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Diethyl bromodifluoromethylphosphonate: a highly efficient and environmentally benign difluorocarbene precursor

Yossi Zafrani *, Gali Sod-Moriah, Yoffi Segall *

Department of Organic Chemistry, Israel Institute for Biological Research, Ness-Ziona 74100, Israel

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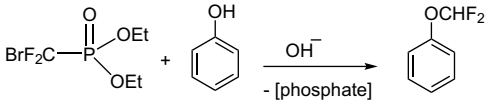
ABSTRACT

A convenient method for the difluoromethylation of phenols and thiophenols, using diethyl bromodifluoromethylphosphonate (**1**) as a difluorocarbene precursor, is described. This commercially available phosphonate was found to undergo an extremely facile P–C bond cleavage on basic hydrolysis (−78 °C to rt), presumably leading to the bromodifluoromethyl anion, which subsequently converts to a difluorocarbene intermediate. The latter is trapped by phenolates **2** or thiophenolates **3** to give the corresponding difluoromethyl ethers and thioethers in good to excellent yield. The resulting eco-friendly side product, diethyl phosphate ion, is easily separated from the reaction mixture due to its excellent solubility in water. Due to the mild conditions applied to this reaction, phenolate ions bearing carbonyl or enolate functions are selectively difluoromethylated.

1. Introduction

Difluorocarbene is a useful intermediate in the synthesis of organofluorine compounds such as *gem*-difluorocyclopropanes, and difluoromethyl ethers, sulfides and amines. Replacing a hydrogen atom by fluorine or, more specifically, insertion of a difluoromethyl group into organic molecules, may cause pronounced biological as well as physical and chemical effects.[1] Thus, it is not surprising that various synthetic methods to the in situ generation of difluorocarbene have been developed in the past half-century.[2] These methods include the use of the following difluorocarbene precursors: $ClCF_2H$,[3] $ClCF_2COONa$,[4,5] $(CF_3)_3PF_2$,[6] $(CH_3)_3SnCF_3$,[7] $RHgCF_3$,[8,9] hexafluoropropylene oxide,[10] CF_2Br_2,[11,12] FSO_2CF_2COOH,[13] $FSO_2CF_2COOTMS$[14] and $ClCF_2X(O)_nPh$ (X=C, n=1;[15] X=S, n=1, 2[16]). However, the majority part of them suffered from low yields and required harsh conditions and excess of non-commercial ozone-depleting difluorocarbene precursors. In order to overcome the latter disadvantage, Hu and co-workers have recently reported the synthesis of a new class of non-ODS-based (ozone-depleting substances) precursors to difluorocarbene (the latter example).[15,16] These synthesized precursors were successfully used for difluoromethylation[17] of phenols and aniline derivatives under basic conditions. Stimulated by this work we found out that commercial diethyl bromodifluoromethylphosphonate (**1**, in Table 1)[18] can be used as a difluorocarbene precursor, via a facile hydrolysis-based P–C bond cleavage. Herein we wish to disclose a simple and convenient method for the difluoromethylation of phenols and thiophenols, using this compound as a difluorocarbene precursor. From a 'green chemistry' point of view, this

Table 1
Reactions of phosphonate **1** with phenol **2a** in various conditions



1 **2a** **3a**

Run	**1** (equiv)	Base (equiv)	Solvent	Temperature (°C)	t[a] (h)	Yield[b]
1	1	LiOH (3)	THF	−78 to rt	1.5	8
2	1	LiOH (3)	THF	rt	1	21
3	2	LiOH (4)	THF	rt	1	16
4	2	LiOH (20)	THF	rt	1	10
5	*2*	*KOH (20)*	*CH_3CN–H_2O*	*−78 to rt*	*0.6*	*87*
6	2	KOH (20)	CH_3CN–H_2O	rt	0.6	82
7	1	KOH (20)	CH_3CN–H_2O	−78 to rt	0.6	77
8	2	KOH (10)	CH_3CN–H_2O	−78 to rt	0.6	47
9	2	KOH (4)	CH_3CN–H_2O	−78 to rt	0.6	20
10	2	KOH (20)	H_2O	−78 to rt	1	36
11	1	KF–Al_2O_3 (ca. 5)[c]	CH_3CN	rt	48	32

[a] Reaction times for full conversion of phosphonate **1**.
[b] Yield was determined by ^{19}F NMR of the reaction mixture prior to work-up, using α,α,α-trifluorotoluene as reference standard due to the volatility of product **3a**.
[c] In this experiment phosphonate **1** (1 mmol) was added to a heterogeneous mixture of the solid support KF–Al_2O_3 (20, H_2O, 160) (2.5 g), H_2O (2 mmol), phenol (1 mmol) and CH_3CN (4 mL).

