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Synthesis and Reactivity Studies of α,α -Difluoromethylphosphinates

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Abstract

The preparation and reactivity of some α,α -difluorophosphinates is investigated. Alkylation of *H*-phosphinates with LiHMDS and ClCF_2H gives the corresponding α,α -difluorophosphinates in good yield. Deprotonation of these reagents with alkyllithium or LDA is then studied. Subtle electronic effects translate into significant differences in the deprotonation/alkylation of the two “Ciba-Geigy reagents” $(\text{EtO})_2\text{CRP}(\text{O})(\text{OEt})\text{H}$ ($\text{R} = \text{H}, \text{Me}$). On the other hand, attempted methylation of difluoromethyl-octyl-phosphinic acid butyl ester resulted in the exclusive alkylation of the octyl chain. Finally, reaction with carbonyl compounds results in the formation of 1,1-difluoro-2-phosphinoyl compounds.

Keywords

phosphinate; phosphonate; fluorine; conformational analysis; pyrophosphate analogs

1. Introduction

α -Fluorophosphorus compounds have gained popularity as potential pharmacophores. In the case of phosphonates, the fluorine substituent(s) is known to modulate the pKa of the phosphonic acid group, sometimes improving the mimicry of a natural phosphate monoester, and the inhibitory potency of the resulting analog.¹ α,α -Difluorophosphinates have been much less studied, and in their case, the effect of fluorine on the pKa is unimportant since the phosphinic monoacids are always deprotonated at physiological pH. Nonetheless, the CF_2 moiety is a known mimic of an oxygen atom. Using our radical hydrophosphinylation reaction (NaH_2PO_2 , $\text{Et}_3\text{B}/\text{air}$)² Piettre and coworkers have pioneered the synthesis of α,α -difluorophosphinates, from 1,1-difluoro-2,2-disubstituted olefins (Equation 1).³

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Supporting Information. Additional experimental and spectral data are provided.

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(Eq. 1)

Fifteen years ago, Hall and coworkers reported the only example we could find of the base-promoted alkylation of a difluoromethylphosphinate $\text{RP(O)(OEt)CF}_2\text{H}$, as well as its subsequent elaboration into a GABA analog (Scheme 1).⁴ Two GABA analogs $\text{H}_2\text{NCH}_2\text{CH(X)CH}_2\text{P(O)(OH)CF}_2\text{H}$ ($\text{X} = \text{H, OH}$) were also studied, but these were less potent agonists in a GABA_B binding assay than the corresponding non-fluorinated methyl phosphinate by a factor of $\sim 3\text{--}5$.⁴ Phosphonate $\text{H}_2\text{N(CH}_2)_3\text{P(O)(OH)}_2$ behaves instead as an antagonist.⁴ The deprotection of the acetal followed by functionalization was also reported in this work (Scheme 1). A few years ago, we reported a general alkylation of *H*-phosphinates, and the preparation of a few α,α -difluoromethylphosphinates.⁵ Herein, we report a study of the alkylation of these and other precursors, which expands upon the Hall precedent.⁴

2. Results and Discussion

2.1. Synthesis of difluoromethylphosphinate $\text{RP}(\text{O})(\text{OEt})\text{CF}_2\text{H}$ precursors

Three precursors **1–3** were synthesized previously (Equation 2).⁵ A fourth compound **4** was synthesized similarly from (EtO)₂CHP(O)(OEt)H. We have been referring to (EtO)₂CRP(O)(OEt)H (R = H, Me) as the “Ciba-Geigy reagents”, after their development in that company. As will be discussed below, significant differences exist between compounds **3** and **4**.

(Eq. 2)

The alkylation of *H*-phosphinate esters with lithium hexamethyldisilazide (LiHMDS)⁵ and F₂CHCl (R-22) and mild deoxygenation, gives good yields of products **1–4** (71–78%). As we have reported previously, moderate deoxygenation is necessary to achieve good yields of product (this is because the P(III) anion is easily oxidized).^{5,6}

2.2. Functionalization of the difluoromethylphosphinates

Although the P(O)CF₂H group is acidic, electrophilicity of the phosphorus atom is also increased so that P-substitution is an expected competitive pathway. Table 1 shows the outcome of the deprotonation-alkylation process with compound **3** (and methyl iodide as

electrophile) as a function of the base employed. *t*-BuLi gives the best results because it is a strong base and less nucleophilic than other butyllithium reagents.

The role of electrophile was also investigated (Table 2). Not surprisingly, the less reactive electrophiles gave a lower alkylation yield.

2.3. Scope of the alkylation

Compound **3** was treated with several electrophiles (Table 3). The yields are moderate to good. When 0.5 equivalent of a dielectrophile is employed, the disubstituted product is obtained.

