Hz, 1F); -119.9 (dd, *J* = 238 Hz, 21 Hz, 1F). MS (EI, *m/z*): 298 (M⁺), 156, 140, 127, 107, 77. The data are consistent with the previous report [12].

Table 3 Julia ol

$\begin{array}{c} \text{HO} \text{CF}_2\text{SO}_2\text{Ph} \\ \text{R} \text{H} \\ 1 \text{ eq.} \\ \textbf{3} \end{array}$	2 eq. MsCl 4 eq. Et ₃ N, cat. DMAP CH ₂ Cl ₂ , 0 °C, 1 hr	OSO ₂ CH ₃ R CF ₂ SO ₂ Ph H 1 eq. 5	6 eq. 10% Na(Hg) 4 eq. Na ₂ HPO ₄ , MeOH -40 ℃ ~ 0 ℃, 1 hr	H R F 6	
Entry	Carbin	nol 3		RCH=CF ₂ 6	Yield ^a (%)
a	OH Ph	∠CF₂SO₂Ph `H		PhCH=CF ₂	60
c	Ph	HO_CF ₂ SO ₂ Ph H		Ph(CH ₂) ₂ CH=CF ₂	84
e	<i>p</i> -BrC	OH ₆ H ₄ CF ₂ SO ₂ Ph		<i>p</i> -BrC ₆ H ₄ CH=CF ₂	70

Julia olefination reactions of (benzenesulfonyl)difluoromethyl alcohols ${\bf 3}$

^a Isolated yields.

(*E*)-1-Benzenesulfonyl-1, 1-difluoro-4-phenyl-3-buten-2ol (**3b**): 40% yield, white solid. ¹H NMR (CDCl₃): δ 3.07 (d, J = 5.5 Hz, 1H); 5.15 (m, 1H); 6.25 (dd, J = 15.8 Hz, 6.7 Hz, 1H); 6.89 (d, J = 15.8 Hz, 1H); 7.29–7.43 (m, 5H); 7.63(t, J = 8 Hz, 2H); 7.77 (t, J = 8 Hz, 1H); 8.00 (d, J = 8 Hz, 2H). ¹³C NMR (CDCl₃): δ 70.8 (dd, J = 23 Hz, 21 Hz); 120.3 (dd, J = 293 Hz, 290 Hz); 120.3 (t, J = 2.3 Hz); 126.9; 128.5; 128.6; 129.3; 130.6; 132.8; 135.5; 135.6; 136.4. ¹⁹F NMR (CDCl₃): δ –107.0 (dd, J = 237 Hz, 6 Hz, 1F); –116.6 (dd, J = 237 Hz, 17 Hz, 1F). MS (EI, *m*/*z*): 324 (M⁺), 207, 133, 115, 105, 77. HRMS (EI): *m*/*z* calcd for C₁₆H₁₄F₂O₃S (M⁺) 324.0632, found 324.0642.

1-(Benzenesulfonyl)difluoromethyl-3-phenylpropanol (**3c**): 53% yield, colorless liquid. ¹H NMR (CDCl₃): δ 2.09 (m, 2H); 2.77 (m, 1H); 2.97 (m, 1H); 3.05 (b, 1H); 4.45 (m, 1H); 7.22–7.34 (m, 5H); 7.62 (t, J = 8 Hz, 2H); 7.77 (t, J = 8 Hz, 1H); 8.00 (d, J = 8 Hz, 2H). ¹³C NMR (CDCl₃): δ 30.9 (b, 2C); 68.6 (dd, J = 24 Hz, 20 Hz); 121.2 (dd, J = 294 Hz, 292 Hz); 126.2; 128.4; 128.5; 129.3; 130.5; 132.7; 135.5; 140.5. ¹⁹F NMR (CDCl₃): δ –109.2 (dd, J = 238 Hz, 6 Hz, 1F); –116.9 (dd, J = 238 Hz, 19 Hz, 1F). MS (EI, *m/z*): 326 (M⁺), 308, 167, 143, 104, 91, 77. HRMS (EI): m/z calcd for $C_{16}H_{16}F_2O_3S$ (M⁺) 326.0788, found 326.0795.