* Corresponding authors. Tel.: +972 89381741; fax: +972 89381548.
E-mail addresses: yossiz@iibr.gov.il (Y. Zafrani), yoffis@iibr.gov.il (Y. Segall).

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method benefits significant advantages: (1) using nearly equivalent amounts (1–2) of non-ODS difluorocarbene precursor, (2) mild conditions and good to excellent yields, (3) production of easily separable diethyl phosphate ion as a major eco-friendly water soluble side product and (4) possible chemoselectivity in multifunctional systems.

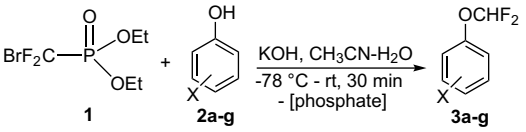
2. Results and discussion

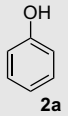
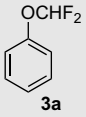
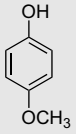
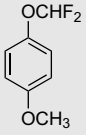
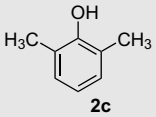
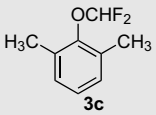
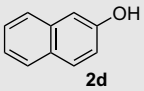
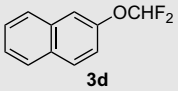
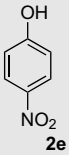
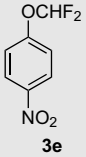
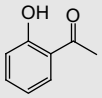
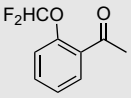
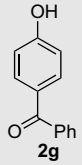
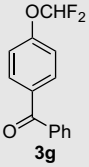
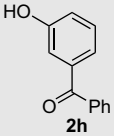
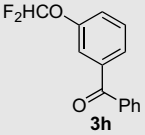
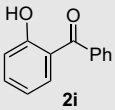
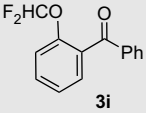
2.1. Difluoromethylation of phenols

We initially examined the difluoromethylation of phenol (**2a**) using phosphonate (**1**) as a hydrolysis-based difluorocarbene precursor in basic conditions such as protic (KOH, CH_3CN–H_2O), aprotic (LiOH, THF) and solid supported (KF–Al_2O_3, CH_3CN) media (Table 1). Preliminary results revealed that in basic aqueous solution, this phosphonate instantly and quantitatively converts to the corresponding phosphate ion at rt, via an unusual P–C bond cleavage (vide infra). In a homogeneous organic medium, using THF as solvent and LiOH as base, phosphonate **1** was rapidly consumed (according to both ^{31}P and ^{19}F NMR) but the difluoromethylation yield was fairly low (runs 1–4). In a heterogeneous medium, in which the reagent KF–Al_2O_3 (20, H_2O, 160) was used as a strong basic solid support, phosphonate **1** reacted slower and the difluoromethylation product **3a** was obtained in a moderate yield (run 11). The expression KF–Al_2O_3 (20, H_2O, 160) refers to KF–Al_2O_3 that contains 20 wt % of KF, prepared in water, and finally dried at 160 °C.[19] However, modification of the process reported by Hu and co-workers[15,16] led to optimal conditions for the difluoromethylation reaction. This modification includes lowering the reaction temperature and reducing the excess of the difluorocarbene precursor (in our case phosphonate **1**). Thus, treatment of phosphonate **1** (2 equiv) with a mixture of phenol (**2a**) and potassium hydroxide in CH_3CN–H_2O (1:1) at −78 °C to rt resulted in formation of the corresponding difluoromethyl ether **3a** in 87% yield (run 5). When equivalent amounts of phosphonate **1** and phenol (**2a**) are used or if the reaction is initiated at rt, the yield of the reaction is reduced only by 10 and 5%, respectively (runs 7 and 6). Reducing the excess of hydroxide ions (runs 8 and 9) or performing the reaction without co-solvent (run 10) significantly lowered the difluoromethylation yield. Therefore, the conditions depicted in run 5 seem to be satisfactory for the expanded study of this reaction.