(Eq. 3)

Alkylation with a carbohydrate-derived iodide also gave satisfactory results but the product was obtained as the fully hydrolyzed *H*-phosphinic acid (Equation 3). It is interesting to note that **3** was successful in this reaction, but **4** was not, under otherwise identical conditions. In fact, the reactions of compound **4** are typically very different from that of **3**. Table 4 summarizes the results with methyl iodide and **4** (compare with Table 1). It is expected that the electron-donating methyl substituent in compound **3** will somewhat deactivate the phosphorus atom toward nucleophilic attack. However, the subtle electronic effects translate into significant differences when compared to compound **4**.

Compounds $\text{RP}(\text{O})(\text{OEt})\text{CF}_2\text{R}'$ are hydrolyzed very easily during chromatography on silica gel, even in the presence of some base (like Et_3N) in the eluent. This is not surprising due to the increased electrophilicity of the phosphorus atom with the powerful electron-withdrawing CF_2H group. Thus, products are often isolated and/or characterized as the corresponding *H*-phosphinic esters or acids. *H*-Phosphinate esters $\text{RP}(\text{O})(\text{OEt})\text{H}$ are typically hydrolyzed rather easily, and the difluoro-substituted compounds $\text{RCF}_2\text{P}(\text{O})(\text{OEt})\text{H}$ are even more prone to further hydrolysis to the corresponding *H*-phosphinic acids $\text{RCF}_2\text{P}(\text{O})(\text{OH})\text{H}$.

2.4. Alkylation of **2**

Alkylation of compound **2** resulted in an unexpected chain functionalization, as opposed to the difluoromethyl deprotonation/alkylation (Equation 4).

(Eq. 4)

Table 5 shows the results. Even with excess *t*-BuLi, no alkylation of the difluoromethyl group is taking place (indicating that the dianion could not be formed). A possible

explanation for this initially surprising result (the lower pK_a of the methylene group over that of the CF₂H group in **2**, Equation 4) might be due to the general anomeric effect (negative hyperconjugation, HOMO-LUMO interactions): the carbanion lone pair must be antiperiplanar to P=O ($\leftrightarrow$ P⁺-O⁻) to take advantage of stabilization (lone pair n $\rightarrow$ $\sigma^*(\text{P}^+-\text{O}^-)$), whereas the P=O bond might instead prefer to be antiperiplanar to C-F ($\sigma(\text{P}^+-\text{O}^-) \rightarrow \sigma^*(\text{C}-\text{F})$, dipole minimization). In order to better understand these effects, a brief computational investigation on the two possible anions derived from CH₃P(O)(OMe)CF₂H as simplified models (conformational search followed by optimization at the 6-311+G** level) was conducted (Scheme 2).⁷ It revealed that, in fact, all conformers of the CF₂ anion **B** are always higher in energy than the corresponding CH₂ anion **A**, thereby supporting the experimental results (Equation 4 and Table 5).⁷ In the case of **B**, the energy difference between the three rotamers **B1–B3** is small, indicating that the intensities of the competing stereoelectronic effects are similar.⁸ Interestingly, the conformation in which the anion's lone-pair is antiperiplanar to P=O (lone pair n $\rightarrow$ $\sigma^*(\text{P}^+-\text{O}^-)$) is higher in energy even for **A**. This is because the accepting ability decreases in the following order: $\sigma^*(\text{C}-\text{CF}_2\text{H}) > \sigma^*(\text{P}-\text{OR}) > \sigma^*(\text{P}^+-\text{O}^-)$, as shown in the stability order **A1** > **A2** > **A3**. Experimentally, the (same) fact that HCF₂ is more electron-withdrawing (lower lying σ^*) than OR can easily be established: the second pK_a of (HO)₂P(O)CF₂H is 5.4 versus 7.2 for (HO)₃P(O) [and 7.6 for (HO)₂P(O)CH₃]; or the pK_a of HCF₂COOH is 1.24 versus 3.6 for HOCOOH and 10.6 for HOCOO⁻.^{1c,9} The pK_a of phosphinate's **2** methylene group should thus be a little lower than that in a phosphonate diester RCH₂P(O)(OR')₂, whereas that of the CF₂H is significantly higher.

While in compound **2** the side-chain methylene is more easily deprotonated than the difluoromethyl group, in the case of compound **4**, deprotonation at the difluoromethylene moiety is clearly preferred but then steric effects (steric hindrance for acetal deprotonation) also exist (Table 4).¹⁰ Electrophiles other than MeI have not been tried, but the nature of the electrophile should not affect the regioselectivity.

