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Cuprous chloride promoted coupling reaction of diethoxyphosphinyldifluoromethylcadmium reagent with aryl iodides: A practical and convenient preparation of α,α-difluoro benzylic phosphonates

Weiming Qiu, Donald J. Burton *

Department of Chemistry, University of Iowa, Iowa City, IA 52242, USA

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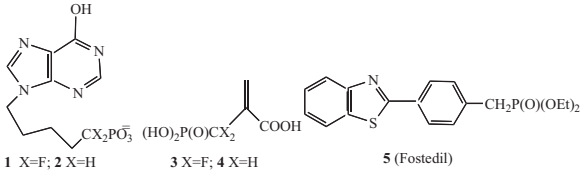
ABSTRACT

The cross coupling reaction of diethoxyphosphinyldifluoromethylcadmium reagent with aryl iodides was promoted by CuCl under mild conditions to give α,α-difluoro benzylic phosphonates in good yields. A variety of functional groups, including halides, phosphonate, nitro, ketone, carboxylic acid and ester in aryl iodides, could be tolerated. This methodology has been successfully applied to prepare α,α-difluoro Fostedil **9**.

1. Introduction

Introduction of difluoromethylenephosphonate into organic molecules has attracted much attention generally due to the biological properties exhibited by these analogs as compared to the non-fluorinated phosphonate analog [1]. For example, 9-(5,5-difluoro-5-phosphonopentyl)guanine **1** has been found 26 times more effective than its non-fluorinated analog **2** as an inhibitor of purine nucleoside phosphorylase [2a]. More recently, it was found that disodium salt of 2-[(dihydroyphosphinyl)difluoromethyl]propenoic acid **3** in the presence of S3P (shikimate 3-phosphate) irreversibly inhibited EPSP (5-enolpyruvoylshikimate 3-phosphate) synthase 50% in 6 h, whereas the corresponding non-fluorinated analog **4** had no effect on EPSP synthase [2b]. It is also known that benzylic phosphonates are of importance of biological activity [3–5]. Fostedil **5**, for instance, is an effective antihypertensive, vasodilator, antiarrhythmic and Ca antagonist [4]. In addition, the (diethoxyphosphinylmethyl)phenyl moiety has been incorporated into peptides to prepare phosphotyrosine containing peptides, which act as either product analog inhibitors of protein tyrosine kinases or as substrate analog inhibitors of protein tyrosine phosphoatases [5]. The preparation of α,α-difluro alkylphosphonates have been well documented [6] and the biological activities of some α,α-difluoro alkylphosphonates have been discussed [2,7]. However, there has been only one report describing the synthesis of α,α-difluoro benzylic phosphonate; achieved by the reaction of benzoylphosphonate with 15 equivalents of DAST (as solvent) to form 43–79% of α,α-difluoro benzylphosphonates [8]. The lack of general synthetic methodology for the preparation of α,α-difluoro benzylic phosphonates has encumbered the investigation of this class of phosphonates. Here, we wish to report a facile and general method for the preparation of α,α-difluoro benzylic phosphonates.



1 X=F; **2** X=H **3** X=F; **4** X=H **5** (Fostedil) (1)

2. Results and discussion

Fluorinated copper compounds are useful reagents for the introduction of a fluorinated group into organic molecules [9]. For example, Kobayashi reported the coupling reaction of ethoxycarbonyldifluoromethylcopper reagent with aryl iodides to give the corresponding α,α-difluoroesters [10]. In our laboratory, we have

* Corresponding author. Tel.: +1 319 335 1363; fax: +1 319 335 1270.
E-mail addresses: donald-burton@uiowa.edu, mburton105@gmail.com (D.J. Burton).

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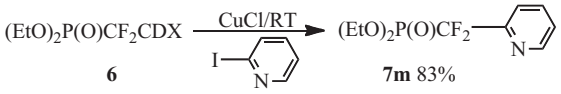
found that the CuBr catalyzed reaction of diethoxyphosphinyldifluoromethylzinc reagent with a number of electrophiles, such as allylic halides, methyl iodide, and acid chlorides, affords the corresponding α,α-difluorophosphonates [6f,11].

In the course of our continuing study of the introduction of the α,α-difluorophosphonate moiety into organic molecules, we have found that the coupling reaction of diethoxyphosphinyldifluoromethylcadmium reagent **6** [6k] generated from diethyl bromodifluoromethylphosphonate and cadmium proceeds readily with aryl iodides in the presence of CuCl in DMF to give excellent yields of α,α-difluoro benzylic phosphonates at room temperature. For example, in the presence of CuCl reaction of the cadmium reagent **6** with iodobenzene afforded α,α-difluoro benzylphosphonate [7b] in 80% isolated yield. Table 1 summarizes the results of the CuCl reaction with **6** with a variety of substituted aryl iodides.

$$(EtO)_2P(O)CF_2Br \xrightarrow{Cd/DMF/RT} \underset{\mathbf{6}}{(EtO)_2P(O)CF_2CdX} \xrightarrow{CuCl/ArI/RT} \underset{\mathbf{7}\ 55-88\%}{(EtO)_2P(O)CF_2Ar} \quad (2)$$

With halo-substituted aryl iodides (entries 5, 8, 12 in Table 1), the reaction selectively gave aryl iodide coupled products. Upon the reaction of excess cadmium reagent **6** with 1,4-diiodobenzene, the corresponding bisphosphonate was obtained (entry 11). The coupling reaction also works well with heterocyclic iodides, such as 2-iodopyridine and 2-iodothiophene, to give the corresponding phosphonates in good yields. In the presence of CuCl, diethoxyphosphinylmethylzinc reagent also coupled with 4-nitroiodobenzene to afford **7a** in 80% yield. In the presence of CuCl, phosphonate **8** was obtained by the reaction of 4-iodonitrobenzene with dibutoxyphosphinyldifluorocadmium reagent, which was generated from dibutyl bromodifluoromethylphosphonate and cadmium. However, none of the coupling product was isolated from the reaction of **6** with bromobenzene under similar conditions.



