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A difluorosulfide as a Freon-free source of phosphonodifluoromethyl carbanion †

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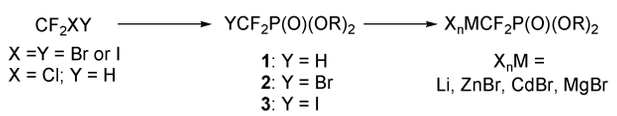
The synthesis of difluoromethylphosphonates is becoming difficult due to environmental protective laws restricting the use of HCFCs and CFCs as starting chemicals. To circumvent this limitation, we report the preparation of a thioether as a new source of the lithiodifluoromethylphosphonate. This methodology avoiding the use of HCFCs involves a selective fluorination of sulfide followed by a thiaphilic addition of an organometallic reagent, which offers an alternative route to obtain phosphonodifluoromethyl carbanion. A contrasted reactivity, due to a medium effect, was also noted which allows addition of a wide range of electrophiles including nitroalkenes and DMF to thioethers.

Introduction

It is well established that phosphate analogues bearing the difluoromethylenephosphonate moiety present a better bioactivity than the corresponding methylenephosphonates. This property has been widely applied in the preparation of important enzyme inhibitors and new drugs.[1] The synthesis of such complex molecules can be realised by direct introduction or construction of the difluoromethylenephosphonate function,[1,2] or by using building blocks already fluorophosphorylated.[3] In the majority of cases, the most popular starting materials are the organolithium and the organozinc reagents. The former was originally used by Kondo,[4] from the diethyl difluoromethylphosphonate **1**,[5] and the latter from the diethyl bromodifluoromethylphosphonate **2**[6] in the Burton's group.[7] Following the discovery of these reagents several other nucleophilic organometallic reagents have been reported. They have been prepared by transmetalation reaction, reduction of alkyl halides,[1,3,7] or nucleophilic displacement of halogen atom,[8] from **1**–**3**. Later *gem*-difluoroalkenes as free radical acceptors and halogenated or chalcogenated phosphonates as free radical precursors were used to trap phosphonyl radicals,[2] or form phosphonodifluoromethyl radicals,[9] as alternative routes to the carbanionic reactions. However, all these methodologies were developed from CFC or HCFC as starting chemicals (Scheme 1), and are now problematic due to environmental protective laws.

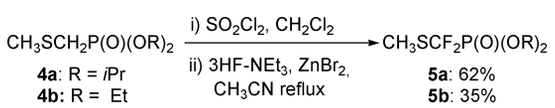


Scheme 1

Since the beginning of the 21st century, the Montreal Protocol has regulated the use and the freight of CFCs, HCFCs and halogenated derivatives,[10] and compromised the future development of these strategies. To circumvent this limitation, the electrophilic or nucleophilic fluorination of phosphonates represented a competitive alternative to prepare activated, benzylic or propargylic difluoromethylphosphonate derivatives.[11] Nevertheless, the fluorination technique presented some limitations and the syntheses of functionalised or heterosubstituted difluoromethylenephosphonates appear much more difficult.[12] To date, the building blocks or the carbanionic and the free radical approaches remain the best routes to prepare various aliphatic difluorophosphonates. To maintain these promising strategies, we investigated the synthesis of sulfides as building-blocks, which do not depend on CFCs or HCFCs as starting materials, and explored their uses as precursors for both phosphonodifluoromethyl radical and carbanion.

Results and discussion

First, the synthesis of alkylsulfanyl fluorophosphonates was investigated through a halogen-exchange reaction using our previous protocol for the synthesis of fluoroacetates.[13] As reported the rate of the halex reaction was strongly dependent on the nature of the alkylsulfanyl moiety. In the present case, all attempts to prepare arylsulfanyl difluoromethylphosphonates were unsuccessful. Alkylsulfanyl derivatives were more reactive and the chlorine–fluorine exchange was observed when performed with the 3HF–NEt_3complex in the presence of zinc bromide (Scheme 2). In this way isopropylic ester **5a** was isolated in 62% overall yields from **4a**,[14] while the more sensitive ethyl ester **5b** was obtained in 35% yield.[15]



Scheme 2

In connection with our work concerning the synthesis and the use of fluorosulfides, we explored their potential as carbanion precursors by heterolytic cleavage of the carbon–sulfur bond. The cleavage of the carbon–sulfur bond is well known to produce free radicals.[16] In contrast, production of the corresponding carbanion by heterolytic cleavage of the carbon–sulfur or -selenium bond is less well studied. In general, the selective displacement of the sulfur atom can be realised with nucleophilic organometallic reagents if assisted by the presence of carbanion stabilizing group (aryl, alkylsulfanyl) or with reductive metals in the presence or absence of arene.[17] Other alternative methods consist of the nucleophilic attack upon the corresponding sulfoxide by organomagnesium reagents.[18]

† In memory of Arnaud who passed away in his 25th year.

