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Short Communication

A one-step synthesis of *gem*-difluoroolefins from alcohols

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ABSTRACT

The development of efficient protocols for the synthesis of *gem*-difluoroolefins has received increasing attention. Given the ubiquity of hydroxyl group in biologically active molecules and synthetic intermediates, we developed a one-step protocol for the conversions of alcohols into *gem*-difluoroolefins. The reactions of alcohols with $Ph_3P^+CF_2CO_2^-$/Burgess reagent in DMSO occurred smoothly to afford the final products in moderate to high yields. DMSO is not only necessary for the oxidation process, but also important for the stabilization of phosphonium ylide by trapping difluorocarbene.

1. Introduction

As fluorine element possesses many special properties, such as high electronegativity, small atomic radius, and low polarizability, the incorporation of fluorine atoms into organic molecules may significantly change their physicochemical properties [1]. For example, the presence of fluorine atoms in pharmaceuticals can increase their metabolic stability and enhance lipophilicity [2,3]. Many fluorinated groups have been identified as isosteres of various functional groups and thus have been usually incorporated into pharmaceuticals [4–6]. *gem*-Difluoroolefinic moiety has proved to be an isostere of carbonyl group [4,7], and it serves as an important motif in a phase II drug candidate, Seletracetam [8]. Furthermore, *gem*-difluoroolefins have been widely used as versatile intermediates for the preparations of fluorinated compounds [9,10]. Therefore, significant efforts have been directed towards the development of efficient methods for the synthesis of *gem*-difluoroolefins.

Some synthetic strategies have been well established, including coupling of difluorocarbene with other carbenes generated from diazo compounds (Scheme 1, eq 1), defluorination of trifluoromethyl alkenes via an S_N2' type displacement (eq 2), the incorporation of a *gem*-difluoroolefinic moiety by using a *gem*-difluoroolefin building block (eq 3), and *gem*-difluoroolefination of carbonyls (eq 4) [11,12]. Although the coupling with difluorocarbene can efficiently construct the C═CF_2 bond, the use of potentially explosive diazo compounds is required (eq 1) [13–15]. S_N2' displacement of trifluoromethyl alkenes can be used to synthesize various functionalized *gem*-difluoroolefins, but suffers from the tedious synthesis of CF_3-alkenes (eq 2) [16–18]. *gem*-Difluoroolefin building blocks may be used for coupling or nucleophilic reactions, but the need for the synthesis of the building blocks may limit the wide applications of this strategy [12,19]. *gem*-Difluoroolefination of carbonyls, including Wittig reaction [20–22], Julia Reaction [23] or Julia-Kocienski reaction [24–26], and Horner–Wadsworth–Emmons reaction [27], is an attractive and straightforward strategy. Apparently, it is also desirable to install the *gem*-difluoroolefinic moiety from other functional groups which are commonly found in natural products or widely used in organic synthesis.

The hydroxyl group is commonly found in natural products, biologically active molecules, and synthetic intermediates. Given the ubiquity of hydroxyl group, dehydroxylative functionalization of alcohols has received increasing attention. We have been interested in both the dehydroxylation of alcohols [28–31] and the efficient synthesis of *gem*-difluoroolefins [15,22,25]. In continuation of our research interest, herein we describe a one-step synthesis of *gem*-difluoroolefins from alcohols by using $Ph_3P^+CF_2CO_2^-$ (PDFA), a reagent developed by us recently [32], as a phosphonium ylide precursor.

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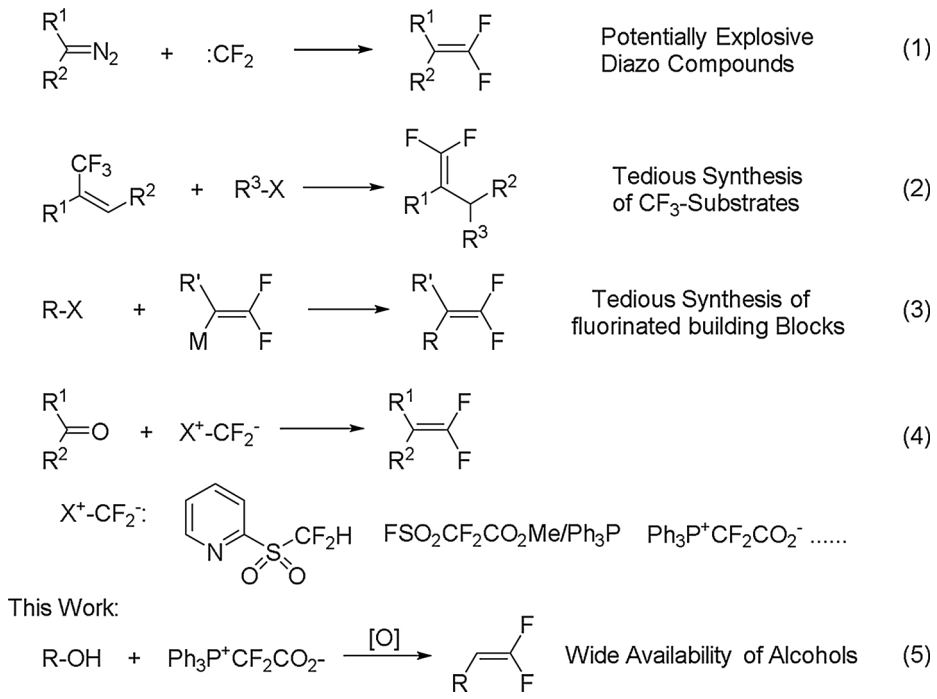
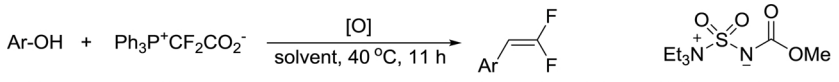