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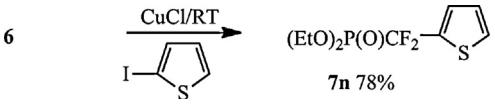

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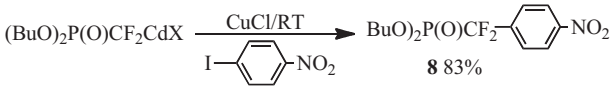


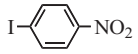
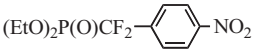
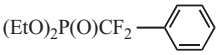
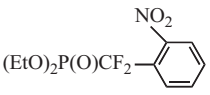
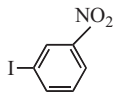
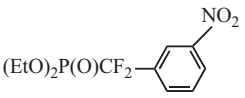
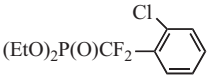
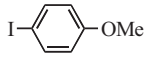
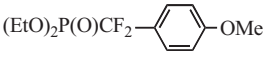
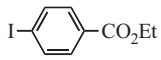
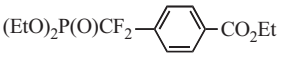
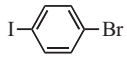
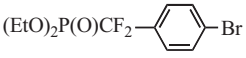
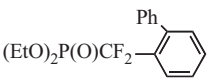
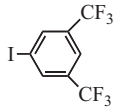
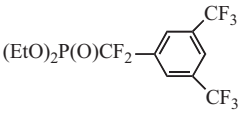
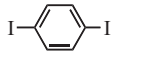
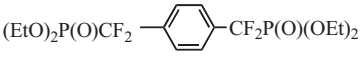
(5)

The coupling reaction requires a stoichiometric amount of CuCl to obtain a good yield of phosphonate **7**. When 10 mol% of CuCl was used, the reaction of **6** with iodobenzene gave **7b** (less than 40%) and a significant amount of bisphosphonates $(EtO)_2P(O)CF{=}CFCFP(O)(OEt)_2$ (*cis* and *trans* mixture). It has been reported that a catalytic amount of CuX decomposes $(Et)_2P(O)CF_2ZnX$ to give the same bisphosphonates [12].

It is believed that this coupling reaction proceeds via the diethoxyphosphinyldifluoromethylcopper reagent. $(EtO)_2P(O)CF_2Cu$, since we have converted the cadmium reagent **6** to $(EtO)_2P(O)CF_2Cu$, followed by coupling with iodobenzene to give phosphonate **7b**. ^{19}F NMR analysis revealed the formation of the copper reagent, $(EtO)_2P(O)CF_2Cu$, doublet at −118.2 ppm with $J = 95$ Hz [80% NMR yield based on the starting phosphonate $(EtO)_2P(O)CF_2Br$]. The stability of $(EtO)_2P(O)CF_2Cu$ has been investigated and summarized in Table 2. The main decomposition compounds were $(EtO)_2P(O)F$ and $(EtO)_2P(O)CF_2CF_2Cu$, the minor decomposition compounds were $(EtO)_2P(O)CF_2H$ and $(EtO)_2P(O)CF{=}CFP(O)(OEt)_2$.

Table 1
CuCl promoted coupling reaction of cadmium reagent 6 with aryl iodides.

$$(EtO)_2P(O)CF_2Br \xrightarrow{Cd/DMF/RT} \underset{\mathbf{6}}{(EtO)_2P(O)CF_2CdX} \xrightarrow{CuCl/ArI/RT} \underset{\mathbf{7}}{(EtO)_2P(O)CF_2Ar}$$

Entry	Aryl iodide	Product	Yield (%)[a]
1			84
2			80
3			83
4			80
5			88
6			85
7			84
8			70
9			65
10			83
11			75
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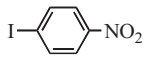
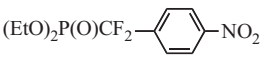
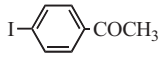
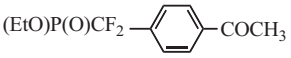
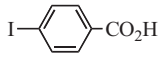
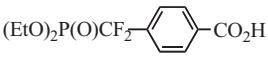
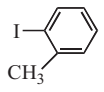
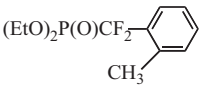
13			80[b]
14			75[c]
15			75
16			55
17			83

[a] Isolated yields.
[b] From $(EtO)_2P(O)CF_2ZnX$ and CuCl.
[c] From pregenerated $(EtO)_2P(O)CF_2Cu$.

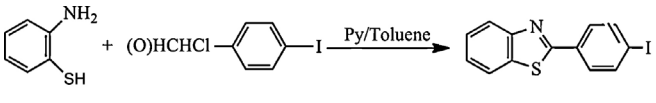
Small amounts (1–7%) of $(EtO)_2P(O)CF_2CF_2Ar$ were formed from the CuCl reaction of **6** with aryl iodides. For example, 5% of $(EtO)_2P(O)CF_2CF_2Ph$ [^{19}F NMR −110.3 ppm (s) and −121.4 ppm (d, $J = 96$ Hz] was observed in the preparation of $(EtO)_2P(O)CF_2Ph$. The formation of $(EtO)_2P(O)CF_2Ar$ may involve carbene insertion [13]

Table 2
Stability of $(EtO)_2P(O)CF_2Cu$ in DMF at room temperature.

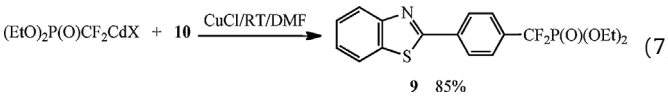
Time	Remained $(EtO)_2P(O)CF_2Cu$ (%)
3 h	80
19 h	53
4 days	38
7 days	25

into the copper reagent **6** (as shown in Scheme 1). Phosphonate **7** and $(EtO)_2P(O)CF_2CF_2Ar$ could be readily separated by silica gel column chromatography.

As discussed earlier, Fostedil (**5**) is a biologically important compound. We have applied our methodology for the preparation of the α,α-difluorinated analog **9**. The precursor 2-(4-iodophenyl)benzothiazole (**10**) was prepared by the reaction of 2-aminothiophenol with 4-iodobenzoyl chloride and pyridine in toluene [14]. In the presence of CuCl, the reaction of the cadmium reagent **6** with benzothiazole **10** afforded α,α-difluorinated Fostedil **9** in 85% isolated yield.

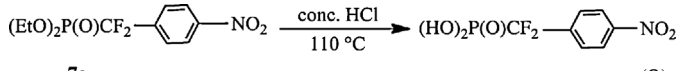


10 65% (6)

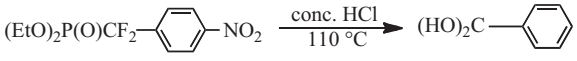


9 85% (7)

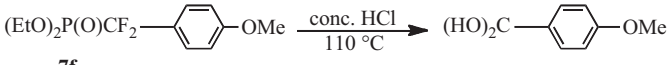
Concentrated hydrochloric acid hydrolysis [15] of **7a** gave the corresponding phosphonic acid **11a** in 92% yield. However, under similar conditions, hydrolysis of **7b** and **7f** produced benzoic acid and 4-methoxybenzoic acid, respectively.



7a (8)

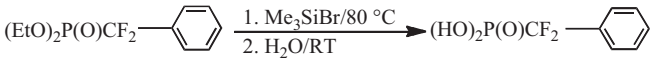


7b (9)

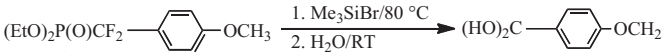


7f (10)

Phosphonate **7b** has been successfully converted into the corresponding phosphonic acids **11b** by the reaction with Me_3SiBr at 80 °C followed by the treatment with water at room temperature [16]. However, 4-methoxybenzoic acid was obtained again when this methodology applied for hydrolysis of phosphonate **7f**.