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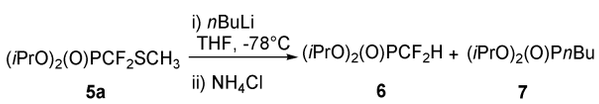
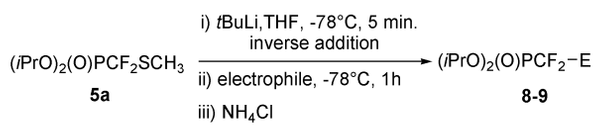
In a previous communication, we reported the free radical reactions from methylsulfanyldifluoromethylphosphonate ester **5a**.[9e] In this case the yields of addition products were lower than those observed from phosphonosulfides.[19] This difference was attributed to the poor radicophilicity of difluorosulfides, which reacted slowly with tin radical. This particular polarity of the sulfur atom prompted us to examine its behaviour in nucleophilic displacements using organometallic reagents. Using alkylmagnesium bromide (MeMgBr or *i*PrMgBr) no reaction occurred even at room temperature, and sulfide **5a** was recovered quantitatively. When using the *n*-butyllithium at −78 °C, diisopropyl phosphonate **6**[7b] was obtained by acidic hydrolysis of the crude mixture (Scheme 3). The cleavage of the carbon–sulfur bond was regioselective, only affecting the sulfur-difluoromethylene bond.[18c] The displacement was slow, and the complete consumption of the sulfide **5a** was observed when the reaction was performed over 40 min of stirring in the presence of slight excess of alkyllithium (1.3 eq.).



Scheme 3

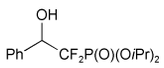
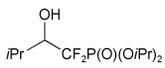
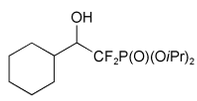
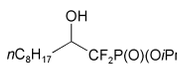
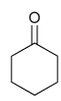
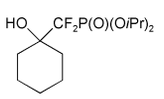
Nevertheless, the formation of difluorophosphonoester **6** was accompanied by a variable amount (20–30%) of butylphosphonate **7**,[20] formed by nucleophilic attack at the phosphorus centre by the *n*-butyllithium.[21] When the more sterically hindered nucleophile *tert*-butyllithium was used, this competitive nucleophilic substitution was avoided. With *tert*-butyllithium, the sulfur displacement was faster and spontaneous affording diisopropyl difluoromethylphosphonate **6** in 97% yield. As previously described, **6** was accompanied by the formation of less than 3% of *tetra*isopropyldifluoromethylenediphosphonate (δ_F −122.4 ppm (t, $^2J_{PF}$ 87.2)).[8a,22] Following this procedure the lithiophosphonate was also trapped with various representative electrophiles (Table 1–2, Scheme 4). Results were compared to those observed from **1** and **2**.



Scheme 4

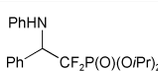
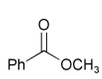
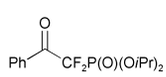
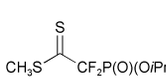
With chlorotrimethylsilane, silylated phosphonate **8a** was isolated in 69% yield and with carbonyl compounds, the corresponding alcohols **8b**–**8f** were obtained in 67–86% yields (Table 1). In all cases, no deprotonation of the methylsulfanyl group was observed.[23] The scope of the method was extended to a wide range of electrophiles (Table 2). The addition of the carbanion species was not limited to aldehydes or ketones and it reacted with esters and imines to afford β-amino and β-ketophosphonates in 70–73% yields. A range of building blocks **9c**–**9f** can be obtained in fair to good yields from the methylphosphonate **5a**. The sulfanyl exchange can be achieved, by using the diphenyldisulfide or diselenide as electrophiles. In this way useful free radical precursors **9d**–**9e** can be obtained in fair yields.[9] In addition, by reacting the anion directly with iodine, diisopropyl iododifluoromethylphosphonate **9f** was prepared in 70% yield. This was generally obtained directly from CF_2I_2 or the organomagnesium and organocadmium reagents.[8a,24] In the case of the preparation of **9d**–**9f**, excess of electrophile (3 equivalents) was required to observe a complete consumption of the lithiophosphonate. It is noteworthy that these yields were similar and competitive to those observed when experiments are run from the difluoromethyl- and bromodifluoromethylphosphonates **1** or **2**.[4,8]