Scheme 1. The Synthesis of *gem*-Difluoroolefins.

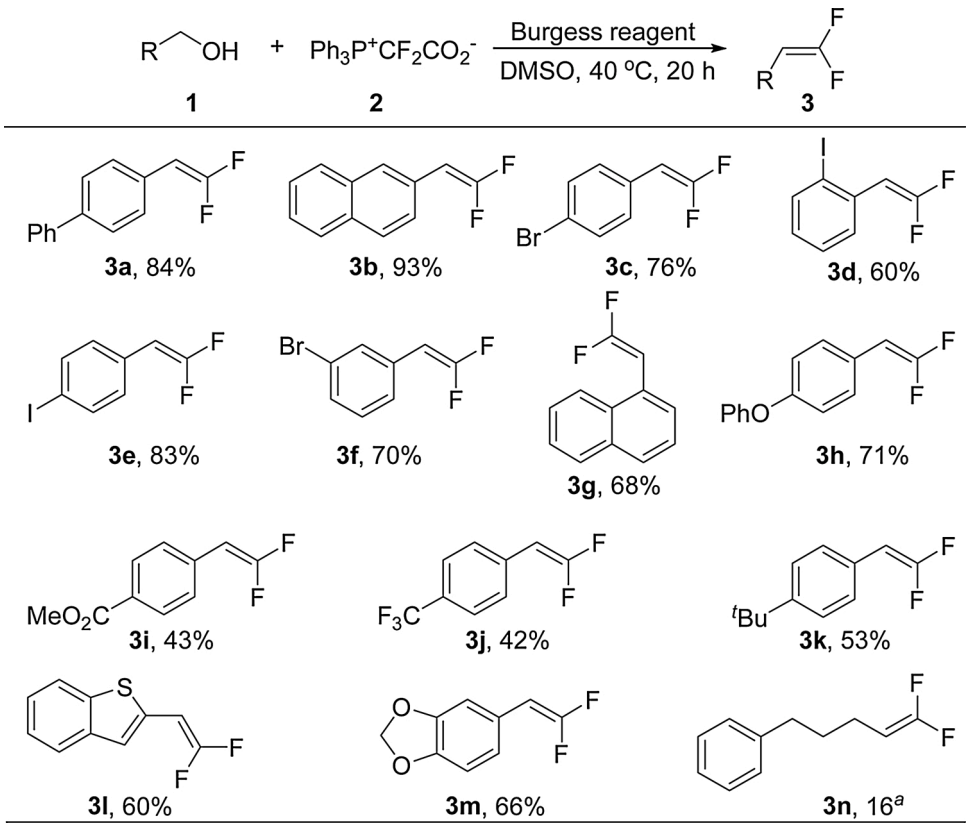
Table 1
The optimization of reaction conditions.[a]



1a **2** **3a** (Ar = 4-PhC_6H_4) **4** (Burgess Reagent)

entry	molar ratio[b]	[O]	solvent	yield (%)[c]
1[d]	1:1.5:1.3	$PhI(OCOCF_3)_2$	DMSO	4
2[d]	1:1.5:1.3	$PhI(OAc)_2$	DMSO	3
3[d]	1:1.5:1.3	Dess Martin reagent	DMSO	8
4[d]	1:1.5:1.3	$K_2Cr_2O_7$	DMSO	ND
5[d]	1:1.5:1.3	^tBuOOH	DMSO	ND
6[d]	1:1.5:1.3	$K_2S_2O_8$	DMSO	ND
7[d]	1:1.5:1.3	$KMnO_4$	DMSO	ND
8[d]	1:1.5:1.3	**4**	DMSO	14
9[e]	1:1.5:1.3	**4**	DMSO	20
10	1:1.5:1.3	**4**	DMSO	35
11[f]	1:1.5:1.3	**4**	DMSO	32
12	1:1.5:1.3	**4**	DMF	ND
13	1:1.5:1.3	**4**	DMAc	ND
14	1:1.5:1.3	**4**	NMP	ND
15	1:1.5:1.3	**4**	THF	ND
16	1:1.5:1.3	**4**	*p*-xylene	ND
17	1:1.5:2	**4**	DMSO	29
18	1:2:1.3	**4**	DMSO	46
19	1:3:1.3	**4**	DMSO	67
20[i]	1:3:1.3	**4**	DMSO	92
21[i,j]	1:3:1.3	**4**	DMSO	92