7a **11a 93%** (11)



7f (12)

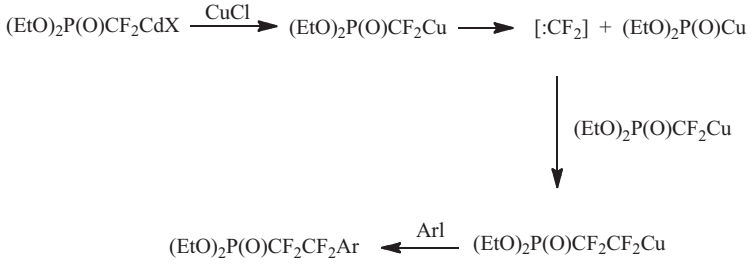
3. Conclusions

We have demonstrated a practical and convenient method for the synthesis of potentially biologically important α,α-difluoro benzylic phosphonates under mild reaction conditions. This methodology has been successfully applied for the synthesis of α,α-difluorinated Fostedil **9**. α,α-Difluoro benzylphosphonate **7b** and electron-withdrawing group substituted phosphonate **7a** are hydrolyzed into the corresponding α,α-difluoro benzylic phosphonic acids, whereas electron-donating group substituted α,α-difluoro benzylic phosphonate **7f** decomposes during hydrolysis.

4. Experimental

4.1. General experimental procedures

All boiling points and melting points are uncorrected and taken after purification by silica gel column chromatography. All boiling points were determined during distillation using a partial immersion thermometer. ^{19}F NMR, ^{1}H NMR and ^{13}C {H} NMR spectra were recorded on a Bruker AC 300 spectrometer. ^{31}P {H} NMR spectra were recorded on a JEOL FX 90Q spectrometer. All chemical shifts are reported in parts per million downfield (positive) of the standard. ^{1}H NMR and ^{13}C NMR chemical shifts are reported relative to internal TMS. ^{19}F NMR chemical shifts are reported relative to internal $CFCl_3$. ^{31}P NMR chemical shifts are reported relative to external H_3PO_4 (85%). ^{13}C NMR and ^{31}P NMR spectra were broadband decoupled from hydrogen nuclei. $CDCl_3$ served as the solvent for all NMR spectra. IR spectra were recorded on a Mattson Cygnus 100 FTIR spectrometer. GC–MS and DIP–MS were recorded on a VG TRIO-1 spectrometer operating at 70 eV. High resolution MS were performed by the Midwest Center for Mass Spectrometry which is partially supported by the National Science Foundation, Biology Division (Grant No. DIR 9017262). All of the products gave greater than 97% purities based on ^{13}C NMR, ^{1}H NMR, ^{31}P NMR and ^{19}F NMR spectroscopic analysis. Diethyl bromodifluoromethylphosphonate and dibutyl bromodifluoromethyl-phosphonate were prepared by the reported method [6k] and DMF was distilled from CaH_2. Cadmium and zinc were washed with acid, water and acetone. All other starting materials were used without further purification.



Scheme 1. Proposed mechanism for the formation of $(EtO)_2P(O)CF_2CF_2Ar$.

*4.1.1. Representative general procedure for the preparation of diethyl α,α-difluoro benzylic phosphonate (**7**): diethyl α,α-difluoro-4-nitrobenzylphosphonate (**7a**)*

A 100-mL flask fitted with a stir bar and a condenser topped with a nitrogen inlet was charged with 2.67 g (10.0 mmol) of diethyl bromodifluoromethylphosphonate, 1.25 g (11 mmol) of Cd and 10 mL of dry DMF. The mixture was stirred at room temperature for 2 h. ^{19}F NMR analysis revealed the formation of $(EtO)_2P(O)CF_2CdX$ (two doublets at −122.8 and −123.6 ppm with J = 83 Hz, the ration of the two doublets was 1:1) in 91% NMR yield based on starting phosphonate $(EtO)_2P(O)CF_2Br$. The unreacted Cd was removed by filtration through a medium frit funnel under a nitrogen atmosphere and the filtrate was treated with 0.69 g (7.0 mmol) of CuCl and 1.5 g (6.0 mmol) of 4-nitroiodobenzene at room temperature for 3 h. 100 mL of ether was added to the reaction mixture and the precipitated solids were removed by filtration and washed with 50 mL of ether. The combined ether solutions were washed with NH_4Cl(aq) and H_2O, dried over Na_2SO_4, and evaporated to give a residue, which was further purified by silica gel column chromatography. Eluent (CH_2Cl_2/EtOAc 9:1) gave 1.55 g (84%) of **7a**, mp 47–48 °C. ^{19}F NMR: −110.1 (d, J = 111 Hz). ^{1}H NMR: 1.35 (t, J = 7 Hz, 6 H), 4.26 (m, 4 H), 7.83 (d, J = 8 Hz, 2 H), 8.33 (d, J = 8 H, 2 H). ^{13}C NMR: 16.4 (d, J = 6 Hz), 65.2 (d, J = 7 Hz), 117.3 (td, J = 264, 216 Hz), 123.6 (s), 127.8 (s), 139.0 (td, J = 22, 14 Hz), 149.5 (s). ^{31}P NMR 5.3 (t, J = 110 Hz). GC–MS (m/z) (relative intensity) 309 (M^+, 0.31), 279 (M^+ –NO, 3.18), 263 (M^+ – NO_2, 0.42), 172 ($CF_2C_6H_4NO_2^+$, 8.92), 137 {$(EtO)_2P(O)^+$, 28.49}, 109 {$(HO)(EtO)P(O)^+$, 100}. FTIR: (CCl_4) 2986 (m), 2933 (w), 2914 (w), 1614 (w), 1533 (s), 1351 (s), 1275 (s), 1068 (s), 1047 (s), 1026 (vs), 856 (m) cm^{-1}. HRMS: calc'd for $C_{11}H_{14}F_2NO_5P$ [M^+] 309.0578, obsv'd: 309.0578.

*4.1.2. Diethyl α,α-difluoro benzylphosphonate (**7b**)*

80%; bp 85 °C (0.03 mm); ^{19}F NMR: −108.9 (d, J = 116 Hz). ^{1}H NMR: 1.30 (t, J = 7 Hz, 6 H). 4.19 (m, 4 H), 7.47 (m, 3 H), 7.62 (m, 2 H). ^{13}C NMR: 16.3 (d, J = 6 Hz), 64.8 (d, J = 7 Hz), 118.1 (td, J = 263, 218 Hz), 126.3 (td, J = 7, 2 Hz), 128.5 (s), 130.8 (s), 132.7 (td, J = 22, 14 Hz). ^{31}P NMR 6.34 (t, J = 116 Hz). GC–MS (m/z) (relative intensity) 264 (M^+, 2.19), 127 ($PhCF_2^+$, 100), 137 {$(Et))_2P(O)^+$, 5.55}, 109 {$HO)(EtO)P(O^+$), 37.64}, 77 (Ph^+, 30.33). FTIR: (CCl_4) 2984 (m), 2933 (w), 2913 (w), 1273 (s), 1129 (s), 1050 (s) 1025 (vs), 771 (m), 698 (m) cm^{-1}. HRMS: calc'd for $C_{11}H_{15}F_2O_3P$ [M^+] 264.0727, obsv'd 264.0715.