The generality of the reaction was examined using various phenols, possessing electron-donating (**2b**,**c**) and electron-withdrawing (**2e**–**i**) groups, *o*-substituted (relatively steric-hindered) phenols (**2c**,**f**,**i**), β-naphthol (**2d**) and carbonyl-bearing phenols such as **2f**–**i** (Table 2). The data presented in Table 2 reveal that the reaction is indeed general with good to excellent yields. The yields were found to be higher for *p*- or *m*-electron-withdrawing substituted difluoromethyl ethers **3e**,**g**,**h**, supposedly due to a combination of electronic (lower pK_a's of phenols) and steric (less hindrance) effects (runs 5, 7, and 8). Compounds **2f**–**i** were further tested for possible chemoselectivity in the difluoromethylation, stemming from its mild conditions. As demonstrated by Figure 1, compound **2f** can react with difluorocarbene at four different nucleophilic sites. In addition to the expected difluoromethylation of the phenolate ion, the carbonyl function can convert, in the presence of difluorocarbene, into a *gem*-difluoro methylene group.[20] The enolate form of **2f** may undergo difluoromethylation and/or difluorocyclopropanation at the oxygen and the electron rich double bond, respectively, as recently reported by Dolbier and co-workers.[21] These three competitive reactions are known to occur at relatively low to moderate temperatures (35 and 80–120 °C, respectively). It was found that reaction of **2f** with phosphonate **1**, under the above-mentioned conditions, gave 72% of the desired

Table 2
Reactions of phosphonate **1** with phenols **2a–i** to give difluoromethylphenyl ethers **3a–i**



Run	Phenols **2a–i**	Products **3a–i**	Yield[a] (%)
1	 **2a**	 **3a**	87[b] (77)[b,c] [34][b,d]
2	 **2b**	 **3b**	63
3	 **2c**	 **3c**	60
4	 **2d**	 **3d**	78 (60)[c] [10][d]
5	 **2e**	 **3e**	98 (74)[c] [53][d]
6	 **2f**	 **3f**	72
7	 **2g**	 **3g**	93
8	 **2h**	 **3h**	92
9	 **2i**	 **3i**	73 (40)[c] [34][d]

[a] Isolated yield.
[b] Yield was determined by ^{19}F NMR of the reaction mixture prior to work-up, using α,α,α-trifluorotoluene as reference standard due to the volatility of product **3a**.
[c] Using 1.1 equiv of phosphonate **1**.
[d] Using KF–Al_2O_3 (20, H_2O, 160) as basic solid support and 1.1 equiv of phosphonate **1**, as mentioned in Table 1.

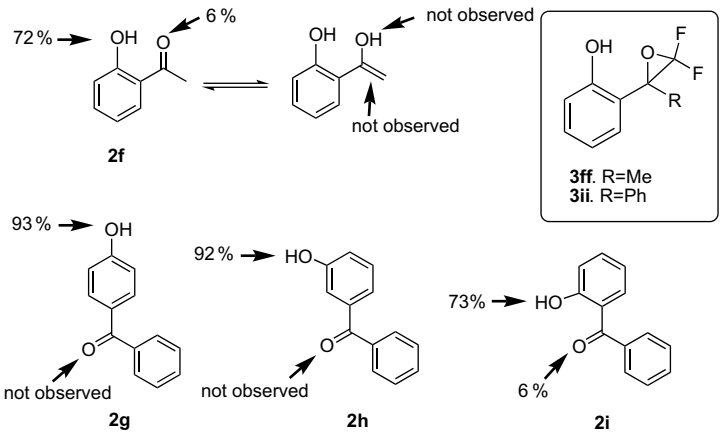


Figure 1. Chemoselectivity in the difluoromethylation of carbonyl-bearing phenols **2f**–**i**.

product **3f** together with ca. 6% (isolated yields) of the unexpected difluoro oxirane **3ff** product (run 6 and Fig. 1). Similarly, the analogue 2-hydroxybenzophenone (**2i**) gave 73% of the desired product **3i** together with ca. 6% (isolated yields) of the corresponding difluoro oxirane **3ii** product (run 9 and Fig. 1). However, their 4- and 3-hydroxybenzophenone analogues **2g**,**h** react exclusively with phosphonate **1** to give the corresponding difluoromethyl ethers **3g**,**h** in 93 and 92%, respectively (runs 7 and 8). These observations obviously demonstrate a good chemoselective difluoromethylation, using phosphonate **1** as a difluorocarbene precursor. The formation of **3ff** and **3ii** is presumably due to the anchimeric assistance of the *o*-hydroxyl substituent (vide infra).

