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Chlorodifluoromethyl aryl ketones and sulfones as difluorocarbene reagents: The substituent effect

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ABSTRACT

We have investigated the different chlorodifluoromethyl aryl ketones **1a**–**1g** and sulfones **2a**–**2h** as difluorocarbene reagents for *O*- and *N*-difluoromethylations. It was found that the sulfone reagents **2** were generally more efficient in difluoromethylation than the ketone reagents **1**. Furthermore, while the different substituents on ketone reagents **1** did not show a remarkable impact on the difluoromethylation reaction, the substituent effect on the sulfone reagents **2** was much more significant. Finally, we found that *p*-chlorophenyl chlorodifluoromethyl sulfone **2d** and *p*-nitrophenyl chlorodifluoromethyl sulfone **2h** were among the most powerful difluorocarbene reagents in this category for *O*-difluoromethylations.

1. Introduction

Since the pioneering study by Hine et al. in the late 1950s [1], difluorocarbene (:CF_2) has become one of the most important fluorinated reactive intermediates in modern organic chemistry [2,3]. Owing to the interaction of the lone pairs of its fluorine substituents with the carbene center, difluorocarbene is a relatively stabilized carbene species (with a singlet ground state) and is therefore less reactive than other dihalocarbenes [3]. Over the past half century, it has been realized that the reactivity of difluorocarbene is significantly influenced by the way it is generated, and as a result, enormous efforts have been devoted to seek new methods and/or reagents for generation of reactive difluorocarbene species for practical organic synthesis [2,3]. One of the important synthetic applications of difluorocarbene species is the difluoromethylation of *O*-, *N*-, *S*-, *C*-, and *P*-nucleophiles, using $CHClF_2$, $ClCF_2CO_2Na$, $ClCF_2CO_2CH_3$, CF_2Br_2, CF_3CO_2Na, $FSO_2CF_2CO_2H$, CF_3ZnBr, and CHF_2I as difluorocarbene precursors [2–5]. The difluoromethyl group (CF_2H) has been proposed both as an isostere of OH (or CH_2OH) group [6] and as a more lipophilic hydrogen donor (than typical donors such as OH and NH), which makes it an interesting group with respect to the design of bioactive molecules [7]. In 2006, we reported that 2-chloro-2,2-difluoroacetophenone ($PhCOCF_2Cl$, **1a**) can be used as a non-ozone-depleting substance-based (non-ODS-based) difluorocarbene precursor for *O*-difluoromethylation of phenols [5]. Thereafter, we found that chlorodifluoromethyl phenyl sulfone ($PhSO_2CF_2Cl$, **2a**) can also serve as a more efficient non-ODS-based difluorocarbene reagent for *O*- and *N*-difluoromethylations [8]. The different reactivity between **1a** and **2a** as difluorocarbene precursors inspired us to investigate the relationship between the structure of difluorocarbene reagents [including chlorodifluoromethyl aryl ketones (**1**, $ArCOCF_2Cl$) and chlorodifluoromethyl aryl sulfones (**2**, $ArSO_2CF_2Cl$)] and their reactivity in *O*-difluoromethylations.

2. Results and discussion

A series of chlorodifluoromethyl aryl ketones **1a**–**1g** were prepared by using the previously known method [9]. Therefore, we carried out the *O*-difluoromethylation reactions by using biphenyl-4-ol (**3c**) as a model compound. The reaction condition of *O*-difluoromethylation was similar to our previous report [5]. Potassium hydroxide (25 wt% in H_2O) was used both as a base to deprotonate phenol (**3a**) and as an activating agent to react with **1** to generate difluorocarbene species. CH_3CN–H_2O (1:1, v/v) system was used as the mixed solvent for the reaction. As shown in Table 1 and Fig. 1, the reaction between **3c** and **1** gave product **4c** in 63–86% yields. By comparing the chemical yields of the reactions at different temperatures (50 °C and 80 °C), we found that the reaction temperature did not have a significant impact on the reaction (Fig. 1). We also compared the product yields of the reactions with different difluorocarbene reagents **1a**–**1g** under the same reaction condition, and found that reagents **1a**–**1g** bearing different substitution groups (R = H, Me, OMe, halo, CF_3, etc.) on the phenyl ring showed similar reactivity, as evidenced by the fact that

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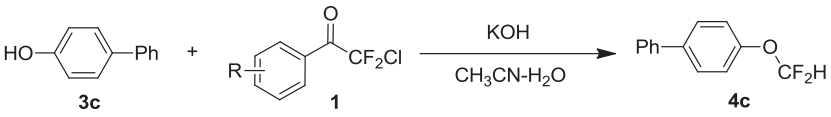
Table 1
Difluoromethylation with different reagents **1**.