2.5. Anion reactivity with carbonyl compounds

Another unexpected reaction was uncovered when the anion derived from (EtO)₂CRP(O)(OEt)CF₂H (**3**, **4**) were treated with carbonyl compounds.

A possible mechanism for the formation of **5** is shown in Scheme 3. The first step is the expected 1,2-addition of anion **6** to produce **7**. At this point, formation of oxaphosphetane **8** can take place (as in olefination reactions), and this intermediate collapses to form a strong P-O bond and to cleave the P-CF₂ bond to produce **9**. The driving force for this rearrangement is easily understood with the more accurate semi-polar representation of P=O as P⁺-O⁻: the CF₂ moiety enhances the electrophilicity of the phosphorus (destabilizes P⁺) toward nucleophilic attack by the alkoxide **7**, and in oxaphosphetane **8**, the C-F bonds cannot be antiperiplanar [$\sigma(\text{P}^+-\text{O}^-) \rightarrow \sigma^*(\text{C}-\text{F})$ interaction discussed earlier]. Hydrolysis of **9** (or possibly **8**) gives the rearrangement product **5**. It is interesting to note that the 1,1-difluoroolefin **10** or phosphonate monoester **11** were not observed, although the reaction mixtures were not heated (since the formation of **10** would not be competitive with other synthetic methods). It is known that unactivated phosphonates/phosphinates are generally poor olefination reagents. Obayashi and coworkers reported a similar rearrangement producing 1,1-difluoro-2-phosphonyl esters **12** (R = OR³ = OEt, Scheme 3) or **17** (Scheme 4) in the reaction of (EtO)₂P(O)CF₂H and (EtO)₂P(O)CF₂SiMe₃ with carbonyl compounds, although **17** is only a minor side-reaction, with either 1,2-addition product **16** or difluoroolefin **10** as the major products (Scheme 4).¹¹ These authors also reported the base-dependent isomerization of **16** into **17**.¹¹

Again, stereoelectronic effects could explain the much greater propensity for rearrangement in phosphinates **7** over phosphonate **15**. In the case of phosphonate **15**, an additional oxygen lone-pair in the second ethoxy group [antiperiplanar lone pair $n \rightarrow \sigma^*(P^+-O^-)$] decreases the electrophilicity at phosphorus compared to the acetal group in phosphinates **7**. Thus, it is perhaps not surprising that our case gives rearrangement to **5**, whereas the phosphonate **15** only gives small amounts of **17**.

There is only a handful of reported compounds having structure **12** ($R = C$, Scheme 3).¹² They are generally synthesized by phosphorylation of the corresponding fluorinated alcohol using P-Cl containing reagents.¹²

2.6. Pyrophosphate analogs

Pyrophosphate analogs are medicinally important in the treatment of bone and other diseases. For example, bisphosphonates constitute a major class of drugs against osteoporosis.¹³ Thus, we briefly investigated the preparation of novel PCF_2P building blocks. Alkylation of **4** with $ClP(O)(OEt)_2$ gave the corresponding difluorophosphonate/phosphinate **18** quite cleanly (>90%) after a simple work-up (Equation 5).

(Eq. 5)

(Eq. 6)

Unfortunately, attempts at deprotecting acetal **18** were not successful at delivering a clean product after chromatography, even though the desired $(EtO)_2P(O)CF_2P(O)(OEt)H$ product was major. A similar reaction with **3** also worked, but was not as clean and gave even more uncontrolled hydrolysis (the $MeC(OEt)_2$ group is much more labile) during attempted purification. On the other hand, reaction of **3** with $ClP(BH_3)(OEt)_2$ gave a rather clean pyrophosphate analog **19** (>90%, Equation 6), but once again, attempts at further elaboration of **19** to the corresponding intermediate $(EtO)_2P(BH_3)CF_2P(O)(OEt)H$ were largely unsuccessful, and although hydrolysis is even more facile, we were unable to secure any pure product. This line of research would require more work to produce the synthetically useful pyrophosphate analog precursors, since the novel products $(EtO)_2P(O)CF_2P(O)(OEt)H$ and $(EtO)_2P(BH_3)CF_2P(O)(OEt)H$ could be very useful compounds for potential medicinal applications. Perhaps crude deprotected **18** and **19** might be used, but this was not attempted in the present work. A current literature approach to the corresponding pyrophosphate analog **20** is shown in Scheme 5, and relies on the conversion of a phosphonate diester into the phosphonochloridate, followed by displacement with the well-known anion **21**.¹⁴

Difluorophosphinates, like their phosphonate counterparts,¹⁵ could become useful in chemical biology. For example, difluorophosphonate analogs of phosphorylated isoprenoids

and hexoses have tremendous current interest. Since *H*-phosphinates are also versatile functional groups for the synthesis of other organophosphorus functionalities,¹⁶ the chemistry described above could be employed to synthesize various biologically-active analogs of phosphates.

