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Synthesis and reactivity studies of α,α-difluoromethylphosphinates

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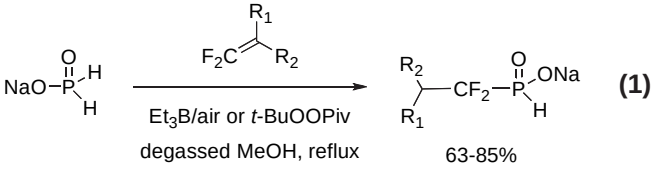
ABSTRACT

The preparation and reactivity of some α,α-difluorophosphinates are 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' $(EtO)_2CRP(O)(OEt)H$ (R=H, 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.

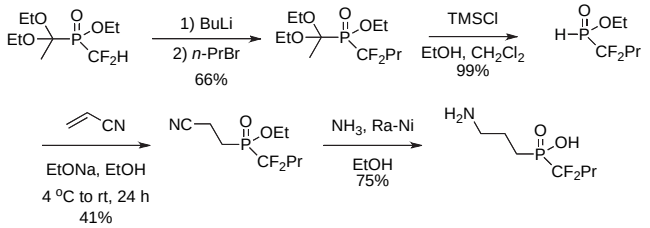
1. Introduction

α-Fluorophosphorus compounds have gained popularity as potential pharmacophores. In the case of phosphonates, the fluorine substituent(s) is known to modulate the pK_a 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 pK_a 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, Et_3B/air)[2] Piettre and co-workers have pioneered the synthesis of α,α-difluorophosphinates, from 1,1-difluoro-2,2-disubstituted olefins (Eq. 1).[3]



(1)

Fifteen years ago, Hall and co-workers reported the only example we could find of the base-promoted alkylation of a difluoromethylp hosphinate $RP(O)(OEt)CF_2H$, as well as its subsequent elaboration into a GABA analog (Scheme 1).[4] Two GABA analogs $H_2NCH_2CH(X)CH_2P(O)(OH)CF_2H$ (X=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 ~3–5.[4] Phosphonate $H_2N(CH_2)_3P(O)(OH)_2$ 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]



Scheme 1. Hall's synthesis and elaboration of an α,α-difluorophosphinate.[4]

2. Results and discussion

2.1. Synthesis of difluoromethylphosphinate $RP(O)(OEt)CF_2H$ precursors

Three precursors **1**–**3** were synthesized previously (Eq. 2).[5] A fourth compound **4** was synthesized similarly from $(EtO)_2CHP(O)$

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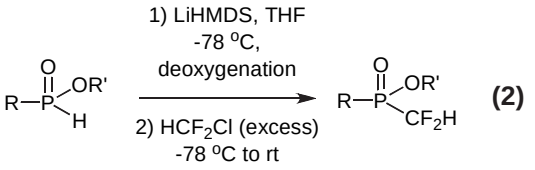
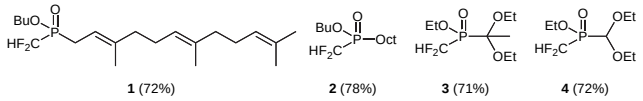
(OEt)H. We have been referring to $(EtO)_2CRP(O)(OEt)H$ (R=H, Me) as the 'Ciba-Geigy reagents', after their development in that company. As will be discussed below, significant differences exist between compounds **3** and **4**.





The alkylation of *H*-phosphinate esters with lithium hexamethyldisilazide (LiHMDS)[5] and F_2CHCl (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 $P(O)CF_2H$ 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.

Table 1
Role of the base in the alkylation of **3** with CH_3I

Entry	Base (equiv)	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	*t*-BuLi (1.0)	Deoxygenated	80	—
4a	*t*-BuLi (1.1)	Deoxygenated	100	91
4b		Without deoxygenation	53	—

[a] Unless otherwise noted, all reactions were deoxygenated for 30 min to 1 h prior to adding the base.

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

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

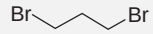
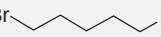
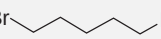
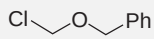
Entry	Electrophile	Crude NMR, ^{31}P and ^{19}F (%)	Isolated yield (%)
1	OctI	100	85
2	OctBr	100	82
4	OctOTs	45	—
3	OctCl	30	—

[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.