*4.1.3. Diethyl α,α-difluoro-2-nitrobenzylphosphonate (**7c**)*

83%; oil; ^{19}F NMR: −103.4 (d J = 99 Hz). ^{1}H NMR: 136 (t, J = 7 Hz, 6 H), 4.29 (m, 4 H), 7.63 (m, 3 H), 7.84 (m, 1H). ^{13}C NMR: 16.3 (d, J = 6 Hz), 65.5 (d, J = 7 Hz), 117.2 (td, J = 266, 217 Hz), 124.0 (s), 125.4 (td, J = 22, 14 Hz), 129.9 (t, J = 8 Hz), 131.4 (s), 132.1 (s), 148.8 (s). ^{31}P NMR: 4.63 (t, J = 98 Hz). GC–MS: (m/z) (relative intensity) 310 (M^+ + 1, 0.12), 263 (M^+ –NO_2, 2.30), 172 ($CF_2C_6H_4NO_2^+$, 6.84), 137 {$(EtO)_2P(O)^+$, 2.47}, 109 {$(HO)(EtO)P(O)^+$, 42.57}. FTIR: (CCl_4) 2986 (m), 2933 (w), 2913 (w), 1545 (s), 1370 (s), 1275 (s), 1042 (s), 1027 (vs), 941 (m), 982 (m) cm^{-1}.

*4.1.4. Diethyl α,α-difluoro-3-nitrobenzylphosphonate (**7d**)*

80%; oil; ^{19}F NMR: −109.6 (d, J = 112 Hz). ^{1}H NMR 1.36 (t, J = 7 Hz, 6 H), 4.27 (m, 4 H), 7.69 (t, J = 8 Hz, 1 H), 7.99 (d, J = 8 Hz, 1 H), 8.37 (d, J = 8 Hz, 1 H), 8.47 (s, 1 H). ^{13}C NMR: 16.4 (d, J = 6 Hz), 65.2 (d, J = 7 Hz), 117.1 (td, J = 264, 218 Hz), 121.6 (td, J = 7 Hz), 125.7 (s), 130.0 (s), 132.4 (td, J = 7, 2 Hz), 134.9 (td, J = 22, 14 Hz), 148.3 (s). ^{31}P NMR: 5.36 (t, J = 111 Hz). GC–MS (m/z) (relative intensity) 309 (M^+, 0.18), 279 (M^+ –NO, 0.93), 263 (M^+ –NO_2, 0.25), 172 ($CF_2C_6H_4NO_2^+$. 27.10), 137 {$(EtO)_2P(O)^+$, 18.49}, 109 {$(HO)(EtO)P(O)^+$., 100}. FTIR: (CCl_4) 2986 (m), 2933 (w), 2914 (w), 1624 (w), 1539 (s), 1275 (s), 1065 (s), 1047 (s), 1024 (vs), 981 (m), 951 (m), 681 (m) cm^{-1}. HRMS: calc'd for $C_{11}H_{14}F_2O_4P$ [M^+, –NO] 179.0598, obsv'd 279.0602.

*4.1.5. Diethyl α,α-difluoro-2-chlorobenzylphosphonate (**7e**)*

88%; bp 111 °C (0.03 mm). ^{19}F NMR: −105.4 (d, J = 114 Hz). ^{1}H NMR: 134 (t, J = 7 Hz, 6 H), 4.25 (m, 4 H), 7.34–7.46 (m, 3 H), 7.63 (d, J = 7 Hz, 1 H). ^{13}C NMR: 16.4 (d, J = 5 Hz), 64.9 (d, J = 7 Hz), 118.1 (td, J = 265, 219 Hz), 126.7 (s), 129.5 (td, J = 8.2 Hz), 130.2 (td, J = 21, 14 Hz), 131.8 (s), 131.9 (s), 132.8 (m). ^{31}P NMR: 5.7 (t, J = 114 Hz). GC–MS (m/z) (relative intensity): 263 (M^+, –Cl, 20.63), 235 (M^+ –Cl– 28, 8.25), 207 (M^+ –Cl– 56, 15.53), 161, 163 ($CF_2C_6H_4Cl^+$, 82.52, 25.97), 109 {$(HO)(EtO)P(O)^+$, 100}. FTIR: (CCl_4): 2985 (m), 2933 (w), 2913 (w), 1596 (w), 1277 (s), 1128 (s), 1069 (s), 1040 (s), 1025 (s), 981 (m), 939 (m) cm^{-1}.

*4.1.6. Diethyl α,α-difluoro-4-methoxybenzylphosphonate (**7f**)*

59%; bp 121 °C (0.3 mm). ^{19}F NMR: −107.5 (d, J = 120 Hz). ^{1}H NMR: 1.31 (t, J = 7 Hz, 6 H), 3.82 (s, 3 H), 4.19 (m, 4 H), 6.96 (d, J = 8 Hz, 2 H), 7.55 (d, J = 8 Hz, 2 H). ^{13}C NMR: 16.4 (d, J = 5 Hz), 55.4 (s), 64.7 (d, J = 7 Hz), 113.9 (s), 118.3 (td, J = 263, 221 Hz), 124.7 (td, J = 23, 14 Hz), 127.9 (td, J = 7, 2 Hz), 161.5 (s). ^{31}P NMR: 6.90 (t, J = 119 Hz). GC–MS (e/z) (relative intensity): 294 (M^+, 3.66), 157 ($CF_2C_6H_4OMe^+$, 100), 109 {$(HO)(EtO)P(O)^+$, 6.08}. FTIR (CCl_4): 2984 (m), 2962 (w), 2935 (w), 1616 (m), 1516 (m), 1271 (s), 1254 (s), 1050 (s), 1025 (s), 979 (m) 948 (m), 833 (vs) cm^{-1}. HRMS: calc'd for $C_{12}H_{17}F_2O_4P$ [M^+] 294,0832, obsv'd 294.0834.