Table 1 Addition reaction with representative electrophiles

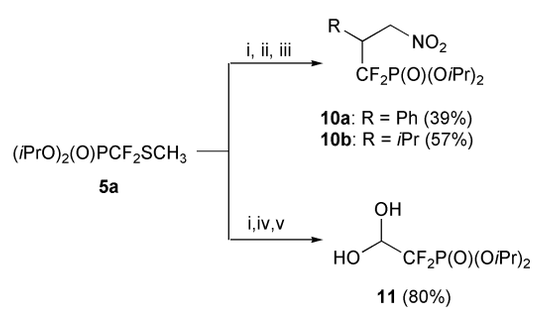
Electrophile[a]	Product		Yield[b]
$(CH_3)_3SiCl$	$(CH_3)_3Si–CF_2P(O)(OiPr)_2$	**8a**	69%
PhCHO		**8b**	67%
*i*PrCHO		**8c**	72%
$cC_6H_{11}CHO$		**8d**	76%
$nC_8H_{17}CHO$		**8e**	86%
		**8f**	69%

[a] Experimental runs at −78 °C in the presence of 1.3 eq. of electrophile. [b] Isolated yield.

Table 2 Syntheses of building blocks from **5a**

Electrophile	Product		Yield[a]
		**9a**	70%
		**9b**	73%
$CS_2–CH_3I$		**9c**	59%[b]
$(PhS)_2$	$PhS–CF_2P(O)(OiPr)_2$	**9d**	49%[c]
$(PhSe)_2$	$PhSe–CF_2P(O)(OiPr)_2$	**9e**	50%[c]
I_2	$I–CF_2P(O)(OiPr)_2$	**9f**	70%[c]

[a] Isolated yield. [b] 5 equivalents of CS_2 and CH_3I were used. [c] Experimental runs with 3 equivalents of electrophile.



Scheme 5 *Reagents and conditions:* (i) *t*BuLi inverse addition, THF, −78 °C, 5 min; (ii) $RCH{=}CHNO_2$ (3 eq.); (iii) NH_4Cl; (iv) DMF (1.2 eq.); (v) HCl 1 M.

Trapping the lithiophosphonate prepared from **5a** was also attempted with electrophiles that failed to react with the lithiated species issued from **1** (Scheme 5). First, the reaction was performed with nitroalkenes. From aryl- and alkylnitroalkenes, the conjugate addition was successful, affording secondary difluoromethylphosphonates **10a**–**b**. These were isolated in 39–57% when excess of Michael acceptor (3 eq.) was used. In addition, the anion generated from **5a** reacted with DMF. In this particular case, crystalline aldehyde hydrate **11**,[25] was isolated in 80% yield and identified by X-ray analysis (Scheme 5, Fig. 1).

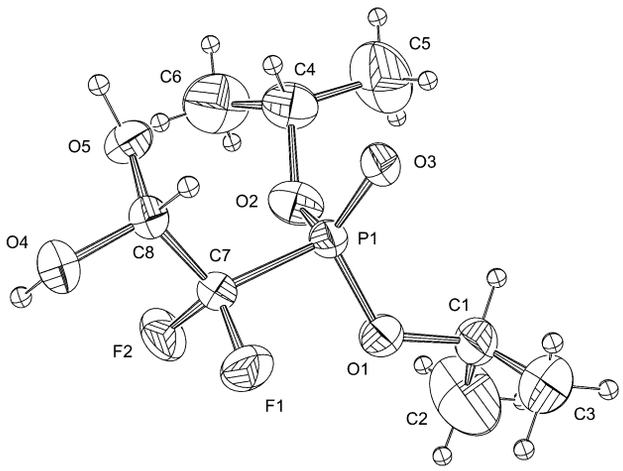


Fig. 1 ORTEP diagram of **11**.