2.2. Difluoromethylation of thiophenols

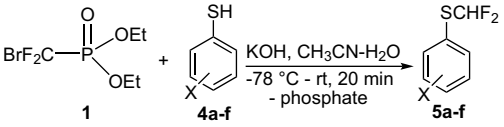
Encouraged by these results we proceeded to examine the reactivity of some thiophenols, possessing electron-withdrawing (**4b**–**d**) and electron-donating (**4e**,**f**) groups (Table 3). The data presented in Table 3 reveal that the difluoromethylation reaction takes place smoothly with excellent yields. These results emphasize advantages of the current method compared with others[17a,f] that suffer from lower yields and use of CHF_2Cl (Freon-22) as difluorocarbene precursor. The high yields of the thioether products versus their ether counterparts may be attributed to the high polarizability of the sulfur versus oxygen atom in the starting material, possessing a higher nucleophilicity in protic medium.

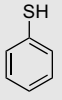
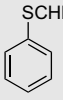
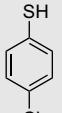
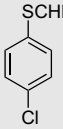
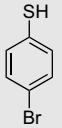
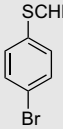
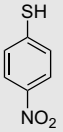
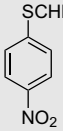
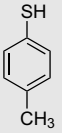
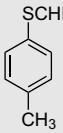
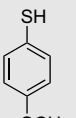
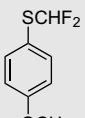
2.3. Mechanism

The proposed mechanism, depicted in Scheme 1, involves the hydrolysis-based P–C bond cleavage as a key step in the difluoromethylation process. The strength of the P–C bond in phosphonate compounds (and other *P*-alkyl substituted) is 62 kcal/mol.[22] Such P–C bond cleavage is possible only in cases in which the carbon adjacent to the phosphorus atom is activated by electron-withdrawing substituents, as in phosphonate **1**. The hydrolysis of **1**, therefore, produces bromodifluoromethyl anion, as an unstable reactive intermediate, and diethyl phosphate as byproduct. The former product instantaneously eliminates bromide to give difluorocarbene, which is subsequently trapped by a phenolate or thiophenolate ion and further protonated by water to produce the final difluoromethyl ether product.

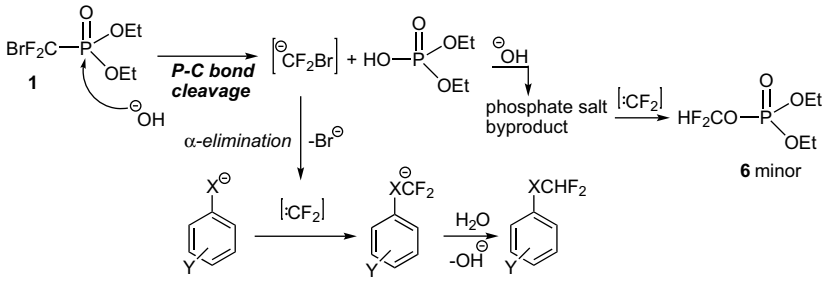
The minor products **3ff** and **3ii**, obtained on difluoromethylation of **2f** and **2i**, are presumably formed by an intramolecular attack of the carbanion intermediate on the carbonyl group prior to its protonation (Scheme 2). This cyclization leads to the appropriate

Table 3
Reactions of **1** with thiophenols **4a**–**f** to give difluoromethylphenyl thioethers **5a**–**f**



Run	Thiophenols **4a**–**f**	Products **5a**–**f**	Yield[a] (%)
1	 **4a**	 **5a**	88[b]
2	 **4b**	 **5b**	90
3	 **4c**	 **5c**	96
4	 **4d**	 **5d**	95
5	 **4e**	 **5e**	96
6	 **4f**	 **5f**	74

[a] Isolated yield.
[b] Yield was determined by ^{19}F NMR of the reaction mixture prior to work-up, using α,α,α-trifluorotoluene as reference standard due to the volatility of product **5a**.