4-Chloro-[difluoro(phenylsulfonyl)methyl]-benzenemethanol (**3d**): 65% yield, white solid. ¹H NMR (CDCl₃): δ 3.46 (s, 1H); 5.57 (dd, J = 20.9 Hz, 2.3 Hz, 1H); 7.35 (d, J = 8.5 Hz, 2H); 7.42 (d, J = 8.4 Hz, 2H); 7.62 (t, J = 8.1 Hz, 2H); 7.78 (t, J = 8.1 Hz, 1H); 7.99 (d, J = 8.1 Hz, 2H). ¹³C NMR (CDCl₃): δ 70.6 (dd, J = 26.4 Hz, 20.2 Hz); 119.8 (dd, J = 298.7 Hz, 289.6 Hz); 128.6; 129.38; 129.41; 130.6; 131.9; 132.3; 135.5; 135.7. ¹⁹F NMR (CDCl₃): δ -104.6 (d, J = 241.5 Hz, 1F); -119.8 (dd, J = 241.5 Hz, 20.1 Hz, 1F). MS (EI, m/z): 332 (M⁺), 143, 141, 77.

4-Bromo-[difluoro(phenylsulfonyl)methyl]-benzenemethanol (**3e**): 55% yield, light yellow solid. ¹H NMR (CDCl₃): δ 3.57 (s, 1H); 5.55 (d, J = 21.0 Hz, 1H); 7.35 (d, J = 8.4 Hz, 2H); 7.51 (d, J = 8.6 Hz, 2H); 7.62 (t, J = 8.2 Hz, 2H); 7.77 (t, J = 7.4 Hz, 1H); 7.99 (d, J = 8.1 Hz, 2H). ¹³C NMR (CDCl₃): δ 70.6 (dd, J = 25.5 Hz, 19.5 Hz); 119.8 (dd, J = 300.4 Hz, 289.8 Hz); 123.7; 129.4; 129.7; 130.6; 131.6; 135.7. ¹⁹F NMR (CDCl₃): δ -104.6 (d, J = 235.8 Hz, 1F); -119.7 (dd, J = 239.8 Hz, 21.0 Hz, 1F). MS (EI, m/z): 376 (M⁺), 306, 235, 218, 185, 157, 136, 125, 106, 94. HRMS (EI): m/z calcd for C₁₄H₁₁O₃SF₂Br (M⁺) 375.9580, found 375.9577.

α-[(Benzenesulfonyl)difluoromethyl]-1-naphthalenemethanol (**3f**): 70% yield, white solid. ¹H NMR (CDCl₃): δ 3.72 (d, J = 4.2 Hz, 1H); 5.77 (ddd, J = 21.6 Hz, 4.2 Hz, 2.9 Hz, 1H); 7.48–7.60 (m, 5H); 7.71 (t, J = 7.4 Hz, 1H); 7.81–7.87 (m, 3H); 7.95–8.03 (m, 3H). ¹³C NMR (CDCl₃): δ 71.3 (dd, J = 26.4 Hz, 19.7 Hz); 120.3 (dd, J = 298.9 Hz, 289.1 Hz); 124.9; 126.3; 126.7; 127.6; 128.0; 128.18; 128.21; 129.3; 130.6; 131.0; 132.6; 132.8; 133.7; 135.5. ¹⁹F NMR (CDCl₃): δ –104.0 (d, J = 238.6 Hz, 1F); –119.2 (dd, J = 241.8 Hz, 21.6 Hz, 1F). MS (EI, *m/z*): 348 (M⁺), 157, 129, 77.