[a] Reaction conditions: **1a** (0.2 mmol), **2** and [O] in solvent (1 mL) at 40 °C for 11 h under a N_2 atmosphere.
[b] Molar ratio of **1a**:**2**:[O].
[c] The yields were determined by ^{19}F NMR spectroscopy.
[d] The reaction temperature was 80 °C.
[e] The reaction temperature was 60 °C.
[f] The reaction temperature was 30 °C.
[i] The reaction time was 20 h.
[j] The reaction conditions: **1a** (0.8 mmol), **2** (2.4 mmol) and Burgess reagent (1.04 mmol) in DMSO (4 mL) at 40 °C for 20 h under a N_2 atmosphere.



Scheme 2. The one-step synthesis of *gem*-difluoroolefins from alcohols. Reaction conditions: **1** (0.8 mmol), **2** (2.4 mmol) and Burgess reagent (1.04 mmol) in DMSO (4 mL) at 40 °C for 20 h under a N_2 atmosphere. Isolated yields are shown. [a]The yield was determined by ^{19}F NMR spectroscopy.

2. Results and discussion

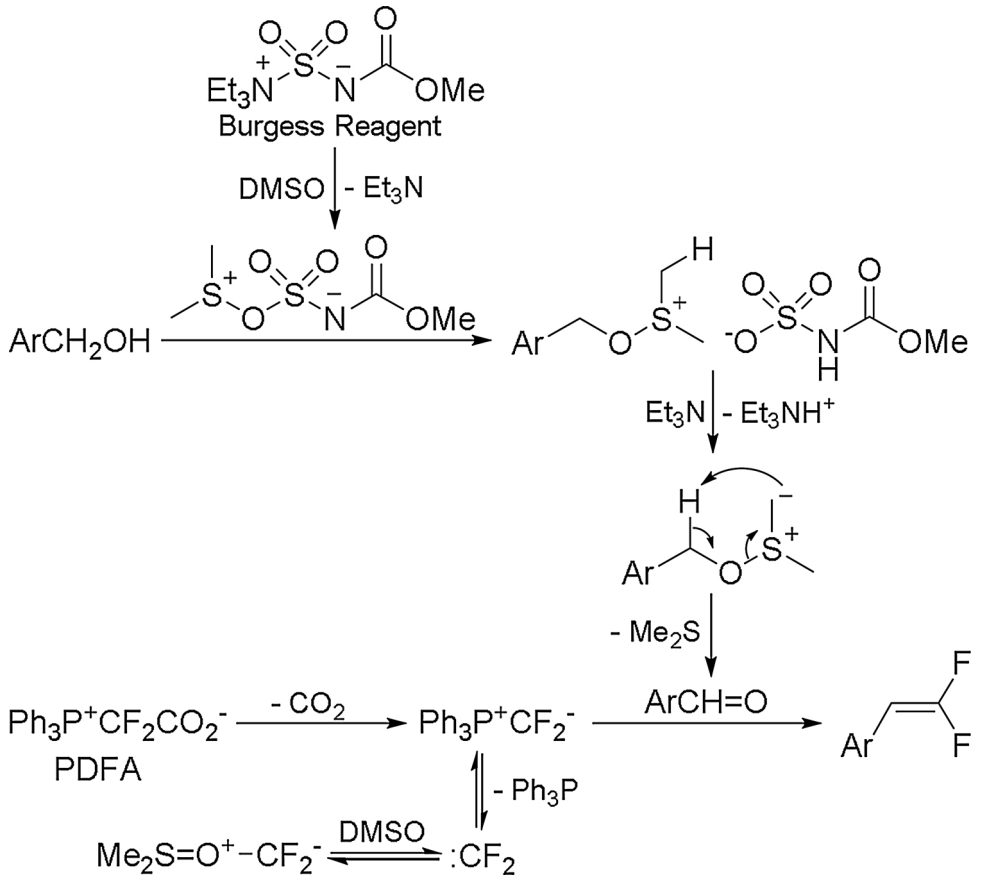
Since aldehydes can undergo a Wittig reaction smoothly with PDFA [22], the presence of an oxidant in a PDFA/alcohol system may lead to the conversion of the alcohol into a *gem*-difluoroolefin via the oxidation of the alcohol to an aldehyde followed by a Wittig reaction. Therefore, a variety of oxidants were screened for the conversion of alcohol **1a** into *gem*-difluoroolefin **3a** (Table 1). Most oxidants were not effective at all for this transformation (entries 1–8). Burgess reagent has found widespread applications in organic synthesis [33], and it has been reported that it can easily oxidize alcohols in DMSO [34]. To our delight, a 14 % yield was obtained by using Burgess reagent as the oxidant (entry 8). The yield was increased slightly with lowering the reaction temperature (entries 9–10), and a reaction temperature of 40 °C gave the desired product in 35 % yield (entry 10). A brief survey of reaction solvents revealed that DMSO was a better choice (entry 10 vs entries 12–16). Increasing the loading of Burgess reagent did not increase the yield (entry 17). The yield was significantly increased by increasing the loading of PDFA (entries 18–19). A 92 % yield was obtained by prolonging the reaction time to 20 h (entry 20). Increasing the reaction scale to 0.8 mmol did not lead to a decrease in the yield (entry 21).