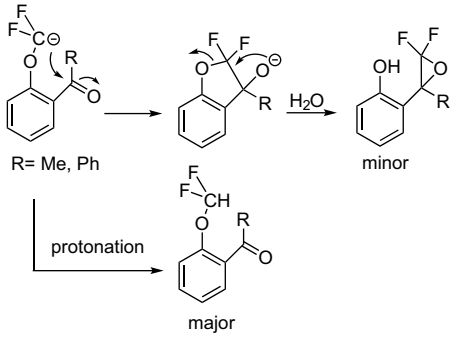


Scheme 1.

five-membered ring that on further rearrangement converts to oxiranes **3ff** and **3ii**.

In the course of our study we found that other byproducts, i.e., fluoride and formate ions, and diethyl difluoromethyl phosphate (**6**) were actually formed in minor quantities, regardless of the identity of the phenolate ions. Presumably, the ionic byproducts result from the hydrolysis of difluorocarbene.[23] Diethyl difluoromethyl phosphate (**6**) may be produced by difluoromethylation of diethyl phosphate salt following a similar mechanism as mentioned above. In other words, these byproducts are generated by competitive reactions, in which hydroxide and phosphate ions versus phenolate and thiophenolate ions compete on trapping the difluorocarbene intermediate. Due to the minority of these byproducts, even in cases in which only 1.1 equiv of phosphonate **1** and an excess of hydroxide were used (Table 2, runs 1, 4, 5, and 9), we must deduce that the mild conditions of our process gave a considerable advantage to the nucleophilicity of the phenolate and thiophenolate nucleophiles in this competition. Therefore, it is not surprising that the latter organo-sulfur intermediates underwent the difluoromethylation reaction in excellent yields, presumably because of their higher polarizability at the sulfur atom.

In addition to the convenient set-up of the reaction and its milder conditions, compared to other commonly used procedures, it is noteworthy that the resulting eco-friendly phosphate ion side product, the phosphate ion, is quantitatively separated from the biphasic reaction mixture due to its excellent solubility in water.



Scheme 2.

3. Summary

In summary, we have disclosed phosphonate **1** as an efficient and convenient precursor to difluorocarbene via a hydrolysis-based P–C bond cleavage. The formation of this unstable intermediate has been proved by its trapping with various phenolate and thiophenolate ions, forming the corresponding difluoromethylaryl ethers/thioethers in good to excellent yields. The reaction proceeds at mild conditions, which enables good chemoselectivity in the presence of carbonyl or enol functions. It is noteworthy that phosphonate **1** is commercially available and convenient to handle. Its reaction with hydroxide ion produced difluorocarbene as intermediate and phosphate salt as an eco-friendly water soluble byproduct. Therefore, this method may be considered as an attractive process, not only in terms of efficient and practical chemistry but also in terms of 'green chemistry'.

4. Experimental section

4.1. General remarks

All reagents are commercially available and were used without further purification. NMR spectra were recorded on Bruker Avance 300 spectrometer (^{1}H NMR: 300.1 MHz, ^{13}C NMR: 75.5 MHz, ^{31}P NMR: 121.5 MHz and ^{19}F NMR: 282.4 MHz). Chemical shifts are reported in parts per million (δ ppm). ^{1}H NMR chemical shifts were referenced to the residual hydrogen signal of deuterated chloroform (δ=7.26 ppm). In ^{13}C measurements the signal of $CDCl_3$ (δ=77.0) was used as a reference. ^{31}P and ^{19}F chemical shifts are reported downfield from external 85% solution of phosphoric acid and trifluoroacetic acid in D_2O, respectively. Mass spectra (EI/CI) were recorded on GC/MS Varian Saturn 2200 instrument at 70 eV. Column chromatography was performed with Merck silica gel 60 (230–400 mesh) using hexane or ethyl acetate–hexane 5:95, as eluent. High-resolution mass data were recorded on an HRMS in the EI or CI modes.

4.2. General procedure for difluoromethylation of phenols and thiophenols

Phosphonate **1** (2 mmol) was added in one portion to a cooled (−78 °C) solution of the appropriate phenol (1 mmol) and KOH (20 mmol) in CH_3CN–H_2O (10 mL, 1:1), placed in a sealed tube and equipped with a magnetic stirrer. The reaction mixture was allowed to warm to rt. After 20 min, the reaction mixture was diluted with ether (10 mL) and the organic phase was separated. The water phase was then washed with a further amount of ether (10 mL), and the combined organic fractions were dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a crude product that was purified by column chromatography (in most cases by just passing the hexane or ethyl acetate–hexane (5:95) solution through a short column of silica gel).