The difluorophosphonato anion prepared from the sulfide **5a** is most surprising in view of the previously reported unsuccessful attempts to carry out additions to DMF and nitroalkenes.[26] This was probably due to the difference of the medium, which seems to be enough to modify the aggregates of the lithiated anion. This avoided the use of additive ($CeCl_3$) to mediate its conjugate addition onto nitroalkenes, and its addition with DMF.

In conclusion, we have reported the synthesis of methylsulfanyl difluoromethylphosphonate ester **5a** and showed that it has great potential as a new source of phosphonodifluoromethyl carbanion by heterolytic cleavage of the carbon–sulfur bond. This method, which avoids HCFCs and CFCs as starting materials, ensures sustainability for well-known and useful fluorophosphorylated building blocks for the next decade. In addition, the resulting lithiophosphonate prepared by this way reacted with a wide range of electrophiles without any need for transmetallation. The complete study of it reactivity towards alkyl halides, triflates and oxacycles are under investigation in our laboratory in order to prepare analogues of β-hydroxyphosphonates.

Experimental

Unless otherwise stated, ^{1}H NMR (250, 400 MHz), ^{13}C NMR (62.9, 100.6 MHz), ^{19}F NMR (235.2 MHz) and ^{31}P NMR (101.2 MHz) spectra were recorded on Bruker DPX or Avance spectrometers relative to $(CH_3)_4Si$, $CDCl_3$, $CFCl_3$ and 85% H_3PO_4, respectively. Chemical shifts are expressed in parts per million (ppm) and J values in Hz. Low resolution and high resolution mass spectra were recorded on Unicam ATI Automass and Nermag R101H spectrometers, and JEOL 500 spectrometers, respectively. IR spectra were recorded on Perkin-Elmer 16PC FT-IR spectrometers. Chemicals were purchased from Aldrich or Acros and were used without further purification.

Diisopropyl methylsulfanyldifluoromethylphosphonate (5a)

Sulfuryl chloride (7.76 mL, 95.4 mmol) was added slowly to a solution of diisopropyl methylsulfanylmethylphosphonate **4a** (9.8 g, 43.4 mmol) in CH_2Cl_2 (80 mL) stirred under nitrogen at 0 °C. After 2 hours of stirring, the solvent was evaporated in vacuum. 12.8 g of diisopropyl methylsulfanyldichloromethylphosphonate were obtained as a pale yellow oil and were used in the next step without any purification. δ_H (250 MHz; $CDCl_3$) 1.4 (12H, dd, $^3J_{HH}$ 6.2, $^4J_{HP}$ 2.6, *i*Pr), 2.6 (3H, d, $^4J_{HP}$ 1.5, CH_3S), 4.9 (2H, dsept, $^3J_{HP}$ and $^3J_{HH}$ 6.2, *i*Pr).

Diisopropylmethylsulfanyldichloromethyl phosphonate (12.8 g, 43.4 mmol) was added to a suspension of freshly dried zinc bromide (4.88 g, 21.7 mmol) in acetonitrile (80 mL) under nitrogen. After 5 minutes of stirring, neat 3HF–NEt_3 complex (25 mL, 152 mmol) were added dropwise. After 2 hours under reflux, the reaction mixture was cooled down to rt and poured into NH_4Cl and extracted with Et_2O–DCM (3 × 30 mL of a 2 : 1 mixture). The organic layers were washed with $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated. The residual oil was purified by distillation using a vigreux column (66–72 °C/10^{-1} mbar) leading to **5a** (7.2 g, 62% overall from **4a**) as a colorless oil. δ_H (250 MHz; $CDCl_3$) 1.4 (12H, dd, $^3J_{HH}$ 6.2, $^4J_{HP}$ 3.3, *i*Pr), 2.4 (3H, s, CH_3S), 4.8 (2H, dsept, $^3J_{HP}$ and $^3J_{HH}$ 6.3, *i*Pr); δ_C (100.6 MHz; $CDCl_3$) 9.7 (dt, $^3J_{CP}$ 2.2, $^3J_{CF}$ 5.4, CH_3S), 23.0 (d, $^3J_{CP}$ 5.3, *i*Pr), 23.6 (d, $^3J_{CP}$ 3.3, *i*Pr), 74.6 (d, $^2J_{CP}$ 6.9, *i*Pr), 124.8 (dt, $^1J_{CP}$ 223.4, $^1J_{CF}$ 296.7, CF_2); δ_P (101.2 MHz; $CDCl_3$) 1.02 (t, $^2J_{FP}$ 103.5); δ_F (235.2 MHz; $CDCl_3$) −89.84 (d, $^2J_{FP}$ 103.5); ν_{max}(film)/cm^{-1} 2984, 2938, 1274 (P=O), 1112 (C–O), 1012 (C–F); *m*/*z* (EI) 262 (M^+, 4%), 205 (21), 178 (71), 161 (15), 132 (100), 123 (27), 112 (22), 97 (40), 79 (32), 47 (19), 45 (18), 43 (38); Anal. Calcd for $C_8H_{17}F_2O_3PS$: C, 36.64; H, 6.53; Found: C, 36.43; H, 6.43%.