2.3. Scope of the alkylation

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

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

Entry	Base (1.1 equiv)	Electrophile		Isolated yield (%)
1	*t*-BuLi		0.5 equiv	69[a]
2	*t*-BuLi		0.5 equiv	62[a]
3	*t*-BuLi		1.05 equiv	65
4	*t*-BuLi		1.0 equiv	70
5	*t*-BuLi	Geranyl bromide	1.0 equiv	52

[a] Disubstitution.

Alkylation with a carbohydrate-derived iodide also gave satisfactory results but the product was obtained as the fully hydrolyzed *H*-phosphinic acid (Eq. 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**.

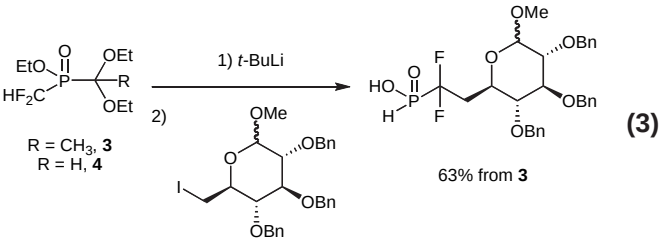


Table 4
Role of the base in the alkylation of **4** with CH_3I

Entry	Base (1.1 equiv)	Conditions[a]	Crude NMR yield, ^{31}P and ^{19}F (%)	Isolated yield (%)
1	LDA	Deoxygenated	100	62
2	BuLi	Deoxygenated	Some addition to P	—
3	*t*-BuLi	Deoxygenated	Addition to P major	—

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

Compounds $RP(O)(OEt)CF_2R'$ 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 RP(O)(OEt)H are typically hydrolyzed rather easily, and the difluoro-substituted compounds $RCF_2P(O)(OEt)H$ are even more prone to further hydrolysis to the corresponding *H*-phosphinic acids $RCF_2P(O)(OH)H$.

2.4. Alkylation of 2

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

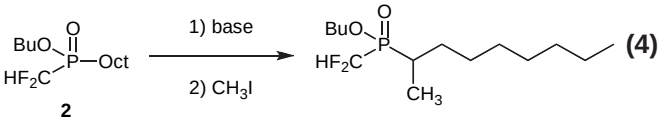


Table 5 shows the results. Even with excess *t*-BuLi, no alkylation of the difluoromethyl group is taking place (indicating that the dianion could not be formed). A possible explanation for this initially surprising result (the lower pK_a of the methylene group over that of the CF_2H group in **2**, Eq. 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 $n\rightarrow\sigma^*(P^+-O^-)$), whereas the P=O bond might instead prefer to be antiperiplanar to C–F ($\sigma(P^+-O^-)\rightarrow\sigma^*(C-F)$, dipole minimization).

Table 5
Alkylation of compound **2** with CH_3I (Eq. 4)

Entry	Base		Crude NMR yield, ^{31}P and ^{19}F (%)	Isolated yield (%)
1	LDA	1.1 equiv	100	87
2	*t*-BuLi	1.1 equiv	100	85
3	*t*-BuLi	2.2 equiv	100	—

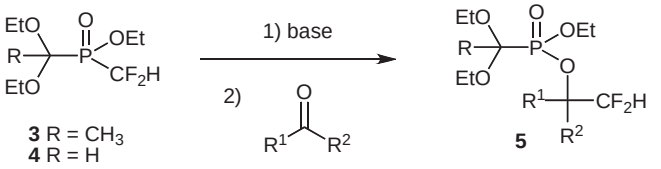
In order to better understand these effects, a brief computational investigation on the two possible anions derived from $CH_3P(O)(OMe)CF_2H$ as simplified models (conformational search followed by optimization at the 6-311+G** level) was conducted (Scheme 2).[7] It revealed that, in fact, all conformers of the CF_2 anion **B** are always higher in energy than the corresponding CH_2 anion **A**, thereby supporting the experimental results (Eq. 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 $n\rightarrow\sigma^*(P^+-O^-)$) is higher in energy even for **A**. This is because the accepting ability decreases in the following order: $\sigma^*(C-CF_2H)>\sigma^*(P-OR)>\sigma^*(P^+-O^-)$, as shown in the stability order **A1**>**A2**>**A3**. Experimentally, the (same) fact that HCF_2 is more electron-withdrawing (lower lying σ^*) than OR can easily be established: the second pK_a of $(HO)_2P(O)CF_2H$ is 5.4 versus 7.2 for $(HO)_3P(O)$ [and 7.6 for $(HO)_2P(O)CH_3$]; or the pK_a of HCF_2COOH 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 $RCH_2P(O)(OR')_2$, whereas that of the CF_2H is significantly higher.