α-[(Benzenesulfonyl)difluoromethyl]-9-anthracenemethanol (**3g**): 82% yield, yellow solid. ¹H NMR (CDCl₃): δ 3.63 (d, *J* = 4.2 Hz, 1H); 7.33 (dd, *J* = 26.9 Hz, 4.2 Hz, 1H); 7.42-7.66 (m, 6H); 7.76 (t, *J* = 7.5 Hz, 1H); 8.01 (dd, *J* = 14.2 Hz, 8.5 Hz, 2H); 8.10 (d, *J* = 7.8 Hz, 2H); 8.21 (d, *J* = 8.9 Hz, 1H); 8.52 (s, 1H); 9.02 (d, *J* = 9 Hz, 1H). ¹³C NMR (CDCl₃): δ 67.8 (dd, *J* = 28.4 Hz, 20.0 Hz); 121.5 (dd, *J* = 305.3 Hz, 289.3 Hz); 122.6; 123.8; 124.8; 125.0; 126.0; 127.3; 128.9; 129.4; 130.67; 130.75; 132.3; 135.7. ¹⁹F NMR (CDCl₃): δ -101.9 (d, *J* = 237.3 Hz, 1F); -113.6 (ddd, *J* = 236.8 Hz, 26.8 Hz, 3.9 Hz, 1F). MS (EI, *m*/*z*): 398 (M⁺), 207, 179, 178, 77.

α-[(Benzenesulfonyl)difluoromethyl]-10-chloro-9anthracenemethanol (**3h**): 57% yield, yellow solid. ¹H NMR (CDCl₃): δ 3.69 (d, J = 4.4 Hz, 1H); 7.35 (dd, J = 26.6 Hz, 4.3 Hz, 1H); 7.49-7.71 (m, 6H); 7.77 (t, J = 7.5 Hz, 1H); 8.09 (d, J = 7.9 Hz, 2H); 8.24 (d, J = 8.2 Hz, 1H); 8.61 (dd, J = 18.1 Hz, 8.6 Hz, 2H); 9.07 (d, 8.2 Hz, 1H). ¹³C NMR (CDCl₃): δ 67.7 (dd, J = 27.9 Hz, 19.6 Hz); 121.3 (dd, J = 305.2 Hz, 289.7 Hz); 122.9; 123.7; 125.2; 126.0; 126.2; 126.5; 127.5; 129.4; 130.8; 132.0; 132.7; 135.8. ¹⁹F NMR (CDCl₃): δ -101.8 (d, J = 237.8 Hz, 1F); -113.3 (ddd, J = 237.3 Hz, 27.1 Hz, 3.6 Hz, 1F). MS (EI, *m/z*): 432 (M⁺), 243, 241, 240, 212, 178, 176, 77.

α-[(Benzenesulfonyl)difluoromethyl]-1-Pyrenemethanol (**3i**): 80% yield, yellow solid. ¹H NMR (CD₃COCD₃): δ 6.18 (d, J = 6.2 Hz 1H); 6.80 (ddd, J = 21.7 Hz, 5.9 Hz, 3.4 Hz, 1H); 7.71 (t, J = 8.0 Hz, 2H); 7.84 (t, J = 7.6 Hz, 1H); 8.01– 8.33 (m, 9H); 8.40 (t, J = 8.8 Hz, 2H). ¹³C NMR (CD₃COCD₃): δ 67.9 (dd, J = 27.9 Hz, 19.6 Hz); 122.8 (dd, J = 299.2 Hz, 286.6 Hz); 123.5; 125.1; 125.2; 125.6; 126.3; 126.6; 127.1; 127.3; 128.2; 128.9; 129.0; 130.00; 130.05; 130.2; 131.3; 131.4; 132.1; 132.6; 135.4; 136.2. ¹⁹F NMR (CD₃COCD₃): δ –102.7 (d, J = 239.1 Hz, 1F) –116.6 (dd, J = 239.7 Hz, 21.3 Hz, 1F). MS (EI, m/z): 422 (M⁺), 231, 203, 202, 77.