With the optimal reaction conditions in hand (Table 1, entry 21), we then investigated the substrate scope of the one-step conversion of alcohols into *gem*-difluoroolefins. As shown in Scheme 2, electron-rich and -neutral benzyl alcohols could be smoothly converted into the desired products in moderate to high yields. In the case of the electron-deficient benzyl alcohols, low yields were obtained (**3i-3j**). The electron-withdrawing substituents may increase the electrophilicity of the CH = CF_2 moiety, and thus the desired *gem*-difluoroolefins may be further attacked by nucleophiles in the reaction system to give complex side products, resulting in the low yields. The compatibility of this method with halide groups (**3d-3f**) may allow for further coupling reactions. Heteroaryl alcohols also showed a good reactivity (3l). For the conversions of alkyl alcohols, these reaction conditions only gave low yields (**3n**).

As shown in Table 1, many reaction solvents were examined, but the reaction occurred only in DMSO. DMSO is necessary for the oxidation of alcohols with Burgess reagent, a process which has been reported before (Scheme 3) [34]. We believe that DMSO is also quite important for the stabilization of phosphonium ylide ($Ph_3P^+CF_2^-$). Decarboxylation of PDFA can occur under warming conditions to generate the phosphonium ylide, and there is an equilibrium between this ylide and difluorocarbene due to the weak strength of the P-CF_2 bond [35]. Difluorocarbene is a highly reactive species and thus side reactions may readily take place, which would lead to the consumption of phosphonium ylide. However, DMSO, the reaction solvent, may easily trap difluorocarbene to form an oxonium ylide, $Me_2S = O^+CF_2^-$ [36]. The formation of the oxonium ylide can stabilize difluorocarbene via the equilibrium between this ylide and difluorocarbene. If difluorocarbene is stabilized, the capture of difluorocarbene by Ph_3P could regenerate phosphonium ylide. Therefore, the reaction solvent DMSO plays an important role in the stabilization of phosphonium ylide.

3. Conclusions

In summary, we have described a one-step synthesis of *gem*-difluoroolefins from alcohols by using PDFA as a phosphonium ylide reagent. The reactions proceeded smoothly via the oxidation of alcohols with Burgess reagent to give aldehydes and the subsequent Wittig reaction of aldehydes with PDFA. The reaction solvent, DMSO, is not only necessary for the oxidation process, but also important for the stabilization of the phosphonium ylide. The convenient transformation may find utility in the structural modifications of biologically active molecules.



Scheme 3. A plausible reaction mechanism.

4. Experimental section

4.1. General remarks

^{1}H, ^{13}C and ^{19}F NMR spectra were detected on a 400 MHz or 300 MHz NMR spectrometer. Data for ^{1}H NMR, ^{13}C NMR and ^{19}F NMR were recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, coupling constant (s) in Hz). Chemical shifts of ^{1}H NMR spectra are reported in ppm relative to TMS (0 ppm), chemical shifts of ^{19}F NMR spectra are reported in ppm relative to $CFCl_3$ as the external standard (0 ppm), and chemical shifts of ^{13}C NMR spectra are reported in ppm relative to $CDCl_3$ (−77.0 ppm) as the reference.

4.2. General procedure for the one-step process

Into a 10 mL sealed tube were added alcohol **1** (0.8 mmol), $Ph_3P^+CF_2CO_2^-$ (855.2 mg, 2.4 mmol), Burgess reagent (1.04 mmol) and anhydrous DMSO (4 mL) under a N_2 atmosphere. The tube was sealed and the resulting mixture was stirred at 40 °C for 20 h. After being cooled to room temperature, the mixture was filtered through a plug of Celite, and the solid was washed with DCM. The combined organic phase was washed with brine (10 mL × 3) and water (10 mL × 3) and dried with Na_2SO_4. The solvent was removed by concentration under vacuum, and the residue was subjected to flash column chromatography to give the final product.

4.3. Characterization of the products

4-(2,2-Difluorovinyl)-1,1′-biphenyl (**3a**) [22], 84 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.67 (m, 4 H), 7.60 – 7.45 (m, 5 H), 5.42 (dd, J = 26.4, 3.8 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -81.81 (dd, J = 30.7, 26.4 Hz, 1 F), -83.71 (dd, J = 30.7, 3.7 Hz, 1 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5 (dd, J = 298.6, 288.5 Hz), 140.6 (s), 139.9 (t, J =2.4 Hz), 129.5 (t, J =6.4 Hz), 128.9 (s), 128.1 (dd, J = 6.4, 3.6 Hz), 127.54 (s), 127.50 (s), 127.1 (s), 82.1(dd, J = 29.2, 13.5 Hz).