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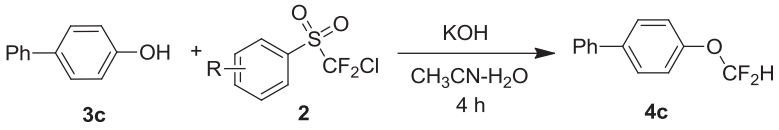
Entry[a]	Reagent	Temp. (°C)	Yield (%)[b]
1	R = H (**1a**)	50	64
2	R = H (**1a**)	80	66
3	R = *p*-Me (**1b**)	50	74
4	R = *p*-Me (**1b**)	80	71
5	R = *o*-Me (**1c**)	50	68
6	R = *o*-Cl (**1d**)	80	78
7	R = *p*-Cl (**1d**)	50	76
8	R = *p*-Cl (**1d**)	80	67
9	R = *p*-F (**1e**)	50	71
10	R = *p*-F (**1e**)	80	86
11	R = *p*-N(Me)$_2$ (**1f**)	50	76
12	R = *p*-N(Me)$_2$ (**1f**)	80	80
13	R = *p*-CF$_3$ (**1g**)	50	63
14	R = *p*-CF$_3$ (**1g**)	80	67

[a] For all classes, the reactant ratio **3c**:**1**:KOH = 1:1.5:16.
[b] Yield was determined by ^{19}F NMR spectroscopy.

Table 2
Difluoromethylation with different reagents **2**.



.

Entry[a]	Reagent	Temp. (°C)	Yield (%)[b]
1	R = H (**2a**)	50	73
2	R = H (**2a**)	80	77
3	R = *p*-Me (**2b**)	50	52
4	R = *p*-Me (**2b**)	80	65
5	R = *p*-OMe (**2c**)	50	29
6	R = *p*-OMe (**2c**)	80	36
7	R = *p*-Cl (**2d**)	50	90
8	R = *p*-Cl (**2d**)	80	91
9	R = *p*-Br (**2e**)	50	83
10	R = *p*-Br (**2e**)	80	86
11	R = *o*-Cl,*p*-Cl (**2f**)	50	76
12	R = *o*-Cl,*p*-Cl (**2f**)	80	73
13	R = *p*-F (**2g**)	50	79
14	R = *p*-F (**2g**)	80	81
15	R = *p*-NO$_2$ (**2h**)	50	91
16	R = *p*-NO$_2$ (**2h**)	80	91

[a] For all classes, the reactant ratio **3c**:**2**:KOH = 1:1.5:16.
[b] Yield was determined by ^{19}F NMR spectroscopy.

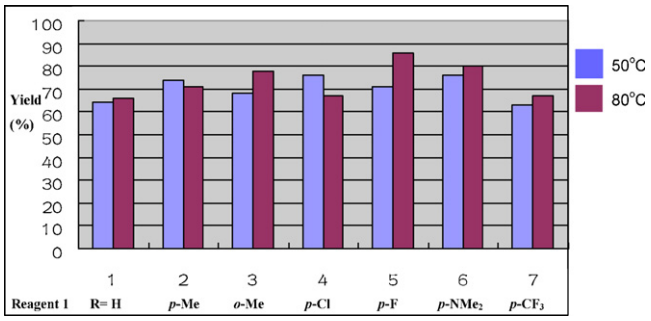


Fig. 1. Difluoromethylation with different reagents **1**.

the product **4c** was obtained in similar yields (both for 50 °C and 80 °C) (Fig. 1). It indicates that for chlorodifluoromethyl aryl ketones **1a–1g**, the different substituents on the aryl group of reagents did not significantly affect their reactivity as the difluorocarbene reagents for *O*-difluoromethylation.

For comparison, we prepared a variety of structurally diverse chlorodifluoromethyl phenyl sulfones **2a–2h** following the known procedure [8]. As shown in Table 2 and Fig. 2, the difluoromethylation power of each sulfone reagent was examined using **3c** as a model substrate under the similar reaction conditions as our previous report [8], except that the reactant ratio **3c**:**2**:KOH = 1:1.5:16. When we investigated the temperature effect, it showed that the yield of **3c** was not sensitive to reaction temperature, with only slightly higher yields obtained at 80 °C (than those at 50 °C) in most cases. However, unlike the reactions

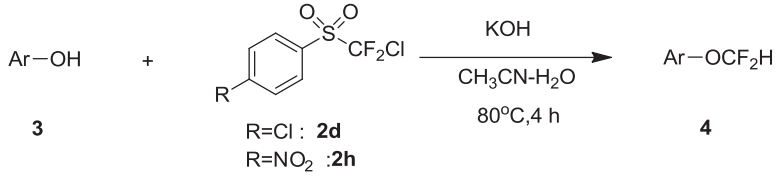
with reagents **1a**–**1g** (Table 1 and Fig. 1), the different substituents on reagents **2a**–**2h** had a remarkable effect on the product yields (Table 2 and Fig. 2). As shown in Fig. 2, the product yield is increasing along the order R = H, *p*-OMe, *p*-Me, H, *p*-F, *p*-Br, *p*-Cl, and *p*-NO_2. Since Hammett constant (σ value) can be used to indicate the relative electronic effect of different substituents on the phenyl ring, we listed the σ_{para} values for different substituents (as shown in Table 3) [10]. It was found that an electron-donating group (with a negative σ_{para} value) resulted in a decrease of product yield, while an electron-withdrawing group (with a positive σ_{para} value) led to an increase of product yield. As shown in Fig. 2 and Table 3, the tendency of product yields is consistent with that of the σ_{para} values. Finally, *para*-chloro and *para*-nitro substituted chlorodifluoromethyl phenyl sulfones **2d** and **2h** behaved as the two most efficient difluorocarbene reagents in this category.