Typical procedure for the preparation of phosphonates (6–11)

Neat diisopropylmethylsulfanyldifluoromethyl phosphonate **5a** (300 mg, 1.15 mmol) was added dropwise to a cold solution (−78 °C) of *tert*-butyllithium (1.15 mL, 1.49 mmol, 1.3 M in pentane) in dry THF (10 mL). After 5 minutes of stirring at −78 °C, neat electrophile (1.3 or 3 eq.) was slowly added and the mixture was stirred for 1 h. Saturated aqueous solution of NH_4Cl (2 mL) was added and the reaction mixture was slowly warmed to 20 °C and extracted with Et_2O–DCM (2 : 1). The organic layer was washed with brine, dried over magnesium sulfate, filtered, concentrated in vacuum. Unless otherwise stated, the crude was purified by flash chromatography or bulb-to-bulb distillation.

Diisopropyl difluoromethylphosphonate (6)[7b]

By quenching the anion with NH_4Cl, 247 mg of **6** (97%) were obtained as a colorless oil. δ_H (250 MHz; $CDCl_3$) 1.38 (12 H, dd, $^3J_{HH}$ 6.4, $^4J_{HP}$ 3.1, *i*Pr), 4.85 (2H, dsept, $^3J_{HP}$ and $^3J_{HH}$ 6.4, *i*Pr), 5.78 (1H, dt, $^2J_{HP}$ 26.8, $^2J_{HF}$ 48.9, *H*CF_2); δ_C (100.6 MHz; $CDCl_3$) 22.8 (d, $^3J_{CP}$ 4.7, *i*Pr), 23.1 (d, $^3J_{CP}$ 5.7, *i*Pr), 72.7 (d, $^2J_{CP}$ 6.7, *i*Pr), 110.9 (dt, $^1J_{CP}$ 214.4, $^1J_{CF}$ 257.9, CF_2); δ_P (101.2 MHz; $CDCl_3$) 4.3 (t, $^2J_{FP}$ 90.7); δ_F (235.2 MHz; $CDCl_3$) −136.0 (dd, $^2J_{FP}$ 90.7, $^2J_{FH}$ 48.9); ν_{max}(film)/cm^{-1} 2984, 1262 (P=O), 1058 (C–O), 1002 cm^{-1} (C–F); *m*/*z* (EI) 216 (M^+, 13%), 202 (16), 55 (16), 51 (100), 42 (17).

Diisopropyl difluoro(trimethylsilyl)methylphosphonate (8a)

From 190 μL of trimethylsilyl chloride (1.49 mmol), 353 mg of crude oil were obtained. By bulb-to-bulb distillation (50 °C/10^{-1} mbar), 226 mg of **8a** (69%) were isolated as a colorless oil. δ_H (250 MHz; $CDCl_3$) 0.24 (9H, br s, $(CH_3)_3Si$), 1.34 (12H, dd, $^3J_{HH}$ 6.2, $^4J_{HP}$ 2.8, *i*Pr), 4.83 (2H, dsept, $^3J_{HP}$ and $^3J_{HH}$ 6.2, *i*Pr); δ_C (62.9 MHz; $CDCl_3$) −3.8 (s, $(CH_3)_3Si$), 23.7 (d, $^3J_{CP}$ 4.9, *i*Pr), 24.2 (d, $^3J_{CP}$ 3.4, *i*Pr), 72.8 (d, $^2J_{CP}$ 7.2, *i*Pr), 126.2 (dt, $^1J_{CP}$ 168.0, $^1J_{CF}$ 271.2, CF_2); δ_P (101.2 MHz; $CDCl_3$) 11.6 (t, $^2J_{FP}$ 94.1); δ_F (235.2 MHz; $CDCl_3$) −131.7 (d, $^2J_{FP}$ 94.1); ν_{max}(film)/cm^{-1} 3484, 2982, 2242, 1468, 1456, 1386, 1254 (P=O), 1106 (C–O), 1004 (C–F), 850, 762, 734; *m*/*z* (EI) 288.108 (M^+, $C_{10}H_{23}F_2O_3PSi$ requires 288.112), 231 (12%), 204 (33), 189 (24), 141 (100), 125 (83), 73 (41), 43 (29).