2-(2,2-Difluorovinyl)naphthalene (**3b**) [35], 93 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86−7.83 (m, 3 H), 7.79 (s, 1 H), 7.58 – 7.47 (m, 3 H), 5.47 (dd, J = 26.3, 3.9 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -81.89 (dd, J = 30.8, 26.3 Hz, 1 F), -83.60 (dd, J = 30.8, 3.8 Hz, 1 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (dd, J = 298.7, 288.5 Hz), 133.5 (s), 132.4 (t, J =1.5 Hz), 128.5 (s), 127.9 (t, J =6.4 Hz), 127.89 (s), 127.7 (s), 126.8 (dd, J = 6.3, 5.0 Hz), 126.5 (s), 126.2 (s), 125.4 (dd, J = 6.7, 2.4 Hz), 82.6 (dd, J = 29.3, 13.3 Hz).

1-Bromo-4-(2,2-difluorovinyl)benzene (**3c**) [35], 76 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J =8.5 Hz, 2 H), 7.19 (d, J =8.5 Hz, 2 H), 5.23 (dd, J = 25.9, 3.6 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -81.31 (dd, J = 29.1, 26.1 Hz, 1 F), -83.14 (dd, J = 29.2, 3.4 Hz, 1 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5 (dd, J = 298.7, 289.2 Hz), 132.0 (s), 129.4 (dd, J = 7.0, 5.9 Hz), 129.3 (dd, J = 6.5, 3.6 Hz), 121.0 (t, J =2.6 Hz), 81.7 (dd, J = 29.9, 13.6 Hz).

1-(2,2-Difluorovinyl)-2-iodobenzene (**3d**) [37], 60 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J =7.8 Hz, 1 H), 7.48 (d, J =7.8 Hz, 1 H), 7.34 (t, J =7.6 Hz, 1 H), 6.95 (t, J =7.6 Hz, 1 H), 5.58 (dd, J = 25.0, 3.6 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -82.34 (dd, J = 25.8, 3.5 Hz, 1 F), -83.90 (t, J =25.8 Hz, 1 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.8 (dd, J = 298.7, 288.9 Hz), 139.6 (s), 134.0 (dd, J = 7.9, 6.0 Hz), 128.9 (s), 128.8 (d, J =1.3 Hz), 128.5 (s), 99.7 (dd, J = 5.7, 1.9 Hz), 86.5 (dd, J = 32.1, 12.6 Hz).

1-(2,2-Difluorovinyl)-4-iodobenzene (**3e**) [38], 83 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J =8.4 Hz, 1 H), 7.07 (d, J =8.4 Hz, 1 H), 5.21 (dd, J = 26.0, 3.6 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.81 (t, J

=27.3 Hz, 1 F), -82.73 (dd, J = 28.5, 3.4 Hz, 1 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5 (dd, J = 298.9, 289.4 Hz), 137.9 (s), 130.0 (dd, J = 6.9, 6.1 Hz), 129.4 (dd, J = 6.4, 3.6 Hz), 92.3 (t, J =2.7 Hz), 81.8 (dd, J = 29.8, 13.5 Hz).

1-Bromo-3-(2,2-difluorovinyl)benzene (**3f**) [35], 70 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1 H), 7.36 (d, J =7.7 Hz, 1 H), 7.25−7.16 (m, 2 H), 5.21 (dd, J = 25.8, 3.5 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.55 (t, J =27.1 Hz, 1 F), -82.49 (dd, J = 27.5, 3.5 Hz, 1 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (dd, J = 300.4, 290.3 Hz), 132.6 (t, J =6.9 Hz), 130.6 (dd, J = 6.7, 3.6 Hz), 130.3 (s), 130.2 (s), 126.3 (dd, J = 6.4, 3.4 Hz), 122.9 (s), 81.5 (dd, J = 30.0, 13.4 Hz).

1-(2,2-Difluorovinyl)naphthalene (**3g**) [15], 68 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J =7.7 Hz, 1 H), 7.90 (d, J =7.3 Hz, 1 H), 7.83 (d, J =8.1 Hz, 1 H), 7.63 (d, J =6.7 Hz, 1 H), 7.60 – 7.47 (m, 3 H), 5.91 (d, J =24.4 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -83.23 (dd, J = 29.3, 2.8 Hz, 1 F), -85.04 (dd, J = 29.0, 24.7 Hz, 1 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.8 (dd, J = 296.1, 288.1 Hz), 133.8 (s), 131.6 (d, J =3.6 Hz), 128.8 (s), 128.1 (s), 126.6 (dd, J = 6.6, 1.6 Hz), 126.5 (s), 126.1 (s), 125.6 (s), 123.9 (s), 78.8 (dd, J = 29.1, 15.7 Hz).