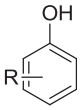
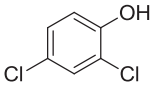
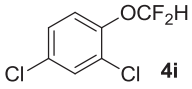
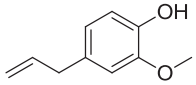
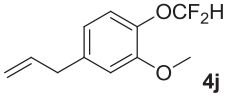
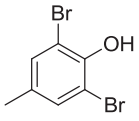
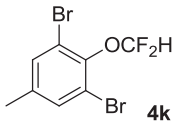
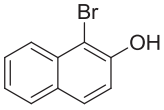
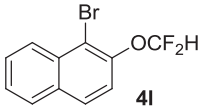
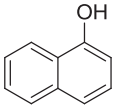
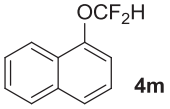
Table 3
σ values for several substituents.

Substituent (R)	*p*-OMe	*p*-Me	H	*p*-F	*p*-Br	*p*-Cl	*p*-NO_2
Hammett constant (σ)	−0.27	−0.17	0	0.06	0.23	0.23	0.78

With the two efficient difluorocarbene reagents **2d** and **2h** in hand, we carefully examined the scope of the *O*-difluoromethylation reaction with these two reagents. The results are summarized in Table 4. Reagent **2d** and **2h** were found to be powerful in reacting with a variety of structurally diverse phenol derivatives to give aryl difluoromethyl ethers in good to excellent yields (entries 1–13). Naphthols were also successfully difluoromethylated to give the corresponding products in good yields (entries 12 and 13). It should be mentioned that, in most cases, only 1.5 equivalents of reagent **2g** or **2h** were used, and the corresponding difluoro-

Table 4
O-Difluoromethylation with reagent **2d** or **2h**.



Entry[a]	Substrate	Reactant	Product	Yield (%)[b]
1		**2d**	**4a** R = H	76[c]
2		**2h**	**4b** R = *p*-*t*Bu	77
3		**2h**	**4c** R = *p*-Ph	93
4		**2h**	**4d** R = *o*-NO_2	90
5		**2h**	**4e** R = *p*-NO_2	93
6		**2d**	**4f** R = *p*-OMe	80[c]
7		**2d**	**4g** R = *p*-I	85
8		**2d**	**4h** R = *p*-Cl	66
9		**2d**	 **4i**	99
10		**2d**	 **4j**	86
11		**2d**	 **4k**	97
12		**2d**	 **4l**	90
13		**2h**	 **4m**	76

[a] For all cases, the reactant ratio **3**:**2**:KOH = 1:1.5:16.
[b] Isolated yield.
[c] Yield was determined by ^{19}F NMR spectroscopy.

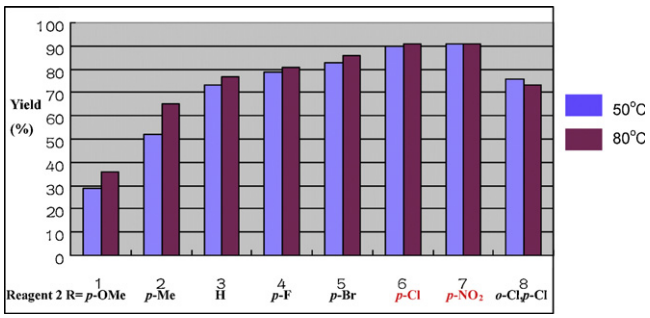
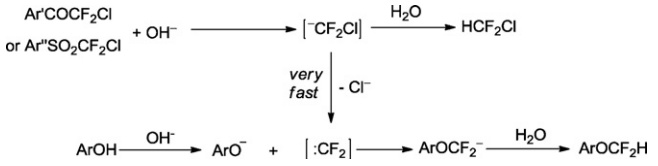


Fig. 2. Difluoromethylation with different reagents **2**.

methylated ethers were obtained in better yields than those of the reported reactions using other difluorocarbene reagents [5,8,11].

p-Chlorophenyl chlorodifluoromethyl sulfone **2d** was also applied in the *N*-difluoromethylation of different *N*-heterocyclic compounds, and the corresponding *N*-difluoromethylated tertiary amines were obtained in moderate yields (Table 5).