Experimental data for products **3a**,**d**,**e** and **5a** were reported previously.[15,16,17f] The data for new compounds or compounds that were previously characterized (**3b**,[17f,g] **3f**,[24] **5b**–**f**[17f,25]) but lack data are listed below. HRMS analysis for all novel compounds is also reported. According to GC–MS and NMR data all products were achieved in a purity of >97%.

*4.2.1. 4-Methoxy-1-(difluoromethoxy)benzene (**3b**)*

Colourless oil (63% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 3H), 6.41 (t, J_{HF}=74.4 Hz, 1H), 6.85–6.88 (m, 2H), 7.05–7.08 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.6, 114.7, 116.3 (t, J_{CF}=258.9 Hz), 121.3, 144, 157.3; ^{19}F NMR (282 MHz, $CDCl_3$): δ −4.13 (d, J=74.4 Hz); MS (CI): m/z 175 (MH^+, 36%), 155 (100), 108 (41). IR (film): 2916, 2848, 1508, 1212, 1125, 1033, 961, 831 cm^{-1}.

*4.2.2. 2,6-Dimethyl-1-(difluoromethoxy)benzene (**3c**)*

Colourless oil (60% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 6H), 6.34 (t, J_{HF}=73.3 Hz, 1H), 7.05–7.09 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.4, 117.7 (t, J_{CF}=258.3 Hz), 126.2, 129.2, 131.6, 148.7; ^{19}F NMR (282 MHz, $CDCl_3$): δ −2.1 (d, J=73.4 Hz); HRMS (CI) calcd for $C_9H_{11}F_2O$ (MH): 173.0778, found: 173.0790. IR (film): 2926, 1469, 1269, 1252, 1240, 1150, 1107, 1034, 770 cm^{-1}.

*4.2.3. 2-(Difluoromethoxy)acetophenone (**3f**)*

Colourless oil (72% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.62 (s, 3H), 6.60 (t, J_{HF}=73.4, 1H), 7.18 (dd, J=9.1, 1.0 Hz, 1H), 7.28 (dt, J=9.1, 1.0 Hz, 1H), 7.51 (dt, J=7.5, 1.8 Hz, 1H), 7.74 (dd, J=7.7, 1.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 31.2, 116.1 (t, J_{CF}=260.4 Hz), 119.7, 125.6, 130.5, 132.0, 133.4, 149.4, 197.0; ^{19}F NMR (282 MHz, $CDCl_3$): δ −4.43 (d, J=73.3 Hz); MS (EI) m/z: 186 (M, 4.5%), 169 (100). IR (film): 3006, 1686, 1601, 1485, 1450, 1382, 1360, 1290, 1245, 1220, 1131, 1104, 1055, 761 cm^{-1}.

*4.2.4. 2-(3,3-Difluoro-2-methyloxiranyl)phenol (**3ff**)*

White solid, mp 70–71 °C (5.5% yield); NMR (300 MHz, $CDCl_3$): δ 1.65 (dd, J_1=2.7, 0.6 Hz, 3H), 6.95 (d, J=8.1 Hz, 1H), 7.11 (t, J=7.5 Hz, 1H), 7.30–7.36 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 21.95 (d, J_{CF}=6.3 Hz), 77.9 (dd, J_{CF}=31.5, 24.9 Hz), 110.8, 123.6, 123.8, 129.7, 130.7 (t, J_{CF}=271.5 Hz), 130.9, 153.6; ^{19}F NMR (282 MHz, $CDCl_3$): δ −12.5 (d, J=144.0 Hz), −11.5 (d, J=143.0 Hz); HRMS (EI) calcd for $C_9H_8F_2O_2$ (M): 186.0492, found: 186.0476. IR (film) 2992, 1604, 1478, 1469, 1302, 1259, 1240, 1140, 1110, 1095, 1065, 753 cm^{-1}.

*4.2.5. 4-(Difluoromethoxy)benzophenone (**3g**)*

Colourless oil (93% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.62 (t, J_{HF}=73.1, 1H), 7.19–7.23 (m, 2H), 7.46–7.51 (m, 2H), 7.57–7.61 (m, 1H), 7.76–7.79 (m, 2H), 7.83–7.86 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 113.1 (t, J_{CF}=261 Hz), 115.1, 117.4, 121.1, 128.1, 128.4, 129.7, 129.8, 129.9, 131.8, 132.6, 132.8, 158.4, 160.5; ^{19}F NMR (282 MHz, $CDCl_3$): δ −3.94 (d, J=73.1 Hz); HRMS (CI) calcd for $C_{14}H_{11}F_2O_2$ (MH): 249.0727, found: 249.0717. IR (film): 3062, 1658, 1601, 1504, 1447, 1384, 1316, 1278, 1230, 1175, 1121, 1048, 924, 740, 698 cm^{-1}.