1-(2,2-Difluorovinyl)-4-phenoxybenzene (**3h**) [39], 71 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.30 (m, 4 H), 7.16 (t, J =7.2 Hz, 1 H), 7.10 – 6.96 (m, 4 H), 5.28 (dd, J = 26.2, 3.8 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -83.58 (dd, J = 34.0, 26.3 Hz, 1 F), -85.26 (dd, J = 34.0, 3.7 Hz, 1 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1 (s), 156.4 (t, J =2.3 Hz), 156.2 (dd, J = 297.2, 287.5 Hz), 129.9 (s), 129.1 (dd, J = 6.4, 3.5 Hz), 125.4 (dd, J = 6.7, 6.0 Hz), 123.6 (s), 119.2 (s), 119.1 (s), 81.6 (dd, J = 29.4, 14.0 Hz).

Methyl 4-(2,2-difluorovinyl)benzoate (**3i**) [37], 43 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J =8.4 Hz, 2 H), 7.39 (d, J =8.3 Hz, 2 H), 5.33 (dd, J = 26.0, 3.6 Hz, 1 H), 3.91 (s, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -79.22 (dd, J = 25.8, 24.0 Hz, 1 F), -81.15 (dd, J = 23.9, 3.6 Hz, 1 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8 (s), 156.9 (dd, J = 300.5, 290.8 Hz), 135.3 (dd, J = 7.8, 6.4 Hz), 130.1 (s), 128.7 (t, J =2.3 Hz), 127.6 (dd, J = 6.7, 3.6 Hz), 82.2 (dd, J = 29.8, 13.1 Hz), 52.3 (s).

1-(2,2-Difluorovinyl)-4-(trifluoromethyl)benzene (**3j**) [38], 42 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J =8.3 Hz, 2 H), 7.44 (d, J =8.2 Hz, 2 H), 5.34 (dd, J = 25.9, 3.4 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.70 (s, 3F), -79.65 (t, J =25.2 Hz, 1F), -81.31 (dd, J = 24.7, 3.4 Hz, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.0 (dd, J = 299.9, 290.7 Hz), 134.3 (t, J =7.2 Hz), 129.2 (q, J =33.5 Hz), 127.9 (dd, J = 6.5, 3.6 Hz), 125.8 (q, J =3.7 Hz), 124.2 (q, J =271.8 Hz), 81.8 (dd, J = 30.1, 13.4 Hz).

1-(*tert*-Butyl)-4-(2,2-difluorovinyl)benzene (**3k**) [24], 53 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J =8.9 Hz, 2 H), 7.31 (d, J =8.3 Hz, 2 H), 5.29 (dd, J = 26.5, 3.8 Hz, 1 H), 1.37 (d, J =2.0 Hz, 9 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -83.09 (dd, J = 33.3, 26.5 Hz, 1 F), -85.09 (dd, J = 33.3, 3.7 Hz, 1 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4 (dd, J = 297.7, 287.5 Hz), 150.2 (t, J =3.6 Hz), 127.6 (dd, J = 7.2, 5.9 Hz), 127.5 (dd, J = 6.1, 3.5 Hz), 125.8 (s), 82.0 (dd, J = 28.8, 13.8 Hz), 34.7 (s), 31.4 (s).

2-(2,2-Difluorovinyl)benzo[*b*]thiophene (3l) [25], 60 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J =7.8 Hz, 1 H), 7.71 (d, J =8.6 Hz, 1 H), 7.37 – 7.28 (m, 2 H), 7.20 (s, 1 H), 5.63 (dd, J = 25.6, 2.1 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -78.85 (dd, J = 25.5, 22.9 Hz, 1 F), -84.77 (dd, J = 22.9, 1.9 Hz, 1 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7 (dd, J = 299.3, 291.0 Hz), 139.69 (s), 139.67 (dd, J = 5.3, 2.1 Hz), 132.5 (t, J =7.2 Hz), 124.7 (s), 124.5 (s), 123.3 (s), 122.7 (dd, J = 7.2, 4.7 Hz), 122.1 (s), 78.5 (dd, J = 33.4, 16.5 Hz).

5-(2,2-Difluorovinyl)benzo[*d*][1,3]dioxole (**3m**) [24], 66 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 – 6.86 (m, 1 H), 6.80 – 6.73 (m, 2 H), 5.96 (s, 2 H), 5.20 (dd, J = 25.9, 3.9 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -83.88 (dd, J = 35.7, 25.9 Hz, 1 F), -86.09 (dd, J = 35.8, 3.9 Hz, 1 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0 (dd, J = 296.8, 286.9 Hz), 148.1 (s), 146.7 (t, J =2.2 Hz), 124.3 (t, J =6.3 Hz), 121.7 (dd, J = 5.3, 4.7 Hz), 108.6 (s), 107.8 (dd, J = 7.8, 2.8 Hz), 101.3 (s), 82.1 (dd, J = 29.9, 13.7 Hz).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jfluchem.2020.109649.