The mechanism for *O*-difluoromethylation using **1** or **2** is proposed in Scheme 1 [5]. Chlorodifluoromethyl anion (CF_2Cl^-) is generated from reagent **1** or **2** under the nucleophilic attack by hydroxide ion, and the CF_2Cl^- species readily undergoes α-elimination of a chloride ion to release difluorocarbene (:CF_2) [12]. It should be noted that chlorodifluoromethyl anion is a highly unstable species, and its decomposition to difluorocarbene and chloride anion was known to proceed swiftly without significant activation barrier [12,13]. Therefore, the generation of:CF_2 from **1** or **2** and hydroxide can be reasonably regarded as one step. It

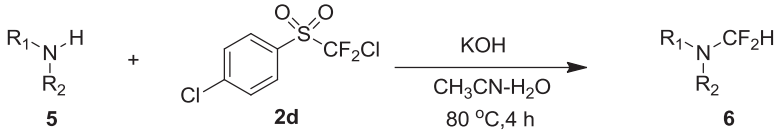


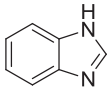
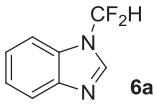
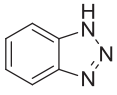
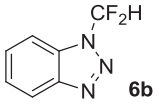
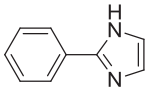
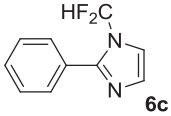
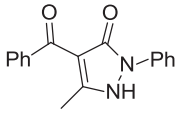
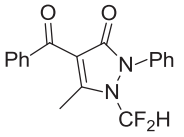
Scheme 1.

should also be realized that the difluorocarbene is a reactive intermediate and possesses only a very short life-time, which suggests that a quick generation of: CF_2 at low temperature may not be beneficial to the desired difluoromethylation reaction that involves a high activation energy and requires a high reaction temperature [2].

The difluorocarbene can be readily captured by phenoxides (ArO^-) to give the difluoromethyl ethers via anionic intermediates ($ArOCF_2^-$). In Table 1 and Fig. 1, we found that the change of different substituents on the phenyl ring of **1a**–**1g** did not show a remarkable impact on the product yield; however, in Table 2 and Fig. 2, we realized that the substituent effect on chlorodifluoromethyl aryl sulfones **2a**–**2h** were more significant. This can be explained by the fact that the reactions between chlorodifluoromethyl aryl ketones **1** and hydroxide is generally much faster than the those with chlorodifluoromethyl aryl sulfones **2** [5,8]. Indeed, the generation of difluorocarbene from ketones **1** and KOH was so facile that a low temperature (−78 °C) condition was required during the reaction set-up stage (see Section 4) [5]. Therefore, the electronic effect of different substituents on **1** had little effect on the product yield of the difluoromethylation reaction. However, since sulfones **2** are more stable and the generation of

Table 5
N-Difluoromethylation with reagent **2d**.



Entry[a]	Substrate	Reactant	Product	Yield (%)[b]
1		**2d**	 **6a**	57
2		**2d**	 **6b**	56
3		**2d**	 **6c**	68
4		**2d**	 **6d**	34

[a] For all cases, the reactant ratio **5:2d**:KOH = 1:1.5:16.
[b] Isolated yield.

difluorocarbene from sulfones **2** is much slower, the electronic effect of different substituents on **2** showed a significant influence on the product yields (Table 2 and Fig. 2). It is reasonable to see that an electron-withdrawing group on sulfone **2** facilitates the generation of difluorocarbene species through the attack of a hydroxide ion, resulting in a beneficial effect for the chemical outcome of the difluoromethylation reaction. The relative stability and the substituent effect of ketones **1** and sulfones **2** also explain why a large excess amount of ketone reagents **1** (5 equiv.) were generally used to obtain satisfactory yield of difluoromethylated products [5].

3. Conclusions

In conclusion, we have investigated structurally different chlorodifluoromethyl aryl ketones **1a**–**1g** and sulfones **2a**–**2h** as difluorocarbene reagents for *O*- and *N*-difluoromethylations. It was found that the sulfone reagents **2** were generally more efficient in difluoromethylation than the ketone reagents **1**. Furthermore, while the different substituents on ketone reagents **1** did not show a remarkable impact on the difluoromethylation reaction, the substituent effect on the sulfone reagents **2** was much more significant. Finally, we found that *p*-chlorophenyl chlorodifluoromethyl sulfone **2d** and *p*-nitrophenyl chlorodifluoromethyl sulfone **2h** were among the most powerful difluorocarbene reagents in *O*-difluoromethylations. *p*-Chlorophenyl chlorodifluoromethyl sulfone **2d** was also applied in the *N*-difluoromethylation of different *N*-heterocyclic compounds, and the corresponding *N*-difluoromethylated tertiary amines were obtained in moderate yields.

4. Experimental

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

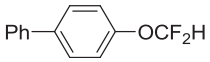
4.1. Typical procedure for difluoromethylation of 3 using 1

Into a pressure tube containing a mixture of biphenyl-4-ol **3c** (170 mg, 1.0 mmol) and aqueous KOH (3 mL, 25 wt%, *ca.* 16 mmol), was added **1a** (963 mg, 5.0 mmol) (dissolved in CH_3CN (3 mL)) at −78 °C. The reaction tube was sealed and heated to 50 °C (or 80 °C) for 4 h. After the addition of 3 mL of water, the reaction mixture was extracted with 5 mL of Et_2O. The yield was determined by ^{19}F NMR spectroscopy using $PhCF_3$ as internal standard (64% for 50 °C; 66% for 80 °C).