*4.2.6. 3-(Difluoromethoxy)benzophenone (**3h**)*

Colourless oil (92% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.57 (t, J_{HF}=73.3, 1H), 7.34–7.37 (m, 1H), 7.46–7.52 (m, 3H), 7.57–7.64 (m, 3H), 7.78–7.81 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 115.6 (t, J_{CF}=261.4 Hz), 120.7, 123.5, 127.0, 128.4, 129.8, 130.0, 132.8, 136.9, 139.4, 150.9, 195.4; ^{19}F NMR (282 MHz, $CDCl_3$): δ −4.95 (d, J=73.3 Hz); HRMS (CI) calcd for $C_{14}H_{11}F_2O_2$ (MH): 249.0727, found: 249.0734. IR (film): 3068, 1662, 1597, 1482, 1447, 1383, 1280, 1215, 1140, 1113, 1047, 717, 697 cm^{-1}.

*4.2.7. 2-(Difluoromethoxy)benzophenone (**3i**)*

Colourless oil (73% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.45 (t, J_{HF}=73.4, 1H), 7.47–7.51 (m, 2H), 7.59–7.68 (m, 5H), 7.94–7.97 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 115.9 (t, J_{CF}=261.2 Hz), 121.0, 125.4, 128.4, 129.8, 129.9, 131.8, 132.4, 133.4, 136.9, 148.2, 194.6; ^{19}F NMR (282 MHz, $CDCl_3$): δ −4.94 (d, J=73.3 Hz); HRMS (CI) calcd for $C_{14}H_{11}F_2O_2$ (MH): 249.0727, found: 249.0738. IR (film): 3064, 1668, 1602, 1486, 1450, 1316, 1294, 1269, 1123, 1052, 929, 758, 700 cm^{-1}.

*4.2.8. 2-(3,3-Difluorophenyloxiranyl)phenol (**3ii**)*

Colourless oil (6.5% yield); NMR (300 MHz, $CDCl_3$): 6.93–6.96 (m, 2H), 7.00–7.05 (m, 2H), 7.11–7.14 (m, 3H), 7.26–7.32 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 82.1 (dd, J_{CF}=30.6, 23.4 Hz), 111.1, 124.3, 125.5, 126.8, 128.2, 128.8, 129.7, 130.3 (t, J=271.6 Hz), 131.6, 136.5, 155.1; ^{19}F NMR (282 MHz, $CDCl_3$): δ −11.9 (d, J=142.3 Hz), −4.8 (d, J=140.4 Hz); HRMS (CI) calcd for $C_{14}H_{11}F_2O_2$ (MH): 249.0727, found: 249.0721. IR (film): 3063, 1659, 1603, 1477, 1467, 1450, 1294, 1233, 1138, 1120, 1067, 930, 755, 700 cm^{-1}.

*4.2.9. 4-Chloro-1-(difluoromethylthio)benzene (**5b**)*

Colourless oil (90% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.81 (t, J_{HF}=56.6, 1H), 7.35–7.39 (m, 2H), 7.51–7.54 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 120.3 (t, J_{CF}=275.9 Hz), 124.2, 129.3, 129.6, 136.7; ^{19}F NMR (282 MHz, $CDCl_3$): δ −15.4 (d, J=57.0 Hz); MS (EI) m/z: 194 (M, 100%), 144 (75), 108 (25). IR (film): 2970, 1574, 1477, 1390, 1318, 1095, 1066, 1039, 1014, 826, 789, 761, 739 cm^{-1}.

*4.2.10. 4-Bromo-1-(difluoromethylthio)benzene (**5c**)*

Colourless oil (96% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.81 (t, J_{HF}=56.6, 1H), 7.43–7.46 (m, 2H), 7.51–7.54 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 120.3 (t, J_{CF}=276.0 Hz), 124.7, 129.4, 132.5, 136.9; ^{19}F NMR (282 MHz, $CDCl_3$): δ −15.2 (d, J=56.5 Hz); MS (EI) m/z: 240 (M, 25%), 190 (100), 109 (97). IR (film): 2916, 1727, 1473, 1457, 1386, 1279, 1128, 1092, 1031, 965, 914, 817, 748 cm^{-1}.