References

[1] P. Kirsch, Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications, 2nd ed., Wiley-VCH, Weinheim, Germany, 2013.
[2] J. Wang, M. Sánchez-Roselló, J.L. Aceña, C. del Pozo, A.E. Sorochinsky, S. Fustero, V.A. Soloshonok, H. Liu, Fluorine in pharmaceutical industry: fluorine-containing drugs introduced to the market in the last decade (2001–2011), Chem. Rev. 114 (2014) 2432–2506.
[3] Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J.L. Aceña, V.A. Soloshonok, K. Izawa, H. Liu, Next generation of fluorine-containing pharmaceuticals, compounds currently in phase II–III clinical trials of major pharmaceutical companies: new structural trends and therapeutic areas, Chem. Rev. 116 (2016) 422–518.
[4] N.A. Meanwell, Synopsis of some recent tactical application of bioisosteres in drug design, J. Med. Chem. 54 (2011) 2529–2591.
[5] E.P. Gillis, K.J. Eastman, M.D. Hill, D.J. Donnelly, N.A. Meanwell, Applications of fluorine in medicinal chemistry, J. Med. Chem. 58 (2015) 8315–8359.
[6] N.A. Meanwell, Fluorine and fluorinated motifs in the design and application of bioisosteres for drug design, J. Med. Chem. 61 (2018) 5822–5880.
[7] C. Leriche, X. He, C.-W.T. Chang, H.-W. Liu, Reversal of the apparent regiospecificity of NAD(P)H-Dependent hydride transfer: the properties of the difluoromethylene group, a carbonyl mimic, J. Am. Chem. Soc. 125 (2003) 6348–6349.
[8] J.R. Pollard, Seletracetam, a small molecule SV2A modulator for the treatment of epilepsy, Curr. Opin. Investig. Drugs 9 (2008) 101–107.
[9] G. Landelle, M. Bergeron, M.-O. Turcotte-Savard, J.-F. Paquin, Synthetic approaches to monofluoroalkenes, Chem. Soc. Rev. 40 (2011) 2867–2908.
[10] X. Lu, Y. Wang, B. Zhang, J.-J. Pi, X.-X. Wang, T.-J. Gong, B. Xiao, Y. Fu, Nickel-catalyzed defluorinative reductive cross-coupling of gem-difluoroalkenes with unactivated secondary and tertiary alkyl halides, J. Am. Chem. Soc. 139 (2017) 12632–12637.
[11] M.J. Tozer, T.F. Herpin, Methods for the synthesis of gem-difluoromethylene compounds, Tetrahedron 52 (1996) 8619–8683.
[12] J. Ichikawa, Gem-difluoroolefin synthesis: general methods via thermostable difluorovinylmetals starting from 2,2,2-trifluoroethanol derivatives, J. Fluorine Chem 105 (2000) 257–263.
[13] M. Hu, C. Ni, L. Li, Y. Han, J. Hu, gem-Difluoroolefination of Diazo compounds with $TMSCF_3$ or $TMSCF_2Br$: transition-metal-free cross-coupling of two carbene precursors, J. Am. Chem. Soc. 137 (2015) 14496–14501.
[14] Z. Zhang, W. Yu, C. Wu, C. Wang, Y. Zhang, J. Wang, Reaction of diazo compounds with difluorocarbene: an efficient approach towards 1,1-difluoroolefins, Angew. Chem. Int. Ed. 55 (2016) 273–277.
[15] J. Zheng, J.-H. Lin, L.-Y. Yu, Y. Wei, X. Zheng, J.-C. Xiao, Cross-coupling between difluorocarbene and carbene-derived intermediates generated from diazocompounds for the synthesis of gem-difluoroolefins, Org. Lett. 17 (2015) 6150–6153.
[16] S.B. Lang, R.J. Wiles, C.B. Kelly, G.A. Molander, Photoredox generation of carbon-centered radicals enables the construction of 1,1-difluoroalkene carbonyl mimics, Angew. Chem. Int. Ed. 56 (2017) 15073–15077.
[17] Z. Lin, Y. Lan, C. Wang, Reductive allylic defluorinative cross-coupling enabled by Ni/Ti cooperative catalysis, Org. Lett. 21 (2019) 8316–8322.