*4.1.7. Diethyl α,α-difluoro-4-ethoxycarbonylbenzylphosponate (**7g**)*

84%; oil. ^{19}F NMR: −109.8 (d, J = 114 Hz). ^{1}H NMR: 1.32 (t, J = 7 Hz, 6 H), 1.41 (t, J = 7 Hz, 3 H), 4.20 (m, 4 H, 7.71 (d, J = 8 Hz, 2 H), 8.14 (d, J = 8 Hz, 2 H). ^{13}C NMR: 14.3 (s), 16.4 (d, J = 5 Hz), 61.4 (s), 64.8 (d, J = 7 Hz), 117.8 (td, J = 263, 217 Hz), 126.4 (td, J = 7, 2 Hz), 129.6 (s), 132.8 (s), 136.9 (td, J = 23, 14 Hz), 165.7 (s). ^{31}P NMR: 5.80 (t, J = 113 Hz). GC–MS (m/z) (relative intensity): 336 (M^+, 1.40), 291 (M^+ –OEt, 3.35), 199 ($CF_2C_6H_4CO_2Et^+$, 26.60), 154 ($CF_2C_6H_4CO^+$, 100), 109 {$(HO)(EtO)P(O)^+$, 59.20}. FTIR (CC_{l4}): 2985 (m), 2933 (w), 1726 (s), 1275 (s), 1063 (s), 1049 (s), 1024 (vs), 981 (m), 943 (m) cm^{-1}. HRMS: calc'd for $C_{14}H_{19}F_2O_5P$ [M^+} 336.0938, obsv'd 336.0932.

*4.1.8. Diethyl α,α-difluoro-4-bromobenzylphosphonate (**7h**)*

70%; bp 96 °C (0.02 mm). ^{19}F NMR: −109.2 (d, J = 115 Hz). ^{1}H NMR: 1.31 (t, J = 7 Hz, 6 H), 4.21 (m, 4 H), 7.49 (d, J = 8 Hz, 2 H), 7.60 (d, J = 8 Hz, 2 H). ^{13}C NMR: 16.4 (d, J = 6 Hz), 65.0 (d, J = 7 Hz), 118.1 (td, J = 263, 217 Hz), 126.7 (s), 129.5 (td, J = 8, 2 Hz), 131.8 (s) 132.7 (s). ^{31}P NMR: 6.05 (t, J = 114 H). GC–MS (m/z) (relative intensity): 342, 344 (M^+, 3.55, 3.39), 263 (M^+, –Br, 16.74), 205, 207 ($CF_2C_6H_4Br^+$, 70.34, 66.95), 137 (24.15), 109 {$(HO)(EtO)P(O)^+$, 100}. FTIR (CCl_4): 2985 (m), 2933 (w), 1597 (m), 1398 (m), 1273 (s), 1059 (s), 1049 (s), 1024 (vs), 981 (m), 938 (m), 783 (vs), 773 (s), 766 (s) cm^{-1}.

*4.1.9. Diethyl α,α-difluoro-2-phenylbenzylphosphonate (**7i**)*

65%; oil. ^{19}F NMR: −109.2 (d, J = 115 Hz). ^{1}H NMR: 1.25 (t, J = 7 Hz, 6 H), 4.12 (m, 4 H), 7.21 (m, 1 H), 7.31–7.44 (m, 7 H), 7.76 (m. 1 H). ^{13}C NMR: 16.3 (d, J = 5 Hz), 64.6 (d, J = 7 H), 119.4 (td, J = 265, 218 Hz), 127.0 (s), 127.1 (s), 127.2 (s), 128.3 (t, J = 8 Hz), 129.4 (s), 130.0 (td, J = 21. 14 H), 130.2 (s), 132.6 (s), 141.3 (s), 141.7 (d, J = 3 Hz). ^{31}P NMR 6.34 (t, J = 116 Hz). GC–MS (m/z) (relative intensity): 340 (M^+, 26.38), 203 ($CF_2C_6H_4Ph^+$, 78.90), 109 {$(HO)(EtO)P(O)^+$, 17.66}. FTIR (CCl_4): 2985 (m), 2933 (w), 2913 (w), 1482 (m), 1273 (s), 1073 (s), 1048 (s), 1036 (s), 1024 (s), 980 (m) cm^{-1}.

*4.1.10. Diethyl α,α-difluoro-3,5-bis(trifluoromethyl)benzylphosphonate (**7j**)*

83%; bp 71 °C (0.03 mm). ^{19}F NMR: −63.5 (s, 6F), −110.2 (d, J = 110 Hz, 2F). ^{1}H NMR: 1.36 (t, J = 7 Hz, 6H), 4.28 (m, 4H), 8.03

(s, 1H), 8.08 (s, 2H). ^{13}C NMR: 16.3 (d, J = 6 Hz), 65.4 (d, J = 7 Hz), 117.0 (td, J = 265, 218 Hz), 123.0 (q, J = 273 Hz), 124.8 (s), 127.0 (s), 132.4 (q, J = 34 Hz), 135.7 (td, J = 23, 14 Hz). ^{13}P NMR: 4.71 (t, J = 110 Hz). GC–MS: (m/z) (relative intensity): 400 (M^+, 059), 381 (M^+, –F, 2.64), 263 ($CF_2C_6H_4(CF_3)_2^+$, 24.40, 137 (25.60), 109 {(HO)(EtO)P(O)$^+$, 100}. FTIR (CCl_4): 2986 (m), 1,384,903 (s), (s), 1280 (s), 1228 (s), 1186 (vs), 1148 (vs), 1072 (s), 1047 (s), 1025 (s), 903 (s), 776 (vs) cm^{-1}. HRMS: calc'd for $C_{13}H_{13}F_8O_3P$ [M^+] 400.0475, obsv'd 400.0456.

*4.1.11. 1,4-Bis(diethoxyphosphinyldifluoromethyl)benzene (**7k**)*

Oil; 75%; ^{19}F NMR: −109.4 (d, J = 114 Hz). ^{1}H NMR: 1.32 (t, J = 7 Hz, 12 H), 4.21 (m, 8 H), 7.73 (s, 4 H). ^{13}C NMR: 16.4 (d, J – 5 Hz), 65.0 (d, J = 7 Hz), 117.8 (td, J = 263, 217 Hz), 126.6 (s), 135.4 (td, J – 22, 15 Hz). ^{31}P NMR: 6.00 (t, J = 114 Hz). GC–MS: (m/z) (relative intensity): 449 ($M^+ - 1$, 100), 313 ($CF_2C_6H_4CF_2P(O)(OEt)_2^+$, 74.34), 109 {(HO)(EtO)P(O)$^+$, 32.24}. FTIR: (CCl_4) 2985 (m), 2933 (w), 2913 (w), 1394 (m), 1274 (s), 1263 (s), 1053 (s), 1024 (s), 980 (m), 941 (m), 806 (m), 806 (m), 777 (m), 763 (m) cm^{-1}. HRMS calc'd for $C_{16}H_{24}F_4O_6P_2$ [M^+] 450.0977, obsv'd 450.0981.