3. Conclusions

In conclusion, the synthesis and reactivity of difluoromethylphosphinates were investigated under basic conditions. α,α -Difluoro substituted compounds can be obtained easily through deprotonation with LiHMDS followed by alkylation with HCF_2Cl . The resulting products could have value as biologically active phosphate analogs. In alkylation reactions of reagents **3** and **4**, significant differences are observed in spite of the relatively subtle electronic effect at phosphorus. The resulting products are easily hydrolyzed sometimes complicating purification. On the other hand, alkylation of reagent **2** gives substitution on the alkyl chain, and an explanation for this observation is provided.

An interesting rearrangement was uncovered when difluoromethylphosphinate anions were treated with carbonyl compounds. Attempts were also made at preparing reagents for the synthesis of pyrophosphate analogs. Although promising, the results require additional investigations in order to obtain pure reagents and to investigate their associated reactivities.

Compounds $\text{RP}(\text{O})(\text{OH})(\text{CF}_2\text{H})$ might also be useful analogs of phosphonic acids but with a reduced charge, and this has apparently not been investigated beyond the two GABA analogs in Hall's seminal work.⁴ Work to study this class of compounds as possible phosphonate mimics is currently underway our laboratory.

4. Experimental Section

General chemistry

^1H NMR spectra were recorded on a 300-MHz spectrometer. Chemical shifts for ^1H NMR spectra are reported (in parts per million) relative to internal tetramethylsilane (Me_4Si , $\delta = 0.00$ ppm) with CDCl_3 or H_2O ($\delta = 4.75$ ppm) in D_2O . ^{13}C NMR spectra were recorded at 75 MHz. Chemical shifts for ^{13}C NMR spectra are reported (in parts per million) relative to CDCl_3 ($\delta = 77.0$ ppm). ^{31}P NMR spectra were recorded at 121 MHz, and chemical shifts are reported (in parts per million) relative to external 85% phosphoric acid ($\delta = 0.0$ ppm). ^{19}F NMR spectra were recorded at 282 MHz, and chemical shifts are reported (in parts per million) relative to external CFCl_3 ($\delta = 0.0$ ppm).

Reagents and solvents

Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under N_2 just before reaction.

Diethoxymethyl-difluoromethyl-phosphinic acid ethyl ester **4**

Neat diethoxymethyl-phosphinic acid ethyl ester (40.0 g, 204 mmol) was placed under vacuum in a dry two-neck flask equipped with a cold finger 10 min before use. Anhydrous THF (410 mL) was then added under N_2 . The flask was cooled to -78°C and deoxygenated under vacuum for 5 min. The reaction flask was back-filled with N_2 , then LiHMDS (1.0 M in THF, 224 mL, 224 mmol) was added at -78°C . After 15 min, condensed chlorodifluoromethane (around 18 mL, 204 mmol) was added under N_2 . After addition, the temperature of the solution was kept at -78°C for 10 min, then slowly allowed to warm to 0°C . After 10 min at 0°C , the reaction mixture was quenched with a saturated solution of NH_4Cl /brine, extracted with ethyl acetate (3 x), and then dried over anhydrous MgSO_4 .

Concentration in vacuo gave an oil which was purified by column chromatography over silica (Hexanes/Ethyl Acetate, 7/3, v/v to Ethyl Acetate 100 %) to afford the ester **4** as a lightly yellow oil (36.0 g, 72 % yield). ^1H NMR (300 MHz, CDCl_3) δ : 6.07 (td, $J_{\text{HCF}} = 49.0$ Hz, $J_{\text{HCP}} = 26.5$ Hz, 1 H, P- CF_2H), 4.90 (dt, $J_{\text{HCP}} = 9.0$ Hz, $J = 1.0$ Hz, 1 H, $(\text{EtO})_2\text{CH-P}$), 4.29–4.41 (m, 2 H, $-\text{CH}_2\text{-O-P}$), 3.85–3.98 (m, 2 H, $-\text{CH}_2\text{-O-C}$), 3.68–3.79 (m, 2 H, $-\text{CH}_2\text{-O-C}$), 1.41 (t, $J = 7.0$ Hz, 3 H, $\text{CH}_3\text{-C-O-P}$), 1.28 (t, $J = 7.0$ Hz, 6 H, $\text{CH}_3\text{-C-O-C} \times 2$); ^{13}C NMR (75.45 MHz, CDCl_3) δ : 112.6 (td, $J_{\text{CF}} = 262.0$ Hz, $J_{\text{CP}} = 129.5$ Hz), 99.2 (d, $J_{\text{CP}} = 152.5$ Hz), 66.2 (d, $J_{\text{COP}} = 10.0$ Hz), 65.8 (d, $J_{\text{COP}} = 10.0$ Hz), 63.9 (d, $J_{\text{COP}} = 7.0$ Hz), 16.6 (d, $J_{\text{CCOP}} = 4.5$ Hz), 15.2, 15.1; ^{31}P NMR (121.47 MHz, CDCl_3) δ : 23.64 (t, $J_{\text{PCF}} = 76.0$ Hz); ^{19}F NMR (282.3 MHz, CDCl_3) δ : -136.5 (ddd, $J_{\text{FF}} = 354.5$ Hz, $J_{\text{FCP}} = 76.0$ Hz, $J_{\text{FCH}} = 49.0$ Hz), -138.5 (ddd, $J_{\text{FF}} = 354.5$ Hz, $J_{\text{FCP}} = 76.0$ Hz, $J_{\text{FCH}} = 49.0$ Hz); HRMS (Chem Ion, NH_3) calcd. for $\text{C}_8\text{H}_{17}\text{F}_2\text{O}_4\text{P}$, $([\text{M}+\text{NH}_3]^+)$ 264.1176, found 264.1168.