4.3. Typical procedure for reductive desulfonylation

In a 50-mL Schlenk flask with Argon protection, 2benzenesulfonyl-2, 2-difluoro-1-phenylethanol (3a)(150 mg, 0.5 mmol) and Na₂HPO₄ (497 mg, 3.5 mmol) in 10 mL anhydrous methanol were added in. After the solution was cooled to -20 °C, Na/Hg amalgam (10 wt.% Na in Hg, 805 mg, 3.5 mmol) was added. The reaction mixture was stirred at -20 to 0 °C for 1.5 h. Then the solution was diluted with Et₂O and the liquid was decanted from the solid. After removing the solvent of the liquid phase by rotate evaporator, 30 mL saturated NaCl solution was added, which was then extracted by Et₂O three times. The combined ether solution was dried with MgSO₄ and the solvent was removed to give pure product 2,2-difluoro-1phenylethanol (4a) (62 mg, 79% yield) as a white solid. ¹H NMR (CDCl₃): δ 2.44 (b, 1H); 4.82 (td, J = 10.5 Hz, 4.8 Hz, 1H); 5.77 (td, J = 56.4 Hz, 4.8 Hz, 1H); 7.41 (m, 5H). ¹³C NMR (CDCl₃): δ 73.6 (t, J = 20.0 Hz); 115.8 (t, J = 245.9 Hz; 127.1; 128.6; 129.0; 135.8 (t, J = 3.7 Hz). ¹⁹F NMR (CDCl₃): δ -127.8 (ddd, 284.8 Hz, 56.5 Hz, 9.9 Hz, 1F); -128.3 (ddd, 284.8 Hz, 56.5 Hz, 11 Hz, 1F). MS (EI, *m/z*): 158 (M⁺), 107, 79, 77. The data are consistent with the previous report [13].

1-Benzenesulfonyl-1,1-difluoro-3-buten-2-ol (**4b**): 84% yield, colorless liquid. ¹H NMR (CDCl₃): δ 2.71 (b, 1H); 4.42 (m, 1H); 5.69 (td, *J* = 56 Hz, 4.6 Hz, 1H); 6.18 (dd, *J* = 16 Hz, 6.4 Hz, 1H); 6.76 (d, *J* = 16 Hz, 1H); 7.24-7.41 (m, 5H). ¹³C NMR (CDCl₃): δ 72.1 (t, *J* = 24.5 Hz); 115.4 (t, *J* = 245 Hz); 122.4 (t, *J* = 4 Hz); 126.7; 128.4; 128.6; 134.8; 135.7. ¹⁹F NMR (CDCl₃): δ -128.7 (ddd, *J* = 285 Hz, 56 Hz, 11 Hz, 1F); -129.6 (ddd, *J* = 285 Hz, 56 Hz, 10 Hz, 1F). MS (EI, *m/z*): 184 (M⁺), 133, 115, 77. The data are consistent with the previous report [14].

1,1-Difluoro-4-phenyl-2-butanol (**4c**): 86% yield, color-less liquid. ¹H NMR (CDCl₃): δ 1.85 (m, 1H); 1.92 (m, 1H); 2.13 (b, 1H); 2.75 (m, 1H); 2.91 (m, 1H); 3.74 (m, 1H); 5.63 (td, *J* = 56 Hz, 4.2 Hz, 1H); 7.20–7.35 (m, 5H). ¹³C NMR (CDCl₃): δ 30.9; 31.5 (t, *J* = 3.3 Hz); 70.2 (t, *J* = 23.5 Hz);

116.3 (t, J = 244 Hz); 126.2; 128.4; 128.5; 140.9. ¹⁹F NMR (CDCl₃): δ -130.0 (dd, J = 56 Hz, 11 Hz). MS (EI, m/z): 186 (M⁺), 168, 117, 91, 77. The data are consistent with the previous report [13].