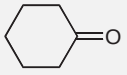
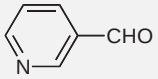
2.5. Anion reactivity with carbonyl compounds

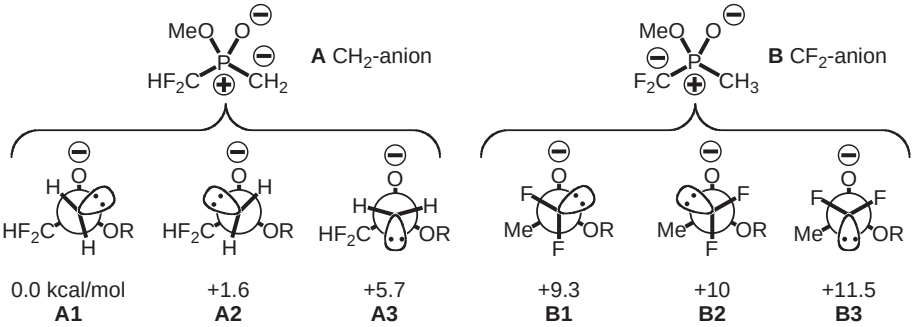
Another unexpected reaction was uncovered when the anion derived from $(EtO)_2CRP(O)(OEt)CF_2H$ (**3**, **4**) was treated with carbonyl compounds (Table 6).

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–CF_2 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 CF_2 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 [$\sigma(P^+-O^-)\rightarrow\sigma^*(C-F)$ 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 co-workers reported a similar rearrangement producing 1,1-difluoro-2-phosphonyl esters **12** (R=OR[3]=OEt, Scheme 3) or **17** (Scheme 4) in the reaction of $(EtO)_2P(O)CF_2H$ and $(EtO)_2P(O)CF_2SiMe_3$ 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]

Table 6
Reaction with carbonyl compounds

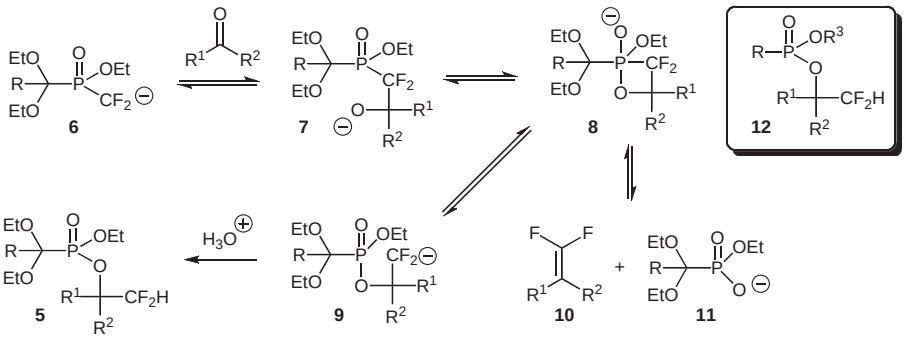


Reagent	Base (1.1 equiv)	Carbonyl compound (1.1 equiv)	Crude NMR yield, ^{31}P and ^{19}F (%)	Isolated yield (%)
3	*t*-BuLi		100	80
4	LDA		100	77
3	*t*-BuLi		85	48

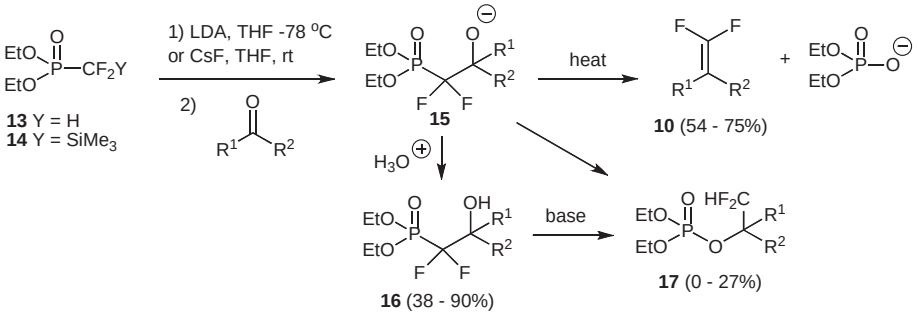


Scheme 2. Computed relative energies (kcal/mol) for anions **A** and **B** (6-311+G**). The P=O group is represented as P(+)–O(−) with only O(−) visible. Rotamers of the CF_2H group in **A** are not shown. As expected, anion **B** is much more pyramidalized than anion **A**.