4.1. Representative procedure for the alkylation of **3** (Tables 1–3): (1,1-Diethoxy-ethyl)-(1,1-difluoro-ethyl)-phosphinic acid ethyl ester

(1,1-Diethoxy-ethyl)-difluoromethyl-phosphinic acid ethyl ester **3** (0.52 g, 2.0 mmol) was placed under vacuum in a dry two-neck flask 10 min before use. Anhydrous THF (6.7 mL, 0.3 M) was then added under N_2 . The flask was cooled to -78°C and deoxygenated under vacuum for 5 min. The reaction flask was back-filled with N_2 , then $t\text{-BuLi}$ (1.7 M in pentane, 1.3 mL, 2.2 mmol, 1.1 equiv.) was added at -78°C . After 30 min, iodomethane (2.0 mmol, 1.0 equiv.) was added under N_2 . After addition, the temperature of the solution was kept at -78°C for 10 min, then slowly allowed to warm to 0°C over 2 h. The reaction mixture was quenched with brine (10 mL). The aqueous layer was extracted with ethyl acetate (3 x). The combined organic layer was dried over anhydrous MgSO_4 and concentrated to afford the product as a slightly yellow oil (0.5 g, 91 % yield). ^1H NMR (300 MHz, CDCl_3) δ : 4.27–4.40 (m, 2 H, $-\text{CH}_2\text{-O-P}$), 3.66–3.93 (m, 4 H, $-\text{CH}_2\text{-O-C} \times 2$), 1.86 (td, $J_{\text{HCF}} = 21.5$ Hz, $J_{\text{HCCP}} = 7.5$ Hz, 3 H, P- $\text{CF}_2\text{-CH}_3$), 1.61 (d, $J_{\text{HCP}} = 12.0$ Hz, 3 H, P-C- CH_3), 1.39 (t, $J = 7.0$ Hz, 3 H, $\text{CH}_3\text{-C-O-P}$), 1.20–1.25 (m, 6 H, $\text{CH}_3\text{-C-O-C} \times 2$); ^{13}C NMR (75.45 MHz, CDCl_3) δ : 122.2 (td, $J_{\text{CF}} = 262.5$ Hz, $J_{\text{CP}} = 126.0$ Hz), 101.6 (d, $J_{\text{CP}} = 145.0$ Hz), 63.5 (d, $J_{\text{COP}} = 8.0$ Hz), 58.9 (d, $J_{\text{COP}} = 5.0$ Hz), 58.2 (d, $J_{\text{COP}} = 8.0$ Hz), 21.6 (dt, $J_{\text{FCC}} = 22.0$ Hz, $J_{\text{PCC}} = 14.0$ Hz), 20.9 (dt, $J_{\text{PCC}} = 12.5$ Hz, $J_{\text{FCPCC}} = 3.0$ Hz), 16.8 (d, $J_{\text{CCOP}} = 5.0$ Hz), 15.6, 15.3; ^{31}P NMR (121.47 MHz, CDCl_3) δ : 29.11 (t, $J_{\text{PCF}} = 90.0$ Hz); ^{19}F NMR (282.3 MHz, CDCl_3) δ : -101.9 (dq, $J_{\text{FCP}} = 90.0$ Hz, $J_{\text{FCH}} = 21.5$ Hz); HRMS (Chem Ion) calcd. for $\text{C}_{10}\text{H}_{21}\text{F}_2\text{O}_4\text{P}$, $([\text{M}+\text{H}]^+)$ 275.1224, found 275.0123.