4.4. Typical procedure for Julia olefination of 3

A solution of 3a (150 mg, 0.5 mmol) and 4-N,Ndimethylaminopyridine (DMAP) (catalytic amount) in 5 mL CH₂Cl₂ under Ar was cooled to 0 °C and treated with Et₃N (0.28 mL, 2 mmol). After stirring for 20 min, methanesulfonyl chloride (0.08 mL, 1 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched by buffer solution and extracted with EtOAc (3×25 mL). The combined organic solution was washed by brine $(2 \times 25 \text{ mL})$ and dried over MgSO₄. After removing the solvent, the crude product was purified by column chromatography (9:1 hexane: EtOAc) to give mesylate **5a** 169 mg, 90% yield. ¹H NMR (CDCl₃): δ 3.06 (s, 3H); 6.26 (dd, J = 16.5 Hz, 6.7 Hz, 1H); 7.44 (m, 3H),7.53 (d, J = 7.8 Hz, 2H); 7.61 (t, J = 7.2 Hz, 2H); 7.76 (t, J = 7.7 Hz, 1H); 7.97 (d, J = 8.2 Hz, 2H). ¹⁹F NMR (CDCl₃): δ -105.5 (dd, J = 243.0 Hz, 6.7 Hz, 1F); -113.2 (dd, J = 243.9 Hz, 16.5 Hz, 1F). MS (EI, m/z): 376.1 (M⁺), 185, 140, 107, 77. The mesylate 5a (100 mg, 0.27 mmol) in anhydrous MeOH (5 mL) was cooled to -40 °C and treated with Na_2HPO_4 (151 mg, 1.06 mmol) and 10% Na(Hg)(368 mg, 1.60 mmol). After stiring for 1 h at -20 °C, the reaction mixture was diluted with 30 mL EtOAc and decanted from the solid Hg residue. The organic solution was washed by brine 30 mL and the brine was extracted with EtOAc $(3 \times 25 \text{ mL})$. The combined organic solution was dried over MgSO₄, condensed by reduced pressure and purified by column chromatography (20:1 hexane: EtOAc) to give 2,2difluoroethenylbenzene (6a) 22 mg, 60% yield as colorless liquid. ¹⁹F NMR (CDCl₃): δ –82.9 (dd, J = 33.6 Hz, 27.4 Hz, 1F), -84.8 (d, J = 31.7 Hz, 1F). The characterization data is consistent with that early reported [15].

Mesylate (**5c**): 87% yield, white solid. ¹H NMR (CDCl₃): δ 3.20 (s, 3H); 5.46 (m, 1H); 7.29 (m, 3H); 7.37 (t, *J* = 6.9 Hz, 2H); 7.68 (t, *J* = 7.4 Hz, 2H); 7.85 (t, *J* = 7.9 Hz, 1H); 8.01 (d, *J* = 8.4 Hz, 2H). ¹³C NMR (CDCl₃): δ 30.7; 31.1; 39.1; 76.2 (dd, *J* = 26.0 Hz, 20.4 Hz); 119.5 (dd, *J* = 286.0 Hz, 283.2 Hz); 126.4; 128.5; 128.6; 129.5; 130.7; 132.2; 135.9; 139.6. ¹⁹F NMR (CDCl₃): δ –107.2 (d, *J* = 242.9 Hz, 1F); –110.0 (d, *J* = 245.0 Hz, 1F).

Mesylate (**5e**): 86% yield, light yellow solid. ¹H NMR (CDCl₃): δ 3.14 (s, 3H); 6.22 (dd, J = .7 Hz, 6.8 Hz, 1H); 7.41 (d, J = 8.3 Hz, 2H); 7.57 (dd, J = 8.7 Hz, 2H); 7.62 (t, J = 7.9 Hz, 2H); 7.78 (t, J = 7.5 Hz, 1H); 7.96 (d, J = 7.4 Hz, 2H). ¹⁹F NMR (CDCl₃): δ -105.6 (d, J = 243.1 Hz, 1F); -113.3 (d, J = 249.9 Hz, 1F).

(4,4-Difluoro-3-butenyl)-benzene (6c): 84% yield, colorless liquid. ¹⁹F NMR (CDCl₃): δ –89.6 (d, *J* = 49 Hz, 1F); -91.6 (dd, *J* = 49 Hz, 28 Hz, 1F). The characterization data is consistent with an early report [16]. *1-Bromo-4-(2,2-difluoroethenyl)-benzene* (**6e**): 70% yield, colorless liquid. ¹⁹F NMR (CDCl₃): δ -81.7 (dd, J = 30.1 Hz, 26.2 Hz, 1F); -83.6 (d, J = 30.1 Hz, 1F). The characterization data is consistent with an early report [17].

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