Diisopropyl 1,1-difluoro-2-hydroxy-2-phenylethylphosphonate (8b)

From 152 μL of benzaldehyde (1.49 mmol), 397 mg of crude oil were obtained. By flash chromatography using petroleum ether–ethyl acetate (7 : 3), 248 mg of **8b** (67%) were isolated as a white solid (mp 94–96 °C/hexane–acetone (8 : 2)). δ_H (400 MHz; $CDCl_3$) 1.31 (12H, dd, $^3J_{HH}$ 6.3, $^4J_{HP}$ 4.2, *i*Pr), 4.05 (1H, br s,

OH), 4.82 (2H, dsept, $^3J_{HP}$ and $^3J_{HH}$ 6.3, *i*Pr), 5.08 (1H, dd, $^3J_{HF}$ 20.2, $^3J_{HF}$ 5.1, CH(OH)), 7.35–7.50 (5H, m, Ph); δ_C (100.6 MHz; $CDCl_3$) 23.5 (d, $^3J_{CP}$ 5.2, *i*Pr), 23.7 (d, $^3J_{CP}$ 5.2, *i*Pr), 24.1 (d, $^3J_{CP}$ 4.0, *i*Pr), 24.2 (d, $^3J_{CP}$ 3.0, *i*Pr), 73.7 (ddd, $^2J_{CF}$ 25.6, $^2J_{CF}$ 21.2, $^2J_{CP}$ 14.9, CH(OH)), 74.4 (d, $^2J_{CP}$ 7.1, *i*Pr), 74.6 (d, $^2J_{CP}$ 7.4, *i*Pr), 117.3 (ddd, $^1J_{CF}$ 271.0, $^1J_{CF}$ 266.4, $^1J_{CP}$ 206.0, CF_2), 127.9, 128.2, 128.8 (s, Ph), 134.7 (t, $^3J_{CF}$ 6.2, Ph); δ_P (101.2 MHz; $CDCl_3$) 8.6 (dd, $^2J_{FP}$ 99.3, $^2J_{FP}$ 105.1); δ_F (235.2 MHz; $CDCl_3$) −115.4 (1F, ddd, $^3J_{HF}$ 5.1, $^2J_{FP}$ 99.3, $^2J_{FF}$ 302.6), −126.30 (1F, ddd, $^3J_{HF}$ 20.2, $^2J_{FP}$ 105.1, $^2J_{FF}$ 302.6); ν_{max}(KBr)/cm^{-1} 3330, 2990, 2936, 2360, 1456, 1386, 1250 (P=O), 1068 (C–O), 996 (C–F), 730, 574; *m*/*z* (EI) 322 (M^+, 4%), 221 (20), 174 (17), 132 (100), 110 (17), 107 (13), 77 (12); Anal. Calcd for $C_{14}H_{21}F_2O_4P$: C, 52.17; H, 6.57; Found: C, 52.41; H, 6.56%.

Diisopropyl 1,1-difluoro-2-hydroxy-3-methylbutylphosphonate (8c)