4.2. Representative procedure for the alkylation of **4** (Table 4): Diethoxymethyl-(1,1-difluoro-ethyl)-phosphinic acid ethyl ester

To diisopropylamine (0.31 mL, 2.2 mmol, 1.1 equiv.) in anhydrous THF (1.0 mL) at -20°C under N_2 was added $n\text{-BuLi}$ (1.6 M, 1.38 mL, 2.2 mmol, 1.1 equiv.). After 30 min, the solution was cooled down to -78°C and a solution of diethoxymethyl-difluoromethyl-phosphinic acid ethyl ester **4** (0.492 g, 2.0 mmol) in anhydrous THF (4.0 mL) was added. After 30 min, iodomethane (0.124 mL, 2.0 mmol, 1.0 equiv.) was added under N_2 . After addition, the temperature of the solution was kept at -78°C for 10 min, then slowly allowed to warm to 5°C over 1 h. The reaction mixture was quenched with brine (10 mL). The aqueous layer was extracted with ethyl acetate (3 x). The combined organic layer was dried over anhydrous MgSO_4 and concentrated. The resulting oil was purified by column chromatography over silica (Hexanes/Ethyl acetate, 1/1, v/v) to afford the product as a slightly yellow oil (0.32 g, 62 %). ^1H NMR (300 MHz, CDCl_3) δ : 4.94 (d, 1 H, $J_{\text{HCP}} = 10.0$ Hz, $-\text{CH-P}$), 4.29–4.42 (m, 2 H, $-\text{CH}_2\text{-O-P}$), 3.68–3.98 (m, 4 H, $-\text{CH}_2\text{-O-C} \times 2$), 1.86 (td, $J_{\text{HCF}} = 21.5$ Hz, $J_{\text{HCCP}} = 8.0$ Hz, 3 H, P- $\text{CF}_2\text{-CH}_3$), 1.40 (t, $J = 7.0$ Hz, 3 H, $\text{CH}_3\text{-C-O-P}$), 1.27 (t, 6 H, $J = 7.0$ Hz, $\text{CH}_3\text{-C-O-C} \times 2$); ^{13}C NMR (75.45 MHz, CDCl_3) δ : 122.2 (td, $J_{\text{CF}} = 262.5$ Hz, $J_{\text{CP}} = 126.0$ Hz), 99.0 (d, $J_{\text{CP}} = 148.5$ Hz), 65.8 (d, $J_{\text{COP}} = 10.0$ Hz), 65.6 (d,

$J_{\text{COP}} = 9.0$ Hz), 63.9 (d, $J_{\text{COP}} = 8.0$ Hz), 21.3 (dt, $J_{\text{FCC}} = 22.0$ Hz, $J_{\text{PCC}} = 13.5$ Hz), 16.8 (d, $J_{\text{CCOP}} = 5.0$ Hz), 15.4, 15.3; ^{31}P NMR (121.47 MHz, CDCl_3) δ : 25.84 (t, $J_{\text{PCF}} = 93.5$ Hz); ^{19}F NMR (282.3 MHz, CDCl_3) δ : -104.0 (dq, $J_{\text{FCP}} = 93.5$ Hz, $J_{\text{FCH}} = 22.0$ Hz); HRMS (Chem Ion) calcd. for $\text{C}_9\text{H}_{19}\text{F}_2\text{O}_4\text{P}$, ($[\text{M}+\text{H}]^+$) 261.1067, found 261.1069.

4.3. Representative procedure for the alkylation of **2** (Table 5, Equation 4): Difluoromethyl-(1-methyl-octyl)-phosphinic acid butyl ester