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.



Scheme 3. Postulated mechanism of the $CF_2 \rightarrow O$ rearrangement.



Scheme 4. Obayashi's reactions with phosphonate reagents.[11]

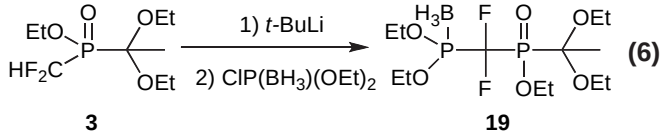
Again, stereoelectronic effects could explain the much greater propensity for rearrangement in phosphinates **7** over phosphonates **15**. In the case of phosphonate **15**, an additional oxygen lone-pair in the second ethoxy group [antiperiplanar lone pair $n \rightarrow \sigma^*(P^+-O^-)$] decreases 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 phosphonylation of the corresponding fluorinated alcohol using P–Cl containing reagents.[12]

2.6. Pyrophosphate analogs

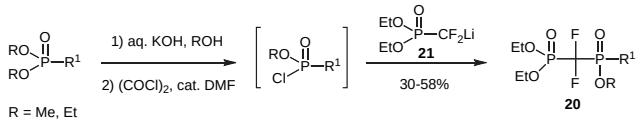
Pyrophosphate analogs are medicinally important in the treatment of bone and other diseases. For example, bisphosphonates constitute a major class of drugs against osteoporosis.[13] Thus, we briefly investigated the preparation of novel PCF_2P building blocks. Alkylation of **4** with $ClP(O)(OEt)_2$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

(5)



(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%, Eq. 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]



Scheme 5. Literature approach to some pyrophosphate analogs.[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 $RP(O)(OH)(CF_2H)$ 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

4.1. General chemistry

^{1}H NMR spectra were recorded on a 300-MHz spectrometer. Chemical shifts for ^{1}H NMR spectra are reported (in parts per million) relative to internal tetramethylsilane (Me_4Si, δ=0.00 ppm) with $CDCl_3$ or H_2O (δ=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 $CDCl_3$ (δ=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 (δ=0.0 ppm). ^{19}F NMR spectra were recorded at 282 MHz, and chemical shifts are reported (in parts per million) relative to external $CFCl_3$ (δ=0.0 ppm).

4.2. Reagents and solvents

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

4.3. 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×), 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). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.07 (td, J_{HCF}=49.0 Hz, J_{HCP}=26.5 Hz, 1H, P−CF_2H), 4.90 (dt, J_{HCP}=9.0 Hz, J=1.0 Hz, 1H, $(EtO)_2CH$−P), 4.29–4.41 (m, 2H, −CH_2−O−P), 3.85–3.98 (m, 2H, −CH_2−O−C), 3.68–3.79 (m, 2H, −CH_2−O−C), 1.41 (t, J=7.0 Hz, 3H, CH_3−C−O−P), 1.28 (t, J=7.0 Hz, 6H, CH_3−C−O−C×2); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ: 112.6 (td, J_{CF}=262.0 Hz, J_{CP}=129.5 Hz), 99.2 (d, J_{CP}=152.5 Hz), 66.2 (d, J_{COCP}=10.0 Hz), 65.8 (d, J_{COCP}=10.0 Hz), 63.9 (d, J_{COP}=7.0 Hz), 16.6 (d, J_{CCOP}=4.5 Hz), 15.2, 15.1; ^{31}P NMR (121.47 MHz, $CDCl_3$) δ: 23.64 (t, J_{PCF}=76.0 Hz); ^{19}F NMR (282.3 MHz, $CDCl_3$) δ: −136.5 (ddd, J_{FF}=354.5 Hz, J_{FCP}=76.0 Hz, J_{FCH}=49.0 Hz), −138.5 (ddd, J_{FF}=354.5 Hz, J_{FCP}=76.0 Hz, J_{FCH}=49.0 Hz); HRMS (Chem Ion, NH_3) calcd for $C_8H_{17}F_2O_4P$, ($[M+NH_3]^+$) 264.1176, found 264.1168.