*4.1.12. Diethyl perfluorobenzylphosphonate (**7l**)*

65%; bp 71 °C (0.03 mm); ^{19}F NMR: −106.3 (dt, J = 107, 30 Hz, 2 F), −138.8 (m, 2 F), −149.3 (t, J = 20 Hz, 1 F), −160.8 (t, J = 19 Hz, 2 F). ^{1}H NMR: 1.39 (t, J = 7 Hz, 6 H), 4.35 (m, 4 H). ^{13}C NMR: 16.3 (d, J = 5 Hz), 65.8 (d, J = 7 Hz), 108.3 (m), 116.1 (td, J = 268, 224 Hz), 138.2 (dm, J = 250 Hz), 143.1 (dm, J = 260 Hz), 145.3 (dm, J = 264 Hz). ^{31}P NMR: 3.86 (t, J = 107 Hz). GC–MS (m/z) (relative intensity): 354 (M^+, 0.54), 217 ($CF_2C_6F_5^+$, 43.00), 137 (56.67), 109 {(HO)(EtO)P(O)$^+$, 100}. FTIR (CCl_4): 2986 (m), 2934 (w), 2915 (w), 1651 (m), 1526 (s), 1502 (s), 1325 (s), 1286 (s), 1175 (s), 1097 (s), 1051 (vs), 1032 (vs), 1027 (vs), 998 (s), 953 (m), 615 (m) cm^{-1}. HRMS calc'd for $C_{11}H_{10}F_7O_3P$ [M^+] 354.0256 obsv'd 354.0239.

*4.1.13. Diethyl (2-pyridyl)difluoromethylphosphonate (**7m**)*

83%; bp 98 °C (0.02 mm). ^{19}F NMR: −110.9 (d, J = 108 Hz). ^{1}H NMR: 1.36 (t, J = 7 Hz, 6 H), 4.30 (m, 4 H), 7.44 (m, 1 H), 7.71 (d, J = 8 Hz, 1 H), 7.85 (t, J = 8 Hz, 1 H), 8.72 (d, J = 5 Hz 1 H), 116.5 (td, J = 264, 213 Hz), 121.7 (s), 125.4 (s), 137.1 (s), 149.5 (s), 1495 (s), 151.8 (td, J = 23, 14 Hz). ^{31}P NMR: 5.73 (t, J = 108 Hz). GC–MS (m/z) (relative intensity): 265 (M^+, 6.51), 128 ($CF_2C_5H_4N^+$, 61.48), 109 {(HO)(EtO)P(O)$^+$, 54.85}. FTIR (CCl_4): 2933 (w), 2914 (w), 1590 (w), 1277 (s), 1137 (s), 1060 (s), 1027 (vs), 981 (m), 948 (m), 783 (m), 574 (m) cm^{-1}. HRMS: calc'd for $C_{10}H_{14}F_2NO_3P$ [M^+] 265.0679 obsv'd 265,0673.

*4.1.14. Diethyl (2-thiophenyl)difluoromethylphosphonate (**7n**)*

78%; bp 88 °C (0.02 mm). ^{19}F NMR: −97.4 (d, J = 115 Hz). ^{1}H NMR: 1.34 (t, J = 7 Hz, 6H), 4.24 (m, 4 H), 7.10 (m, 1 H), 7.49 (m, 2 H). ^{13}C NMR: 16.3 (d, J = 5 Hz), 65.1 (d, J = 7 Hz), 116.6 (td, J = 261, 225 Hz), 127.3 (s), 128.9 (s), 129.1 (td, J = 6, 2 Hz), 134.1 (td, J = 26, 17 Hz). ^{31}P NMR: 5.44 (t, J = 115 Hz). GC–MS (m/z) (relative intensity): 270 (M^+, 3.69), 133 ($CF_2C_4H_3S^+$, 100), 109 {(HO)(EtO)P(O)$^+$, 17.11}. FTIR (CCl_4): 2985 (m), 2933 (w), 2914 (w), 1432 (m), 1276 (s), 1242 (s), 1122 (s), 1039 (vs), 1026 (vs), 980 (m), 960 (m), 709 (s) cm^{-1}. HRMS calc'd for $C_9H_{13}F_2SO_3P$ [M^+] 270.0291 obsv'd 270,9288.

*4.1.15. Diethyl α,α-difluoro-4-acetobenzylphosphonate (**7o**)*

75%; bp 142 °C (0.15 mm). ^{19}F NMR: −109.7 (d J = 113 Hz). ^{1}H NMR: 1.33 (t, J = 7 Hz, 6 H), 2.63 (s) 3 H), 4.21 (m, 4 H), 7.73 (d, J = 8 Hz, 2 H), 8.04 (d, J = 8 Hz, 2 H). ^{13}C NMR: 16.4 (d, J = 6 Hz), 26.8 65.0 (d, J = 7 Hz), 117.8 (td, J = 264, 217 Hz), 126.7 (m, 128.3, 137.0 (td, J = 22, 14 Hz), 197.3. ^{31}P NMR: 5.89 (t, J = 113 Hz). GC–MS (m/z) (relative intensity): 306 (M^+, 14.97), 291 (14.81), 2.64 (26.64), 235 (7.64), 169 ($CF_2C_6H_4C(O)CF_3^+$, 63.69), 155 (74.52, 137 {$(EtO)_2P(O)^+$, 10.83}, 126 (66.88), 109 {(HO)(EtO)P(O)$^+$, 100}, 91 (28.03) FTIR (CCl_4): 2985 (m), 2934 (w), 2914 (w), 1694 (s), 1267 (s), 1226 (s), 1062 (s), 1048 (s), 1025 (vs), 980 (s), 942 (m), 830 (m) cm^{-1}. HRMS calc'd for $C_{14}H_{19}F_2O_4P$ [M^+] 306.00823 obsv'd 306.0815.

*4.1.16. (Diethoyphosphinyldifluoromethyl)benzoic acid (**7p**)*

55%, mp 96–98 °C. ^{19}F NMR: −109.9 (d, J = 114 Hz). ^{1}H NMR: 1.34 (t J = 7 Hz, 6 H), 4.26 (m, 4 H), 774 (d, J = 8 Hz, 2 H), 8.19 (d, J = 8 Hz, 2 H). ^{13}C NMR: 16.3 (d, J = 5 Hz), 65.2 (d, J = 7 Hz), 117.7 (td, J = 264, 218 Hz), 126.6, 130.2, 131.9, 137.5 (m), 1701. ^{31}P NMR: 5.52 (t, J = 113 Hz). DIP–MS (m/z) (relative intensity): 308 (M^+, 5.29), 17 (43.41), 154 (100), 137 {$(EtO)_2P(O)^+$, 13.87}, 126 (62.09), 109 {(HO)(EtO)P(O)$^+$, 69.23}, 81 (36.82).