4.2. Typical procedure for difluoromethylation of 3 (or 5) using 2

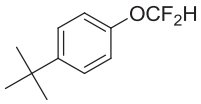
Into a reaction tube containing mixture of biphenyl-4-ol **3c** (170 mg, 1.0 mmol) and aqueous KOH (3 mL, 25% wt%, *ca.* 16 mmol), was added **2g** (340 mg, 1.5 mmol; dissolved in 3 mL of CH_3CN) at −78 °C. The reaction tube was sealed immediately, and the mixture was heated to 80 °C for 4 h. After the addition of 3 mL of water, the reaction mixture was extracted with 5 mL of Et_2O. The yield was determined by ^{19}F NMR spectroscopy using $PhCF_3$ as internal standard (91%). The organic phase was washed with brine, and then dried over anhydrous $MgSO_4$. After the solution was filtered and the solvent was evaporated under vacuum, the residue was subjected to silica gel column chromatography to give product **4c** (205 mg, 93%).

4.2.1. 4-(Difluoromethoxy)biphenyl (4c)



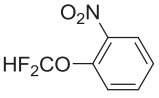
White solid; ^{1}H NMR: δ 7.56 (t, J = 8.1 Hz, 4H), 7.44 (t, J = 7.2 Hz, 2H), 7.39–7.32 (m, 1H), 7.19 (d, J = 7.8 Hz, 2H), 6.55 (t, J = 74.1 Hz, 1H); ^{19}F NMR: δ −80.2 (d, J = 73.7 Hz, 2F); MS (EI, *m*/*z*, %): 220 (M^+, 75.93), 170 (100.00). The characterization data was consistent with the previous report [8].

4.2.2. 1-tert-Butyl-4-(difluoromethoxy)benzene (4b)



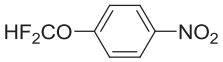
Colorless liquid; ^{1}H NMR: δ 7.37 (d, J = 8.9 Hz, 2H), 7.05 (d, J = 8.9 Hz, 2H), 6.48 (t, J = 74.1 Hz, 1H), 1.31 (s, 9H); ^{19}F NMR: δ −80.4 (d, J = 74.4 Hz, 2F); MS (EI, *m*/*z*, %): 200 (M^+, 17.27), 185 (100.00). The characterization data was consistent with the previous report [8].

4.2.3. 1-(Difluoromethoxy)-2-nitrobenzene (4d)



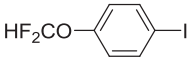
Light yellow liquid; ^{1}H NMR: δ 7.98–7.91 (m, 1H), 7.68–7.59 (m, 1H), 7.44–7.36 (m, 2H), 6.63 (t, J = 72.9 Hz, 1H); ^{19}F NMR: δ −81.3 (d, J = 72.6 Hz, 2F); MS (EI, *m*/*z*, %): 189 (M^+, 82.16), 139 (100.00). The characterization data was consistent with the previous report [8].

4.2.4. 1-(Difluoromethoxy)-4-nitrobenzene (4e)



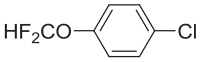
Light yellow liquid; ^{1}H NMR: δ 8.28 (d, J = 9.0 Hz, 2H), 7.26 (d, J = 9.0 Hz, 2H), 6.64 (t, J = 72.0 Hz, 1H); ^{19}F NMR: δ −6.64 (d, J = 72.3 Hz, 2F); MS (EI, *m*/*z*, %): 189 (100.00), 109 (91.91). The characterization data was consistent with the previous report [8].

4.2.5. 1-(Difluoromethoxy)-4-iodobenzene (4g)



Colorless liquid; ^{1}H NMR: δ 7.67 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 6.48 (t, J = 73.8 Hz, 1H); ^{19}F NMR: δ −80.4 (d, J = 73.6 Hz, 2F); MS (EI, *m*/*z*, %): 270 (M^+, 33.27), 58 (100.00). The characterization data was consistent with the previous report [8].

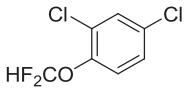
4.2.6. 1-Chloro-4-(difluoromethoxy)benzene (4h)



Colorless liquid; ^{1}H NMR: δ 7.33 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 8.7 Hz, 2H), 6.48 (t, J = 73.5 Hz, 1H); ^{19}F NMR: δ −80.4 (d,

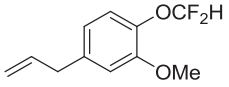
J = 74.0 Hz, 2F); MS (EI, *m/z*, %): 178 (M^+, 33.40), 128 (100.00), 130 (32.16). The characterization data was consistent with the previous report [8].

4.2.7. 2,4-Dichloro-1-(difluoromethoxy)benzene (**4i**)



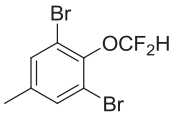
Colorless liquid; ^{1}H NMR: δ 7.48–7.44 (m, 1H), 7.28–7.16 (m, 2H), 6.51 (t, J = 72.6 Hz, 1H); ^{19}F NMR: δ –82.1 (d, J = 73.4 Hz, 2F); MS (EI, *m/z*, %): 212 (M^+, 32.96), 162 (100.00). The characterization data was consistent with the previous report [8].