4.4. 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*-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×). 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). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.27–4.40 (m, 2H, −CH_2−O−P), 3.66–3.93 (m, 4H, −CH_2−O−C×2), 1.86 (td, J_{HCF}=21.5 Hz, J_{HCCP}=7.5 Hz, 3H, P−CF_2−CH_3), 1.61 (d,J_{HCP}=12.0 Hz, 3H, P−C−CH_3), 1.39 (t, J=7.0 Hz, 3H, CH_3−C−O−P), 1.20–1.25 (m, 6H, CH_3−C−O−C×2); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ: 122.2 (td, J_{CF}=262.5 Hz, J_{CP}=126.0 Hz), 101.6 (d, J_{CP}=145.0 Hz), 63.5 (d, J_{COP}=8.0 Hz), 58.9 (d, J_{COCP}=5.0 Hz), 58.2 (d, J_{COCP}=8.0 Hz), 21.6 (dt, J_{FCC}=22.0 Hz, J_{PCC}=14.0 Hz), 20.9 (dt, J_{PCC}=12.5 Hz, J_{FCPCC}=3.0 Hz), 16.8 (d, J_{CCOP}=5.0 Hz), 15.6, 15.3; ^{31}P NMR (121.47 MHz, $CDCl_3$) δ: 29.11 (t, J_{PCF}=90.0 Hz); ^{19}F NMR (282.3 MHz, $CDCl_3$) δ: −101.9 (dq, J_{FCP}=90.0 Hz, J_{FCH}=21.5 Hz); HRMS (Chem Ion) calcd for $C_{10}H_{21}F_2O_4P$, ($[M+H]^+$) 275.1224, found 275.0123.

4.5. 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*-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×). 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%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.94 (d, 1H, J_{HCP}=10.0 Hz, −CH−P), 4.29–4.42 (m, 2H, −CH_2−O−P), 3.68–3.98 (m, 4H, −CH_2−O−C×2), 1.86 (td, J_{HCF}=21.5 Hz, J_{HCCP}=8.0 Hz, 3H, P−CF_2−CH_3), 1.40 (t, J=7.0 Hz, 3H, CH_3−C−O−P), 1.27 (t, 6H, J=7.0 Hz, CH_3−C−O−C×2); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ: 122.2 (td, J_{CF}=262.5 Hz, J_{CP}=126.0 Hz), 99.0 (d, J_{CP}=148.5 Hz), 65.8 (d, J_{COP}=10.0 Hz), 65.6

(d, J_{COCP}=9.0 Hz), 63.9 (d, J_{COCP}=8.0 Hz), 21.3 (dt, J_{FCC}=22.0 Hz, J_{PCC}=13.5 Hz), 16.8 (d, J_{CCOP}=5.0 Hz), 15.4, 15.3; ^{31}P NMR (121.47 MHz, $CDCl_3$) δ: 25.84 (t, J_{PCF}=93.5 Hz); ^{19}F NMR (282.3 MHz, $CDCl_3$) δ: −104.0 (dq, J_{FCP}=93.5 Hz, J_{FCH}=22.0 Hz); HRMS (Chem Ion) calcd for $C_9H_{19}F_2O_4P$, ($[M+H]^+$) 261.1067, found 261.1069.