*4.1.17. Diethyl α,α-difluoro-2-methylbenzylphosphonate (**7q**)*

83%; bp 83 °C (0.02 mm). ^{19}F NMR: −104.7 (d, J = 117 Hz). ^{1}H NMR: 1.31 (t, J = 7 Hz, 6 H), 2.56 (t, J = 3 Hz, 3 H), 418 (m, 4 H), 7.21–7.36 (m, 3 H), 7.52 (d, J = 8 Hz, 1 H). ^{13}C NMR: 16.4 (d, J = 5 Hz), 20.7 (t, J = 4 Hz), 64.7 (d, J = 7 Hz), 119.8 (td, J = 265, 218 Hz), 125.7 (s), 1275 (td, J = 8, 2 Hz), 130.7 (s), 132.3 (s), 137.7 (s). ^{31}P NMR: 6.99 (t, J = 117 Hz). GC–MS (m/z) (relative intensity): 278 (M^+, 4.76), 141 ($CF_2C_6H_4CH_3^+$, 100), 137 {$(EtO)_2P(O)^+$, 18.49}, 109 {(HO)(EtO)P(O)$^+$, 18.00}, 91 ($CH_3C_6H_4^+$, 37.04). FTIR (CCl_4): 2984 (m), 2934 (w), 2913 (w), 1272 (s), 1071 (s), 1045 (s), 1025 (s), 980 (m), 782 (s), 775 (s), 770 (s), 764 (s), 1045 (s), 1025 (s), 980 (m), 936 (m), 782 (s), 775 (s), 770 (s), 764 (s) cm^{-1}. HRMS calc'd for $C_{12}H_{17}F_2O_3P$ [M^+] 278.0883 obsv'd 278.0888.

*4.1.18. Preparation of **7a** via (Et))$_2$P(O)CF$_2$ZnX*

A 100-mL flask fitted with a stir bar and a condenser topped with a nitrogen inlet was charged with 2.67 g (10.0 mmol) of diethyl bromodifluoromethylphosphonate, 0.72 g (11 mmol) of Zn and 10 mL of dry DMF. The mixture was stirred at room temperature for 2 h. The unreacted Zn was removed by filtration through a medium frit funnel under nitrogen atmosphere and the filtrate was treated with 0.69 g (7.0 mmol) of CuCl and 1.25 g (5.0 mmol) of 4-nitroiodobenzene at room temperature for 3 h. 100 mL of ether was added to the reaction mixture and the precipitated solids were removed by filtration and washed with 50 mL of ether. The combined ether solutions were washed with NH_4Cl(aq) and H_2O, dried over Na_2SO_4, and evaporated to give a residue, which was further purified by silica gel column chromatography. Eluent (CH_2Cl_2/EtOAc (9:1) gave 1.24 g (80%) of **7a**, mp 46–48 °C.

*4.1.19. Preparation of **7b** through pre-generated (EtO)$_2$P(O)CF$_2$Cu*

A 100-mL flask fitted with a stir bar and a condenser topped with a nitrogen inlet was charged with 2.67 g (10.0 mmol) of diethyl bromodifluoromethylphosphonate, 1.25 g (11 mmol) of Cd and 10 mL of dry DMF. The mixture was stirred at room temperature for 2 h. The unreacted Cd was removed by filtration through a medium frit funnel under a nitrogen atmosphere and the filtrate was treated with 0.90 g (8.0 mmol) of CuCl. ^{19}F NMR analysis revealed the formation of the copper reagent, $(EtO)_2P(O)CF_2Cu$, doublet at −118.2 ppm with J = 95 Hz (80% NMR yield based on $(EtO)_2P(O)CF_2Br$). Then the copper reagent was treated with 1.00 g 95.0 mmol) of iodobenzene at room temperature overnight. 100 mL of ether was added to the reaction mixture and the precipitated solids were removed by filtration and washed with 50 mL of ether. The combined ether solutions were washed with NH_4Cl(aq) and H_2O, dried over Na_2SO_4, and evaporated to give a residue, which was further purified by silica gel column chromatography. Eluent (CH_2Cl_2/EtOAc 96:4) gave 0.99 g (75%) of **7b**.

*4.1.20. Dibutyl α,α-difluoro-4-nitrobenzylphosphonate (**8**)*

8 (1.10 g, 75%, Oil) was obtained by the similar procedure for the preparation of **7** from 3.23 g (l0 mmol) of dibutyl bromodifluoromethylphosphonate, 1.24 g (11 mmol) of Cd, and 10 mL of DMF; then with 0.69 g (7.0 mmol) of CuCl and 1.0 g (4.0 mmol) of 4-nitroiodobenzene. ^{19}F NMR: −109.8 (d, *J* = 111 Hz). ^{1}H NMR: 0.92 (t, *J* = 7 Hz, 6 H), 1.37 (m, 4 H), 1.66 (m, 4 H), 4.18 (m, 4 H), 7.82 (d, *J* = 8 Hz, 2 H), 8.33 (d, *J* = 8 Hz, 2 H). ^{13}C NMR: 13.5 (s), 19.5 (s), 32.4 (d, *J* = 5 Hz), 68.8 (d, *J* = 7 Hz), 117.3 (td, *J* = 265, 216 Hz), 123.6 (s), 127.7 (td, *J* = 7.2 Hz), 139.1 (td, *J* = 22, 14 Hz), 149.4 (s). ^{31}P NMR: 5.48 (t, *J* = 111 Hz). GC–MS (*m*/*z*) (relative intensity): 365 (M^+, 0.08), 335 (M^+ –NO, 2.55), 279 (4.41), 254 (6.05), 223 (23.79), 172 ($CF_2C_6H_4NO_2^+$, 13.61), 137 (100). FTIR (CCl_4): 2965 (s), 2933 (w), 1613 (m), 1533 (s), 1351 (s), 1277 (s), 1067 (s), 1023 (s), 856 (m) cm^{-1}.

*4.1.21. Preparation of 2-(4-Iodophenyl)benzothiazole (**10**)*

A mixture of 2-aminothiophenol (1.25 g, 10 mmol), 4-iodobenzoylchloride (2.67 g, 10 mmol), pyridine (0.8 mg, 10 mmol) and 4 mL of toluene was stirred at room temperature for 1 h, then refluxed for 30 min. After removal of solvent by vacuum, methanol (30 mL) was added to the mixture. Filtration of the mixture afforded a solid, which was recrystallized (from MeOH) to give 2.2 g (65%) of **10**, mp 156–158 °C [lit. [14] mp 157–158 °C]. ^{1}H NMR: 738 (td, *J* = 8, 1 Hz, 1 H), 7.49 (td, *J* = 7, 1 Hz, 1 H), 7.80 (m, 4 H), 7.88 (d, *J* = 8 Hz, 1 H), 8.06 (d, *J* = 8 Hz, 1 H). ^{13}C NMR: 97.5, 121.6, 123.3, 125.4, 126.5, 128.9, 133.1, 135.0, 138.1, 154.1, 166.8. GC–MS (*m*/*z*) (relative intensity): 337 (M^+, 25.64), 210 (M^+ –I, 100). FTIR (CCl_4) 3067 (w), 1474 (s), 1436 (m), 1394 (m), 1060 (m), 1008 (m), 967 (s), 805 (m), 775 (m), 764 (m), 680 (m) cm^{-1}.