*4.2.11. 4-Nitro-1-(difluoromethylthio)benzene (**5d**)*

Colourless oil (95% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.94 (t, J_{HF}=55.8, 1H), 7.70–7.74 (m, 2H), 8.20–8.25 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 119.8 (t, J_{CF}=276.3 Hz), 123.8, 125.8, 134.3, 134.9; ^{19}F NMR (470 MHz, $CDCl_3$): δ −15.4 (d, J=55.0 Hz); MS (EI) m/z: 205 (M, 100%), 175 (26), 155 (28), 125 (50), 108 (15). IR (film) 2969, 1566, 1474, 1388, 1317, 1296, 1068, 1039, 1010, 822, 789, 758, 724 cm^{-1}.

*4.2.12. 4-Methyl-1-(difluoromethylthio)benzene (**5e**)*

Colourless oil (96% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.39 (s, 3H), 6.80 (t, J_{HF}=57.1, 1H), 7.20–7.23 (m, 2H), 7.48–7.51 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.2, 121.1 (t, J_{CF}=274.9 Hz), 128.5, 130.1, 135.6, 140.3; ^{19}F NMR (282 MHz, $CDCl_3$): δ −15.3 (d, J=57.2 Hz); MS (EI) m/z: 174 (M, 100%), 123 (32), 91 (20). IR (film): 2921, 1489, 1444, 1209, 1180, 1067, 1036, 1017, 803, 757 cm^{-1}.

*4.2.13. 4-Methoxy-1-(difluoromethylthio)benzene (**5f**)*

Colourless oil (74% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 3H), 6.75 (t, J_{HF}=57.2 Hz, 1H), 6.90–6.94 (m, 2H), 7.50–7.53 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.4, 114.9, 120.9 (t, J_{CF}=275 Hz), 132.3, 137.6, 161.1; ^{19}F NMR (282 MHz, $CDCl_3$): δ −15.9 (d, J=58.1 Hz); MS (EI) m/z: 190 (M, 87%), 139 (100), 124 (5). IR (film): 2965, 2840, 1592, 1572, 1495, 1463, 1319, 1291, 1251, 1175, 1098, 1066, 1030, 831, 790 cm^{-1}.

*4.2.14. O-Diethyl difluoromethyl phosphate (**6**)*

Colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (dt, J=7.1, 1.2 Hz, 6H), 4.15–4.27 (m, 4H), 6.69 (dt, $J_{HF,HP}$=73.7, 3.7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.9 (d, J=6.9 Hz), 65.3 (d, J=6.2 Hz), 113.1 (dt, $J_{CF,CP}$=260.2, 2.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ −3.94 (dd, J=73.4, 8.8 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ −11.4 (t, J=9.2 Hz); HRMS (CI) calcd for $C_5H_{12}F_2O_4$ (MH): 205.0418, found: 205.0420. IR (film): 2956, 2916, 2848, 1572, 1565, 1260, 1085, 1018 cm^{-1}.

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18. This low cost diethyl bromodifluoromethylphosphonate is supplied by many famous chemical companies. It may be easily prepared by the procedure of Burton and Flynn in excellent yield (>95%), using nearly equivalent amounts of triethyl phosphite and dibromofluoromethane (a precursor of difluorocarbene itself). Curiously, this version of Michaelis–Arbuzov reaction also involves a difluorocarbene as an unstable intermediate. For the synthesis of diethyl bromodifluoromethylphosphonate see also: (a) Burton, D. J.; Flynn, R. M. *J. Fluorine Chem.* **1977**, *10*, 329; (b) Davisson, V. J.; Woodside, A. B.; Neal, T. R.; Stremler, K. E.; Muehlbacher, M.; Poulter, C. D. *J. Org. Chem.* **1986**, *51*, 4768.
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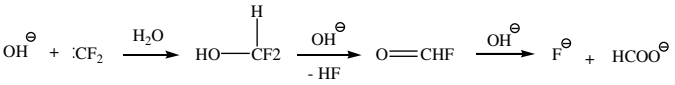
23. In the hydrolysis of difluorocarbene, the hydroxide ion initially reacts with this unstable intermediate to form difluoromethanol, which eventually undergoes an elimination of HF followed by further hydrolysis to give fluoride and formate salts.



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