[18] F. Chen, Y. He, G. Huang, X. Xu, S. Zhu, NiH-catalyzed migratory defluorinative olefin cross-coupling: trifluoromethyl-substituted alkenes as acceptor olefins to form gem-difluoroalkenes, Angew. Chem. Int. Ed 59 (2020) 5398–5402.
[19] J.H. Jeon, J.H. Kim, Y.J. Jeong, I.H. Jeong, Preparation of 2,2-difluoro-1-trialkylsilylethenylstannanes and their cross-coupling reactions, Tetrahedron Lett. 55 (2014) 1292–1295.
[20] D. Burton, Z.-Y. Yang, W. Qiu, Fluorinated ylides and related compounds, Chem. Rev. 96 (1996) 1641–1716.
[21] C.S. Thomoson, H. Martinez, W.R. Dolbier Jr, The use of methyl 2,2-difluoro-2-(fluorosulfonyl)acetate as the difluorocarbene source to generate an in situ source of difluoromethylene triphenylphosphonium ylide, J. Fluorine Chem. 150 (2013) 53–59.
[22] J. Zheng, J. Cai, J.-H. Lin, Y. Guo, J.-C. Xiao, Synthesis and decarboxylative Wittig reaction of difluoromethylene phosphobetaine, Chem. Commun. 49 (2013) 7513–7515.
[23] J.S. Sabol, J.R. McCarthy, A new route to 1,1-difluoro olefins: application to the synthesis of 2'-deoxy-2'-difluoromethylene nucleosides, Tetrahedron Lett. 33 (1992) 3101–3104.
[24] Y. Zhao, W. Huang, L. Zhu, J. Hu, Difluoromethyl 2-pyridyl sulfone: a new gem-difluoroolefination reagent for aldehydes and ketones, Org. Lett. 12 (2010) 1444–1447.
[25] X.-P. Wang, J.-H. Lin, J.-C. Xiao, X. Zheng, Decarboxylative julia-kocienskigem-Difluoro-Olefination of 2-Pyridinyl sulfonyldifluoroacetate, Eur. J. Org. Chem. (2014) 928–932.
[26] B. Gao, Y. Zhao, M. Hu, C. Ni, J. Hu, Gem-difluoroolefination of diaryl ketones and enolizable aldehydes with difluoromethyl 2-pyridyl sulfone: new insights into the Julia-Kocienski reaction, Chem. Eur. J. 20 (2014) 7803–7810.
[27] S.R. Piettre, L. Cabanas, Reinvestigation of the Wadsworth-Emmons reaction involving lithium difluoromethylenephosphonate, Tetrahedron Lett. 37 (1996) 5881–5884.
[28] J. Chen, J.-H. Lin, J.-C. Xiao, Halogenation through deoxygenation of alcohols and aldehydes, Org. Lett. 20 (2018) 3061–3064.
[29] J. Chen, J.-H. Lin, J.-C. Xiao, Dehydroxylation of alcohols for nucleophilic substitution, Chem. Commun. 54 (2018) 7034–7037.
[30] W. Zhang, J. Chen, J.-H. Lin, J.-C. Xiao, Y.-C. Gu, Rapid dehydroxytrifluoromethoxylation of alcohols, iScience 5 (2018) 110–117.
[31] W. Zhang, J.-H. Lin, W. Wu, Y.-C. Cao, J.-C. Xiao, Dehydroxylative Trifluoromethylthiolation, Trifluoromethylation, and Difluoromethylation of Alcohols, Chin. J. Chem 38 (2020) 169–172.
[32] J.-H. Lin, J.-C. Xiao, Fluorinated Ylides/Carbenes and related intermediates from phosphonium/sulfonium salts, Acc. Chem. Res. (2020), https://doi.org/10.1021/acs.accounts.0c00244.
[33] M.M. Heravi, T. Ahmadi, A. Fazeli, N.M. Kalkhorani, Recent advances in the application of the burgess reagent in organic synthesis, Curr. Org. Synth. 12 (2015) 328–357.
[34] P.R. Sultane, C.W. Bielawski, Burgess reagent facilitated alcohol oxidations in DMSO, J. Org. Chem. 82 (2017) 1046–1052.
[35] J. Zheng, J.-H. Lin, J. Cai, J.-C. Xiao, Conversion between difluorocarbene and difluoromethylene ylide, Chem. Eur. J. 19 (2013) 15261–15266.
[36] J. Yu, J.-H. Lin, D. Yu, R. Du, J.-C. Xiao, Oxidation of difluorocarbene and subsequent trifluoromethoxylation, Nat. Commun. 10 (2019) 5362.
[37] L.-T. Yu, M.-L. Tang, C.-M. Si, Z. Meng, Y.-X. Liang, J.-L. Han, X. Sun, Zinc-mediated decarboxylative alkylation of gem-difluoroalkenes, Org. Lett. 20 (2018) 4579–4583.
[38] S. Krishnamoorthy, J. Kothandaraman, J. Saldana, G.K. Surya Prakash, Direct difluoromethylenation of carbonyl compounds by using $TMSCF_3$: the right conditions, Eur. J. Org. Chem. 4965 (2016) 4969.
[39] B. Zhang, X.-F. Zhang, J. Hao, C.-H. Yang, Palladium-catalyzed direct approach to α-Trifluoromethyl alcohols by selective hydroxylfluorination of *gem*-difluoroalkenes, Eur. J. Org. Chem. 5007 (2018) 5015.