*4.1.22. Diethyl α,α-difluoro-4-(2-benzothiazolyl)benzylphosphonate (α,α-difluoro Fostedil (**9**)*

9 (1.05 g, 855, mp 95–96 °C) was obtained by the procedure described for the preparation of 7 from 267 g (10 mmol) of diethyl bromodifluoromethylphosphonate, 1.25 g (11 mmol) of Cd, and 10 mL of DMF; then with 0.69 g (7.0 mmol) of CuCl and 1.0 g (3.0 mmol) of **10**. ^{19}F NMR: −109.4 (d, *J* = 115 Hz). ^{1}H NMR: 1.33 (t, *J* = 7 Hz, 6 H), 4.22 (m, 4 H), 7.40 (ddd, *J* = 8 7, 1 Hz, 1 H), 7.50 (ddd, *J* = 8, 7, 1 Hz, 1 H), 7.76 (d, *J* = 8 Hz, 2 H), 7.90 (d, *J* = 7 Hz, 1 H), 8.09 (d, *J* = 8 Hz, 1 H), 8.18 (d, *J* = 8 Hz, 2 H). ^{13}C NMR: 16.4 (d, *J* = 6 Hz), 65.0 (d, *J* = 7 Hz), 117.8 (td, *J* = 264, 218 Hz), 121.7 (s), 123.5 (s), 125.7 (s), 126.6 (s), 127.1 (td, *J* = 7.2 Hz), 127.5 (s), 134.9 (td, *J* = 22, 14 Hz), 135.2 (s), 135.8 (s), 154.1 (s), 166.6 (s). ^{31}P NMR: 6.38 (t, *J* = 114 Hz). DIP–MS (*m*/*z*) (relative intensity): 397 (M^+, 19.15), 369 (M^+ −28, 1.05), 341 (M^+ −56, 1.16), 260 {M^+–$(EtO)_2P(O)$, 100}, 109 {$(HO)(EtO)P(O)^+$, 9.98}. FTIR (CCl_4): 3067 (w), 2985 (m), 2933 (w), 2913 (w), 1489 (w), 1463 (m), 1273 (s), 1120 (m), 1063 (s), 1049 (s), 1023 (vs), 968 (s), 941 (m), cm^{-1}.

*4.1.23. α,α-Difluoro-4-nitrobenzylphosponic acid (**11a**)*

Diethyl α,α-difluoro-4-nitrobenzylphosphonate (052 g, 1.7 mmol) was refluxed in 5 mL concentrated HCL for 2 h. The reaction mixture was pumped at full vacuum overnight at room temperature to give 0.41 g of **11a** (96%), mp 123.6 °C. ^{19}F NMR (DMSO-d_6): −109.1 (d, *J* = 101 Hz). ^{1}H NMR (DMSO-d_6) 7.82 (d, *J* = 9 Hz, 2 H), 7.96 (br s, 2 H), 8.36 (d, *J* = 9 Hz, 2 H)[19]. ^{13}C NMR (DMSO-d_6) 118.2 (td, *J* = 262, 200 Hz), 123.4 (s), 127.7 (s), 140.3 (td, *J* = 22, 13 Hz), 148.6 (s). ^{31}P NMR (DMSO-d_6) 1.87 (t, *J* = 102 Hz).

*4.1.24. α,α-Difluorobenzylphosphonic acid (**11b**)*

Diethyl α,α-difluoro benzylphosphonate (0.45 g, 1.7 mmol) was treated with Me_3SiBr (0.53 g, 3.5 mmol) at 80 °C for 1 day. Water (0.5 mL) was added to the mixture at rt and the resultant mixture was stirred at rt for 1 h. The reaction mixture was pumped at full vacuum at room temperature for 1 day to give 0.33 g **11b**, 93%, mp 114 °C (dec.). ^{19}F NMR (DMSO-d_6): −107.9 (d, *J* = 107 Hz). ^{1}H NMR (DMSO-d_6) 7.50 (m, Ph), 7.53 (br s, OH) [19]. ^{13}C NMR (DMSO-d_6) 118.7 (td, 262, 205 Hz), 125.6 (s), 128.1 (s), 130.0 (s), 133.8 (td, *J* = 22, 13 Hz). ^{31}P NMR (DMSO-d_6): 309 (t, *J* = 107 Hz).

*4.1.25. Hydrolysis of **7b** with concentrated HCL*

A mixture of **7b** (0.84 g, 3.2 mmol) and 6 mL concentrated HCl were stirred at reflux for 12 h then filtered. The precipitate was washed with water (2 × 10 mL), then dried under vacuum overnight to give 0.30 g of $PhCO_2H$, 77%, mp 121–123 °C [lit. [17] mp 122.5 °C]. The combined filtrate and water solutions were concentrated and dried under vacuum overnight to form 0.20 g of a residue which is a mixture of $PhCO_2H$ and H_3PO_4.

*4.1.26. Hydrolysis of **7f** with concentrated HCl*

A mixture of **7f** (0.42 g, 1.4 mmol) and 4 mL concentrated HCl was stirred at reflux for 12 h then filtered. The precipitate was washed by water (2 × 10 mL), then dried under vacuum overnight to give 0.18 g of 4-methoxybenzoic acid, 86%, mp 182–185 °C]. The combined filtrate and water solutions were concentrated and dried under vacuum overnight to form −15 g of a residue which is a mixture of 4-methoxybenzoic acid and H_3PO_4.

*4.1.27. Hydrolysis of **7f** with Me_3SiBr followed by water*

A mixture of **7f** (0.42 g, 1.4 mmol) and Me_3SiBr (0.45 g, 2.9 mmol) was stirred at 80 °C for 2 h. Water (0.3 g) was added to the mixture at room temperature. The resultant mixture was diluted with water (4 mL) and filtered. The precipitate was washed with water (2× 10 mL), then dried on vacuum overnight to give 0.15 g or 4-methoxybenzoic acid, 71%, mp 181–5 °C. The combined filtrate and water solutions were concentrated and dried under vacuum overnight to give 0.15 g of a residue which is a mixture of 4-methoxybenzoic acid and H_3PO_4.

5. Additional comments

Shortly after our publication [20] appeared, Taylor and co-workers published a complimentary approach to α,α-difluoro benzylic phosphonates [21]. This approach involved the preparation of a non-fluorinated benzylic phosphonate, followed by conversion of the non-fluorinated benzylic phosphonate to the anion and reaction of the anion with an electrophilic fluorinating agent. Yields of the α,α-difluro benzylic phosphonate varied with the choice of base and fluorinating agent [22]. Best results were obtained with NaHMDS in THF at −78 °C and followed by reaction with excess NSBS as the electrophilic fluorinating agent. Under these conditions, comparable yields were obtained compared to our methodology. However, our method utilizes only bromodifluoromethyl phosphonates, which is prepared in 95% isolated yield [23] from dibromodifluoromethane and trimethyl phosphite.

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