4.2.8. 4-Allyl-1-(difluoromethoxy)-2-methoxybenzene (**4j**)



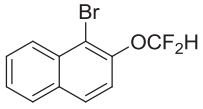
Colorless liquid; IR (film): 2980, 1641, 1599, 1511, 1467, 1421, 1382, 1274, 1216, 1123, 1935, 919 cm^{-1}; ^{1}H NMR: δ 7.07 (d, J = 8.2 Hz, 2H), 6.80–6.25 (m, 3H), 6.02–5.87 (m, 1H), 5.14–5.10 (m, 1H), 5.09–5.06 (m, 1H), 3.86 (s, 3H), 3.36 (d, J = 6.9 Hz, 2H); ^{19}F NMR: δ –80.6 (d, J = 78.6 Hz, 2F); ^{13}C NMR: δ 150.9, 138.9, 136.9, 122.2, 120.2, 116.3 (t, J = 258.3 Hz), 112.9, 55.9, 39.9; MS (EI, *m/z*, %): 214 (M^+, 100.00), 91 (55.30), 147 (53.70); HRMS (EI): calcd. for $C_{11}H_{12}O_2F_2$: 214.0805; found: 214.0807.

4.2.9. 1,3-Dibromo-2-(difluoromethoxy)-5-methylbenzene (**4k**)



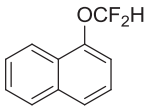
White solid; Mp. 41 °C; IR (film): 1735, 1588, 1554, 1463, 1383, 1257, 1127, 1089, 1068, 849, 746, 582, 562 cm^{-1}; ^{1}H NMR: δ 7.39 (s, 2H), 6.57 (t, J = 74.4 Hz, 1H), 2.32 (s, 3H). ^{19}F NMR: δ –80.3 (d, J = 74.4 Hz, 2F); ^{13}C NMR: δ 143.6, 139.1, 133.6, 117.7, 116.7 (t, J = 262.8 Hz), 20.3; MS (EI, *m/z*, %): 314 (M^+, 22.79), 266(100.00); HRMS (EI): calcd. for $C_8H_6OF_2Br_2$: 313.8753; found: 313.8755; anal. calcd. for $C_8H_6OF_2Br_2$: C, 30.41; H, 1.91; found: C, 30.55; H, 1.75.

4.2.10. 1-Bromo-2-(difluoromethoxy)naphthalene (**4l**)



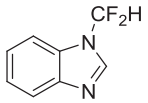
White solid; Mp. 55–56 °C; IR (film): 1504, 1383, 1359, 1231, 1121, 1105, 993, 935, 811, 741, 526 cm^{-1}; ^{1}H NMR: δ 8.29 (d, J = 8.4 Hz, 1H), 7.88–7.81 (m, 2H), 7.68–7.51 (m, 2H) 7.43–7.36 (m, 1H), 6.63 (t, J = 73.8 Hz, 1H); ^{19}F NMR: δ –80.1 (d, J = 73.8 Hz, 2F); ^{13}C NMR: δ 146.0, 132.7, 132.2, 129.2, 128.2, 128.1, 127.1, 126.5, 120.5, 118.9, 116.2 (t, J = 241.3 Hz), 114.7; MS (EI, *m/z*, %): 272 (M^+, 78.09), 222 (100.00); HRMS (EI): calcd. for $C_{11}H_7OF_2Br$: 271.9648; found: 271.9651; anal. calcd. for $C_{11}H_7OF_2Br$: C, 48.38; H, 2.58; found: C, 48.19; H, 2.59.

4.2.11. 1-(Difluoromethoxy)naphthalene (**4m**)



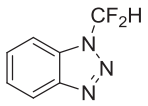
Colorless liquid; ^{1}H NMR: δ 8.22–8.16 (m, 1H), 7.89–7.83 (m, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.60–7.38 (m, 3H), 7.22–7.16 (m, 1H), 6.66 (t, J = 74.1 Hz, 1H); ^{19}F NMR: δ –79.1 (d, J = 74.0 Hz, 2F); MS (EI, *m/z*, %): 194 (M^+, 72.21), 144 (100.00), 115 (93.41). The characterization data was consistent with the previous report [8].

4.2.12. 1-(Difluoromethyl)-1H-benzo[d]imidazole (**6a**)



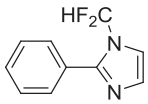
Light yellow liquid; ^{1}H NMR: δ 8.14 (s, 1H), 7.90–7.81 (m, 1H), 7.66–7.57 (m, 1H), 7.56–7.12 (m, 3H); ^{19}F NMR: δ –92.9 (d, J = 60.1 Hz, 2F); MS (EI, *m/z*, %): 168 (M^+, 100.00), 118 (62.21). The characterization data was consistent with the previous report [8].

4.2.13. 1-(Difluoromethyl)-1H-benzo[d][1,2,3]triazole (**6b**)



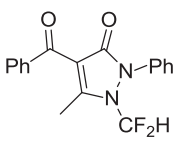
Light yellow liquid; ^{1}H NMR: δ 8.18–8.12 (m, 1H), 8.07–7.61 (m, 3H), 7.55–7.47 (m, 1H); ^{19}F NMR: δ –96.4 (d, J = 59.0 Hz, 2F); MS (ESI): *m/z* 170.2 (M+H$^+$). The characterization data was consistent with the previous report [7].