4.6. Representative procedure for the alkylation of 2 (Table 5, Eq. 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*-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×). 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%). *Two diastereosisomers* ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.03 (td, 1H, J_{HCF}=48.5 Hz, J_{HCP}=23.5 Hz, P−CF_2H), 4.12−4.32 (m, 2H, −CH_2−O−P), 2.01 (m, 1H, P−CH−CH_2−), 1.67−1.85 (m, 3H, P−C−CH_3), 1.20−1.51 (m, 16H, −CH_2−), 0.89−1.00 (m, 6H, −CH_2−CH_3×2); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ: 113.9 (2td, J_{CF}=263.0 Hz, J_{CP}=122.0 Hz), 66.4 (2d, J_{COP}=7.0 Hz), 32.7 (d, J_{CCOP}=5.0 Hz), 31.8, 30.2 (d, J_{CP}=95.0 Hz) and 30.1 (d, J_{CP}=94.5 Hz), 29.3, 29.1, 28.2, 27.1 (2d, J_{CCP}=12.0 Hz), 22.6, 18.7, 14.1, 13.6, 11.6 (d, J_{CCP}=14.5 Hz); ^{31}P NMR (121.47 MHz, $CDCl_3$) δ: 42.14 (t, J_{PCF}=72.0 Hz), 41.75 (t, J_{PCF}=70.5 Hz); ^{19}F NMR (282.3 MHz, $CDCl_3$) δ: −135.2 to −134.4 (m); HRMS (EI) calcd for $C_{14}H_{29}F_2O_2P$, ($[M]^+$) 298.1873, found 298.1875.

4.7. 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*-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×). 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). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.19 (t, 1H, J_{HCF}=56.5 Hz, −CF_2H), 4.22 (m, 2H, −CH_2−O−P), 3.64−3.76 (m, 4H, −CH_2−O−C−P×2), 2.05−2.18 (m, 2H, −CH−×2), 1.53−1.80 (m, 8H, −CH−), 1.55 (d, J_{HCP}=12.0 Hz, CH_3−C−P), 1.34 (t, J=7.0 Hz, CH_3−C−O−P), 1.21 (t, J=7.0 Hz, CH_3−C−O−C), 1.20 (t, J=7.0 Hz, CH_3−C−O−C); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ: 117.0 (d, J_{CF}=248.0 Hz), 100.4 (d, J_{CP}=214.0 Hz), 84.3 (td, J_{CCF}=20.5 Hz, J_{COP}=10.0 Hz), 63.8 (d, J_{COP}=7.0 Hz), 58.4 (d, J_{COCP}=6.5 Hz), 57.9 (d, J_{COCP}=9.0 Hz), 29.9, 29.1, 25.3, 21.2 (d, J_{CCP}=10.0 Hz), 20.8, 20.7, 16.6 (d, J_{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_{FCF}=285.5 Hz, J_{FCH}=56.5 Hz), −132.0 (dd, J_{FCF}=285.5 Hz, J_{FCH}=56.5 Hz); HRMS (ESI) calcd for $C_{15}H_{29}F_2NaO_5P$, ($[M]^+$) 381.1618, found 381.1617.