Difluoromethyl-octyl-phosphinic acid butyl ester **2** (0.426 g, 1.5 mmol) was placed under vacuum in a dry two-neck flask 10 min before use. Anhydrous THF (5.0 mL, 0.3 M) was then added under N_2 . The flask was cooled to -78°C and deoxygenated under vacuum for 5 min. The reaction flask was back-filled with N_2 , then $t\text{-BuLi}$ (1.7 M in pentane, 1.0 mL, 1.65 mmol, 1.1 equiv.) was added at -78°C . After 30 min, iodomethane (0.1 mmol, 1.65 mmol, 1.1 equiv.) was added under N_2 . After addition, the temperature of the solution was kept at -78°C for 30 min, then slowly allowed to warm to rt over 1 h. The reaction mixture was quenched with saturated solution of NH_4Cl /brine (10 mL). The aqueous layer was extracted with ethyl acetate (3 x). The combined organic layer was dried over anhydrous MgSO_4 and concentrated. The resulting oil was purified by column chromatography over silica (Hexanes/Ethyl Acetate, 8/2, v/v) to afford the product as a slightly yellow oil (0.79 g, 85 %). **2 diastereoisomers** ^1H NMR (300 MHz, CDCl_3) δ : 6.03 (td, 1 H, $J_{\text{HCF}} = 48.5$ Hz, $J_{\text{HCP}} = 23.5$ Hz, P- CF_2H), 4.12–4.32 (m, 2 H, $-\text{CH}_2\text{-O-P}$), 2.01 (m, 1 H, P- $\text{CH-CH}_2\text{-}$), 1.67–1.85 (m, 3 H, P- C-CH_3), 1.20–1.51 (m, 16 H, $-\text{CH}_2\text{-}$), 0.89–1.00 (m, 6 H, $-\text{CH}_2\text{-CH}_3$ x 2); ^{13}C NMR (75.45 MHz, CDCl_3) δ : 113.9 (2 td, $J_{\text{CF}} = 263.0$ Hz, $J_{\text{CP}} = 122.0$ Hz), 66.4 (2 d, $J_{\text{COP}} = 7.0$ Hz), 32.7 (d, $J_{\text{CCOP}} = 5.0$ Hz), 31.8, 30.2 (d, $J_{\text{CP}} = 95.0$ Hz) & 30.1 (d, $J_{\text{CP}} = 94.5$ Hz), 29.3, 29.1, 28.2, 27.1 (2 d, $J_{\text{CCP}} = 12.0$ Hz), 22.6, 18.7, 14.1, 13.6, 11.6 (d, $J_{\text{CCP}} = 14.5$ Hz); ^{31}P NMR (121.47 MHz, CDCl_3) δ : 42.14 (t, $J_{\text{PCF}} = 72.0$ Hz), 41.75 (t, $J_{\text{PCF}} = 70.5$ Hz); ^{19}F NMR (282.3 MHz, CDCl_3) δ : -135.2 - -134.4 (m); HRMS (EI) calcd. for $\text{C}_{14}\text{H}_{29}\text{F}_2\text{O}_2\text{P}$, ($[\text{M}]^+$) 298.1873, found 298.1875.

4.4. Representative procedure for the rearrangement with carbonyl compounds (Table 6, entry 1): (1,1-Diethoxy-ethyl)-phosphonic acid 1-difluoromethyl-cyclohexyl ester ethyl ester

(1,1-Diethoxy-ethyl)-difluoromethyl-phosphinic acid ethyl ester **3** (0.52 g, 2.0 mmol) was placed under vacuum in a dry two-neck flask 10 min before use. Anhydrous THF (6.7 mL, 0.3 M) was then added under N_2 . The flask was cooled to -78°C and deoxygenated under vacuum for 5 min. The reaction flask was back-filled with N_2 , then $t\text{-BuLi}$ (1.7 M in pentane, 1.3 mL, 2.2 mmol, 1.1 equiv.) was added at -78°C . After 30 min, cyclohexanone (2.2 mmol, 1.1 equiv.) was added under N_2 . After addition, the temperature of the solution was kept at -78°C for 10 min, then slowly allowed to warm to 0°C over 2 h. The reaction mixture was quenched with brine (10 mL). The aqueous layer was extracted with ethyl acetate (3 x). The combined organic layer was dried over anhydrous MgSO_4 and concentrated. The crude oil was purified by chromatography over silica (Hexanes/Ethyl Acetate, 8/2, v/v) to afford the product as a slightly yellow oil (0.61 g, 80 % yield). ^1H NMR (300 MHz, CDCl_3) δ : 6.19 (t, 1 H, $J_{\text{HCF}} = 56.5$ Hz, $-\text{CF}_2\text{H}$), 4.22 (m, 2 H, $-\text{CH}_2\text{-O-P}$), 3.64–3.76 (m, 4 H, $-\text{CH}_2\text{-O-C-P}$ x 2), 2.05–2.18 (m, 2 H, $-\text{CH-}$ x 2), 1.53–1.80 (m, 8 H, $-\text{CH-}$), 1.55 (d, $J_{\text{HCP}} = 12.0$ Hz, $\text{CH}_3\text{-C-P}$), 1.34 (t, $J = 7.0$ Hz, $\text{CH}_3\text{-C-O-P}$), 1.21 (t, $J = 7.0$ Hz, $\text{CH}_3\text{-C-O-C}$), 1.20 (t, $J = 7.0$ Hz, $\text{CH}_3\text{-C-O-C}$); ^{13}C NMR (75.45 MHz, CDCl_3) δ : 117.0 (d, $J_{\text{CF}} = 248.0$ Hz), 100.4 (d, $J_{\text{CP}} = 214.0$ Hz), 84.3 (td, $J_{\text{CCF}} = 20.5$ Hz, $J_{\text{COP}} = 10.0$ Hz), 63.8 (d, $J_{\text{COP}} = 7.0$ Hz), 58.4 (d, $J_{\text{COP}} = 6.5$ Hz), 57.9 (d, $J_{\text{COP}} = 9.0$ Hz), 29.9, 29.1, 25.3, 21.2 (d, $J_{\text{CCP}} = 10.0$ Hz), 20.8, 20.7, 16.6 (d, $J_{\text{CCOP}} = 5.5$ Hz), 15.6, 15.4; ^{31}P NMR (121.47 MHz, CDCl_3) δ : 15.49 (s); ^{19}F NMR (282.3 MHz, CDCl_3) δ : -133.6 (dd, $J_{\text{FCF}} = 285.5$ Hz, $J_{\text{FCH}} = 56.5$ Hz), -132.0 (dd, $J_{\text{FCF}} = 285.5$ Hz, $J_{\text{FCH}} = 56.5$ Hz); HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{29}\text{F}_2\text{NaO}_5\text{P}$, ($[\text{M}]^+$) 381.1618, found 381.1617.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1. Hall's synthesis and elaboration of an α,α -difluorophosphate⁴