4.2.14. 1-(Difluoromethyl)-2-phenyl-1H-imidazole (**6c**)



Light yellow liquid; ^{1}H NMR: δ 7.64–7.48 (m, 5H), 7.42–7.38 (m, 1H), 7.28–6.86 (m, 2H); ^{19}F NMR: δ –89.7 (d, J = 59.8 Hz, 2F); MS (EI, *m/z*, %): 194 (M^+, 78.17), 193 (100.00). The characterization data was consistent with the previous report [8].

4.2.15. 4-Benzoyl-1-(difluoromethyl)-5-methyl-2-phenyl-1H-pyrazol-3(2H)-one (**6d**)

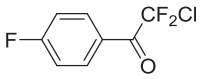


Light yellow liquid; ^{1}H NMR: δ 7.85–7.78 (m, 2H), 7.69–7.57 (m, 3H), 7.56–7.37 (m, 5H), 6.73 (t, J = 73.2 Hz, 1H), 2.23 (s, 3H); ^{19}F NMR: δ –82.3 (d, J = 73.6 Hz, 2F); MS (ESI): *m/z* 329.2 (M+H$^+$). The characterization data was consistent with the previous report [8].

4.3. Typical procedure for preparation of reagents **1**

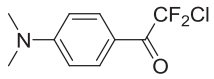
The reagents **1** were prepared following the previous report [9].

*4.3.1. 2-Chloro-2,2-difluoro-1-(4-fluorophenyl)ethanone (**1e**)*



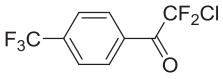
Colorless liquid; IR (film): 2928, 1719, 1602, 1510, 1247, 1159, 988, 894, 747, 601 cm^{-1}; ^1H NMR: δ 8.21–8.08 (m, 2H), 7.22–7.11 (m, 2H); ^{19}F NMR: δ −61.5 (s, 2F), −100.8 (s, 1F); ^{13}C NMR: δ 179.7 (t, J = 29.0 Hz), 166.9 (d, J = 257.6 Hz), 133.5 (d, J = 9.7 Hz), 125.7 (d, J = 3.0 Hz), 120.0 (t, J = 303.0 Hz), 116.3 (d, J = 221.6 Hz); MS (EI, *m/z*, %): 208 (M^+, 4.40), 104 (100.00); HRMS (EI): calcd. for $C_8H_4OF_3Cl$: 207.9903; found: 207.9899.

*4.3.2. 2-Chloro-1-(4-(dimethylamino)phenyl)-2,2-difluoroethanone (**1f**)*



Yellow solid; Mp. 59 °C; IR (film): 2921, 1681, 1602, 1542, 1387, 1153, 977, 888, 742 cm^{-1}; ^1H NMR: δ 7.99 (d, J = 8.8 Hz, 2H), 6.65 (d, J = 8.8 Hz, 2H), 3.09 (s, 6H); ^{19}F NMR: δ −59.1 (s, 2F); ^{13}C NMR: δ 178.9 (t, J = 26.8 Hz), 154.4, 132.9 (d, J = 2.2 Hz), 120.9 (t, J = 303.8 Hz), 116.2, 110.7 (t, 32.0 Hz), 39.9; MS (EI, *m/z*, %): 233 (M^+, 18.44), 148 (100.00); HRMS (EI): calcd. for $C_{10}H_{10}ONF_2Cl$: 233.0419; found: 233.0417; anal. calcd. for $C_{10}H_{10}ONF_2Cl$: C, 51.41; H, 4.31; N, 5.99; found: C, 51.41; H, 4.24; N, 5.90.

*4.3.3. 2-Chloro-2,2-difluoro-1-(4-(trifluoromethyl)phenyl)ethanone (**1g**)*

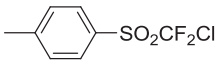


Colorless liquid; IR (film): 1726, 1415, 1330, 1320, 1166, 1139, 1070, 992, 896, 758 cm^{-1}; ^1H NMR: δ 8.28 (d, J = 8.2 Hz, 2H), 7.85 (d, J = 8.6 Hz, 2H); ^{19}F NMR: δ −62.2 (s, 2F), −64.3 (s, 3F); ^{13}C NMR: δ 180.3 (t, J = 29.1 Hz), 136.3 (q, J = 33.5 Hz), 132.2, 130.9, 126.0 (d, J = 13.7 Hz), 124.6, 119.9 (t, J = 230.0 Hz); MS (EI, *m/z*, %): 173 (100.00), 145 (73.18), 239 (3.42); HRMS (EI): calcd. for $C_9H_4OF_5Cl$: 257.9871; found: 257.9871.

4.4. Typical procedure for preparation of reagents **2**

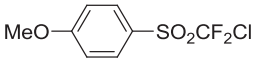
The reagents **2** were prepared according to literature [8].