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Supplementary data

Additional experimental and spectral data are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.04.036. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. For representative and general references, see: (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308; (b) Bégué, J.-P.; Bonnet-Delphon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley: Hoboken, NJ, 2008; (c) Romanenko, V. D.; Kukhar, V. P. *Chem. Rev.* **2006**, *106*, 3868; (d) Lequeux, T. P. General Methods for the Synthesis of Difluoromethylphosphonates In *Fluorine-Containing Synthons. ACS Symposium Series*; 2005; Vol. 911, Chapter 26, pp 440−455; (e) *Modern Fluoroorganic Chemistry*; Kirsch, P., Ed.; Wiley-VCH: Weinheim, Germany, 2004; (f) Savignac, P.; Iorga, B. *Modern Phosphonate Chemistry*; CRC: Boca Raton, FL, 2003.
2. Deprèle, S.; Montchamp, J.-L. *J. Org. Chem.* **2001**, *66*, 6745.
3. (a) Gautier, A.; Garipova, G.; Salcedo, C.; Balieu, S.; Piettre, S. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 5963; (b) Our own studies using NaH_2PO_2 and Et_3B/air on 1,1-difluoro-2-monosubstituted olefins (unpublished results) showed that the regioselectivity is poor (and small amounts of partially defluorinated products also form). Thus, the use of $R_2C{=}CF_2$ appears important to form the tertiary radical intermediate for complete regioselection (formation of P−CF_2). Therefore the present/Hall reaction provides a competing alternative to free radical approaches.
4. (a) Froestl, W.; Mickel, S. J.; Hall, R. G.; von Sprecher, G.; Diel, P. J.; Strub, D.; Baumann, P. A.; Brugger, F.; Gentsch, C.; Jaekel, J.; Olpe, H.-R.; Rihs, G.; Vassout, A.; Waldmeier, P. C.; Bittiger, H. *J. Med. Chem.* **1995**, *38*, 3297; (b) Froestl, W.; Mickel, S. J.; von Sprecher, G.; Diel, P. J.; Hall, R. G.; Maier, L.; Strub, D.; Melillo, V.; Baumann, P. A.; Bernasconi, R.; Gentsch, C.; Hauser, K.; Jaekel, J.; Karlsson, G.; Klebs, K.; Maitre, L.; Marescaux, C.; Pozza, M. F.; Schmutz, M.; Steinmann, M. W.; van Riezen, H.; Vassout, A.; Mondadori, C.; Olpe, H.-R.; Waldmeier, P. C.; Bittiger, H. *J. Med. Chem.* **1995**, *38*, 3313.
5. Abrunhosa-Thomas, I.; Sellers, C. E.; Montchamp, J.-L. *J. Org. Chem.* **2007**, *72*, 2851.
6. The ease of oxidation of P(III) compounds with oxygen is well-known. See for example: (a) Lee, K.; Wiemer, D. F. *J. Org. Chem.* **1991**, *56*, 5556; (b) Fougère, C.; Guénin, E.; Hardouin, J.; Lecouvey, M. *Eur. J. Org. Chem.* **2009**, 6048.
7. Calculations were performed using the Spartan 08 molecular modeling software (Wavefunction, Inc.). Although these are gas-phase computations, it is reasonable to expect similar solvation of anions A and B. For interesting references concerning conformational effects in phosphorus compounds, see: (a) Thatcher, G. R. J.; Campbell, A. S. *J. Org. Chem.* **1993**, *58*, 2272; (b) Stewart, E. L.; Nevins, N.; Allinger, N. L.; Bowen, J. P. *J. Org. Chem.* **1999**, *64*, 5350; (c) Grein, F. *J. Mol. Struct. (Theochem)* **2001**, *536*, 87; (d) Vereshchagina, Y. A.; Ishmaeva, E. A.; Zverev, V. V. *Russ. Chem. Rev.* **2005**, *74*, 297.
8. The preference for antiperiplanar C−F in carbonyl compounds is well known. See for example Ref. 1a and references cited therein. In anions **A1**−**A3**, one of the C−F bonds is always antiperiplanar to P=O.
9. Tossell, J. A. *Environ. Sci. Technol.* **2009**, *43*, 2575.
10. For an interesting reference on the regioselective functionalization of $R^1CH_2P(O)(R)CH_2R^2$, see: Pietrusiewicz, K. M.; Zablocka, M. *Tetrahedron Lett.* **1982**, *30*, 477.
11. (a) Obayashi, M.; Ito, E.; Matsui, K.; Kondo, K. *Tetrahedron Lett.* **1982**, *23*, 2323; (b) Obayashi, M.; Kondo, K. *Tetrahedron Lett.* **1982**, *23*, 2327.
12. (a) Kitazume, T.; Lin, J. T.; Takeda, M.; Yamazaki, T. *J. Am. Chem. Soc.* **1991**, *113*, 2123; (b) Sawa, M.; Kondo, H.; Nishimurab, S.-i *Bioorg. Med. Chem. Lett.* **2002**, *12*, 581; (c) Sawa, M.; Tsukamoto, T.; Kiyoi, T.; Kurokawa, K.; Nakajima, F.; Nakada, Y.; Yokota, K.; Inoue, Y.; Kondo, H.; Yoshino, K. *J. Med. Chem.* **2002**, *45*, 930; (d) Nifant'ev, E. E.; Belov, S. P.; Komlev, I. V.; Petukhov, V. A.; Semenov, M. A.; Mezentseva, G. A.; Tavrizova, M. A.; Ponomareva, O. V. *Russ. J. Gen. Chem.* **2008**, *78*, 383.
13. For example, see: (a) Rodan, G. A. *Annu. Rev. Pharmacol. Toxicol.* **1998**, *38*, 375; (b) Mundy, G. R. *Annu. Rev. Med.* **2002**, *53*, 337; *Annu. Rev. Med.* **2002**, *53*, 537; (c) Prestwood, K. M.; Pilbeam, C. C.; Raisz, L. G. *Annu. Rev. Med.* **1995**, *46*, 249; (d) Fleisch, H. *Bisphosphonates in Bone Disease*; Academic: San Diego, CA, 2000; (e) *Bisphosphonate on Bones*; Bijvoet, O. L. M., Fleisch, H. A., Canfield, R. E., Russell, R. G. G., Eds.; Elsevier: Amsterdam, 1995; (f) Fleisch, H. *Drugs* **1991**, *42*, 919.