Scheme 2.

^a Computed relative energies (kcal/mol) for anions **A** and **B** (6-311+G**).

^aThe P=O group is represented as P(+)-O(-) with only O(-) visible. Rotamers of the CF_2H group in **A** are not shown. As expected, anion **B** is much more pyramidalized than anion **A**.

Scheme 3. Postulated mechanism of the $\text{CF}_2 \rightarrow \text{O}$ rearrangement

Scheme 4. Obayashi's reactions with phosphonate reagents¹¹

Scheme 5. Literature approach to some pyrophosphate analogs¹⁴

Table 1Role of the base in the alkylation of **3** with CH₃I.

Entry	Base (Eq.)	Conditions ^a	Crude NMR yield ³¹ P and ¹⁹ F	Isolated yield
1	LDA (1.0)	Deoxygenated	20 %	-
2	LiHMDS (1.0)	Deoxygenated	0	-
3	<i>t</i> -BuLi (1.0)	Deoxygenated	80 %	-
4a	<i>t</i> -BuLi (1.1)	Deoxygenated	100 %	91 %
4b		Without deoxygenation	53 %	-

^a Unless otherwise noted, all reactions were deoxygenated for 30 min-1 h prior to adding the base

Table 2^a Role of the Electrophile in the Alkylation of **3** with *t*-BuLi

Entry	Electrophile	Crude NMR ³¹ P and ¹⁹ F	Isolated yield
1	OctI	100 %	85 %
2	OctBr	100 %	82 %
4	OctOTs	45 %	-
3	OctCl	30 %	-

^a Conditions: 1) Deoxygenation, 2) Addition of RX at -78 °C, 30 min after the base, 3) -78 °C to 15 °C, 1.5 h, 4) Extractive work-up.

Table 3Reactions of phosphinate **3** with some electrophiles.

Entry	Base (1.1 eq)	Electrophile	Isolated yield	
1	<i>t</i> -BuLi		0.5 eq	69 % ^a
2	<i>t</i> -BuLi		0.5 eq	62 % ^a
3	<i>t</i> -BuLi		1.05 eq	65 %
4	<i>t</i> -BuLi		1.0 eq	70 %
5	<i>t</i> -BuLi	geranyl bromide	1.0 eq	52 %

^aDisubstitution.

Table 4Role of the base in the alkylation of **4** with CH₃I.

Entry	Base (Eq.)	Conditions ^a	Crude NMR yield ³¹ P and ¹⁹ F	Isolated yield
1	LDA (1.1)	Deoxygenated	100 %	62 %
2	BuLi (1.1)	Deoxygenated	Some addition to P	-
3	<i>t</i> -BuLi (1.1)	Deoxygenated	Addition to P major	-

^a All reactions were deoxygenated for 30 min-1 h prior to adding the base.

Table 5Alkylation of compound **2** with CH₃I (Equation 4)

Entry	Base		Crude NMR yield ³¹ P and ¹⁹ F	Isolated yield
1	LDA	1.1 eq	100 %	87 %
2	<i>t</i> -BuLi	1.1 eq	100 %	85 %
3	<i>t</i> -BuLi	2.2 eq	100 %	-

Table 6

Reaction with carbonyl compounds.

Reagent	Base (1.1 eq)	Carbonyl Compound (1.1 eq)	Crude NMR yield ³¹ P and ¹⁹ F	Isolated yield
3	<i>t</i> -BuLi		100 %	80 %
4	LDA		100 %	77 %
3	<i>t</i> -BuLi		85 %	48 %