*4.4.1. 1-(Chlorodifluoromethylsulfonyl)-4-methylbenzene (**2b**)*



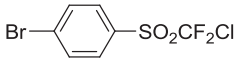
White solid; Mp. 66–67 °C; IR (film): 1592, 1357, 1178, 1124, 1114, 1077, 933, 813, 657, 571,530 cm^{-1}; ^1H NMR: δ 7.90 (d, J = 7.8 Hz, 2H), 7.45 (d, J = 7.8 Hz, 2H), 2.50 (s, 3H); ^{19}F NMR: δ −62.9(s, 2F); ^{13}C NMR: δ 148.1, 131.2, 130.4, 127.4, 126.4 (t, J = 333.5 Hz), 21.9; MS (EI, *m/z*, %): 240 (M^+, 0.30), 91 (100.00), 155 (52.65); HRMS (EI): calcd. for $C_8H_7O_2SF_2Cl$: 239.9823; found: 239.9825; anal. calcd. for $C_8H_7O_2SF_2Cl$: C, 39.93; H, 2.93; found: C, 39.98; H, 2.94.

*4.4.2. 1-(Chlorodifluoromethylsulfonyl)-4-methoxybenzene (**2c**)*



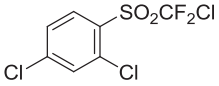
White solid; Mp. 49–50 °C; IR (film): 2992, 1595, 1498, 1353, 1276, 1168, 1123, 1074, 839, 802, 667, 575, 543 cm^{-1}; ^1H NMR: δ 7.96 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 3.94 (s, 3H); ^{19}F NMR: δ −63.8(s, 2F); ^{13}C NMR: δ 166.1, 133.6, 126.4 (t, J = 329.5 Hz), 121.0, 115.1, 55.9; MS (EI, *m/z*, %): 256 (M^+, 1.43), 171 (100.00); HRMS (EI): calcd. for $C_8H_7O_3F_2SCl$: 255.9773; found: 255.9774; anal. calcd. for $C_8H_7O_3F_2SCl$: C, 37.44; H, 2.75; found: C, 37.58; H, 2.75.

*4.4.3. 1-Bromo-4-(chlorodifluoromethylsulfonyl)benzene (**2e**)*



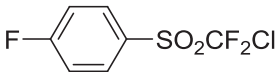
White solid; Mp. 68 °C; IR (film): 3094, 1571, 1393, 1368, 1117, 1011, 930, 738, 590, 560 cm^{-1}; ^1H NMR: δ 7.89 (d, J = 8.7 Hz, 2H), 7.81 (d, J = 8.7 Hz, 2H); ^{19}F NMR: δ −62.3(s, 2F); ^{13}C NMR: δ 133.2, 132.5, 132.4, 129.6, 126.2 (t, J = 233.5 Hz); MS (EI, *m/z*, %): 304 (M^+, 5.46), 155 (100.00); HRMS (EI): calcd. for $C_7H_4O_2F_2ClS$ (M−Br): 224.9589; found: 224.9589; anal. calcd. for $C_7H_4O_2F_2ClBrS$: C, 27.52; H, 1.32; found: C, 27.90; H, 1.62.

*4.4.4. 2,4-Dichloro-1-(chlorodifluoromethylsulfonyl)benzene (**2f**)*



Colorless liquid; IR (film): 3097, 1573, 1552, 1381, 1188, 1151, 1126, 1098, 929, 824, 613, 577, 543, 485 cm^{-1}; ^1H NMR: δ 8.11 (d, J = 8.4 Hz, 1H), 7.69–7.50 (m, 2H); ^{19}F NMR: δ −60.7 (s, 2F); ^{13}C NMR: δ 144.1, 137.5, 136.4, 133.3, 128.5, 127.8, 126.9 (t, J = 345.0 Hz); MS (EI, *m/z*, %): 294 (M^+, 7.87), 209 (100.00), 145 (79.68); HRMS (EI): calcd. for $C_7H_3O_2F_2Cl_3$: 293.8887; Found: 293.8890; Anal. Calcd. for $C_7H_3O_2F_2Cl_3$: C, 28.45; H, 1.02; Found: C, 28.94; H, 0.98.

*4.4.5. 1-(Chlorodifluoromethylsulfonyl)-4-fluorobenzene (**2g**)*



White solid; Mp. 30 °C; IR (film): 3110, 1591, 1494, 1370, 1248, 1187, 1160, 1121, 1079, 930, 844, 664, 574, 530 cm^{-1}; ^1H NMR: δ 8.14−8.06 (m, 2H), 7.36 (d, J = 8.1 Hz, 2H); ^{19}F NMR: δ −63.5 (s, 2F), −98.4 (s, 1F); ^{13}C NMR: δ 167.6 (d, J = 259.8 Hz), 134.3 (d, J = 10.4 Hz), 126.5 (d, J = 3.0 Hz), 126.2 (t, J = 333.5 Hz), 117.4 (d, J = 33.1 Hz); MS (EI, *m/z*, %): 208 (M^+, 4.40), 104 (100.00); HRMS (EI): calcd. for $C_7H_4O_2F_3SCl$: 243.9573; found: 243.9572; anal. calcd. for $C_7H_4O_2F_3SCl$: C, 34.37; H, 1.65; found: C, 34.45; H, 1.77.

Acknowledgements

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