14. (a) Biller, S. A.; Forster, C.; Gordon, E. M.; Harrity, T.; Scott, W. A.; Ciosek, C. P., Jr. *J. Med. Chem.* **1988**, *31*, 1869; (b) Biller, S. A.; Forster, C. *Tetrahedron* **1990**, *46*, 6645; (c) Shipitsin, A. V.; Victorova, L. V.; Shirokova, E. A.; Dyatkina, N. B.; Goryunova, L. E.; Beabealashvilli, R. S.; Hamilton, C. J.; Roberts, S. M.; Krayevsky, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1039; (d) Zakharova, S.; Fulhorst, M.; Łuczak, L.; Wessjohann, L. *Arkivoc* **2004**, 79.
15. For selected references dealing with phosphonate analogs of naturally occurring phosphates, see: (a) Baxter, N. J.; Bowler, M. W.; Alizadeh, T.; Cliff, M. J.; Hounslow, A. M.; Wu, B.; Berkowitz, D. B.; Williams, N. H.; Blackburn, G. M.; Waltho, J. P. *PNAS* **2010**, *107*, 4555; (b) Baron, R. A.; Tavaré, R.; Figueiredo, A. C.; Błazewska, K. M.; Kashemirov, B. A.; McKenna, C. E.; Ebetino, F. H.; Taylor, A.; Rogers, M. J.; Coxon, F. P.; Seabra, M. C. *J. Biol. Chem.* **2009**, *284*, 6861; (c) DeGraw, A. J.; Zhao, Z.; Strickland, C. L.; Taban, A. H.; Hsieh, J.; Jefferies, M.; Xie, W.; Shintani, D. K.; McMahan, C. M.; Cornish, K.; Distefano, M. D. *J. Org. Chem.* **2007**, *72*, 4587; (d) Cheng, F.; Oldfield, E. *J. Med. Chem.* **2004**, *47*, 5149; (e) Li, X.; Bhandari, A.; Holmes, C. P.; Szardenings, A. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4301; (f) Pham, V.; Zhang, W.; Chen, V.; Whitney, T.; Yao, J.; Froese, D.; Friesen, A. D.; Diakur, J. M.; Haque, W. *J. Med. Chem.* **2003**, *46*, 3680; (g) Yokomatsu, T.; Takechi, H.; Akiyama, T.; Shinuya, S.; Kominato, T.; Soeda, S.; Shimeno, H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1277; (h) Berkowitz, D. M.; Bose, M.; Pfannenstiel, T. J.; Doukov, T. *J. Org. Chem.* **2000**, *65*, 4498; (i) Halazy, S.; Ehrhard, A.; Danzin, C. *J. Am. Chem. Soc.* **1991**, *113*, 315; (j) Kim, C. U.; Luh, B. Y.; Misco, P. F.; Bronson, J. J.; Hitchcock, M. J. M.; Ghazzouli, I.; Martin, J. C. *J. Med. Chem.* **1990**, *33*, 1207; (k) Bigge, C. F.; Drummond, J. T.; Johnson, G. *Tetrahedron Lett.* **1989**, *30*, 7013; (l) See also Ref. 1.
16. For examples of functional group interconversions related to *H*-phosphinates: see: (a) Montchamp, J.-L. *Specialty Chemicals Magazine* **2006**, *26*, 44; (b) Belabassi, Y.; Gushwa, A. F.; Richards, A. F.; Montchamp, J.-L. *Phosphorus, Sulfur Silicon Relat. Elem.* **2008**, *183*, 2214; (c) Frank, A. W. *Chem. Rev.* **1961**, *60*, 389; (d) Nifant'ev, E. E. *Russ. Chem. Rev.* **1978**, *47*, 835; (e) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley: New York, NY, 2000; (f) *Methoden der Organischen Chemie (Houben-Weyl)*; Sasse, K., Ed.; Thieme: Stuttgart, 1964; pp 294–337; Band XII/1; (g) *Methoden der Organischen Chemie (Houben-Weyl)*; Regitz, M., Ed.; Thieme: Stuttgart, 1982; Vol. E2.