From 135 µL of isobutyraldehyde (1.49 mmol), 443 mg of crude oil were obtained. By bulb-to-bulb distillation (65 °C/5.10^{-2} mmHg), 237 mg of **8c** (72%) were isolated as a colorless oil δ_H (400 MHz; $CDCl_3$) 1.07 (3H, d, $^3J_{HH}$ 6.4, CH_3), 1.10 (3H, d, $^3J_{HH}$ 6.4, CH_3), 1.37 (12H, dd, $^3J_{HH}$ 6.1, $^4J_{HP}$ 2.6, *i*Pr), 2.12 (1H, dsept, $^3J_{HH}$ and $^3J_{HH}$ 6.4, CH), 3.30 (1H, br s, OH), 3.76 (1H, dddd, $^3J_{HF}$ 22.4, $^3J_{HF}$ 4.4, $^3J_{HP}$ and $^3J_{HH}$ 6.4, CH_a(OH)), 4.85 (2H, dsept, $^3J_{HP}$ and $^3J_{HH}$ 6.4, *i*Pr); δ_C (100.6 MHz; $CDCl_3$) 17.04 (s, CH_3), 18.2 (s, CH_3), 23.6 (d, $^3J_{CP}$ 5.3, *i*Pr), 23.7 (d, $^3J_{CP}$ 5.1, *i*Pr), 24.1 (d, $^3J_{CP}$ 3.3, *i*Pr), 24.2 (d, $^3J_{CP}$ 3.1, *i*Pr), 28.2 (d, $^3J_{CP}$ 5.2, CH), 74.0 (d, $^2J_{CP}$ 7.3, *i*Pr), 74.1 (d, $^2J_{CP}$ 7.1, *i*Pr), 75.5 (ddd, $^2J_{CF}$ 34.3, $^2J_{CF}$ 20.9, $^2J_{CP}$ 13.1, CH_a(OH)), 119.5 (dt, $^1J_{CP}$ 205.5, $^1J_{CF}$ 270.0, CF_2); δ_P (101.2 MHz; $CDCl_3$) 6.8 (dd, $^2J_{FP}$ 108.3, $^2J_{FP}$ 103.6); δ_F (235.2 MHz; $CDCl_3$) −115.7 (1F, ddd, $^3J_{HF}$ 4.4, $^2J_{FP}$ 103.6, $^2J_{FF}$ 306.0), −127.2 (1F, ddd, $^3J_{HF}$ 22.4, $^2J_{FP}$ 108.3, $^2J_{FF}$ 306.0); ν_{max}(film)/cm^{-1} 3744, 3372, 2984, 2360, 1652, 1466, 1254 (P=O), 1184, 1002 (C–F); *m*/*z* (EI) 288 (M^+, 7%), 205 (18), 161 (72), 132 (100), 110 (16); Anal. Calcd for $C_{11}H_{23}F_2O_4P$: C, 45.83; H, 8.04; Found: C, 46.03; H, 8.02%.

Diisopropyl 2-cyclohexyl-1,1-difluoro-2-hydroxyethylphosphonate (8d)

From 180 µL of cyclohexanecarboxaldehyde (1.49 mmol), 545 mg of crude oil were obtained. By bulb-to-bulb distillation (130 °C/7.10^{-2} mbar), 288 mg of **8d** (76%) were isolated as a colorless oil δ_H (250 MHz; $CDCl_3$) 1.20–1.35 (5H, m, CH+CH_2), 1.36–1.40 (12 H, m, *i*Pr), 1.65–1.85 (6H, m, CH_2), 2.91 (1H, br s, OH), 3.75 (1H, dddd, $^3J_{HF}$ 22.2, $^3J_{HF}$ 4.9, $^3J_{HP}$ and $^3J_{HH}$ 6.0, CH(OH)), 4.85 (2H, dsept, $^3J_{HH}$ and $^3J_{HP}$ 6.3, *i*Pr); δ_C (62.9 MHz; $CDCl_3$) 23.6 (d, $^3J_{CP}$ 5.3, *i*Pr), 23.7 (d, $^3J_{CP}$ 5.3, *i*Pr), 24.1 (d, $^3J_{CP}$ 3.1, *i*Pr), 24.2 (d, $^3J_{CP}$ 2.8, *i*Pr), 25.9, 26.1, 26.3, 27.1, 30.0, 37.9 (s, chx), 73.9 (d, $^2J_{CP}$ 7.3, *i*Pr), 74.00 (d, $^2J_{CP}$ 7.1, *i*Pr), 74.8 (ddd, $^2J_{CF}$ 24.0, $^2J_{CF}$ 21.4, $^2J_{CP}$ 13.4, CH(OH)), 119.8 (ddd, $^1J_{CF}$ 270.3, $^1J_{CF}$ 266.8, $^1J_{CP}$ 207.7, CF_2P); δ_P (101.2 MHz; $CDCl_3$) 6.8 (dd, $^2J_{FP}$ 107.2, $^2J_{FP}$ 101.4); δ_F (235.2 MHz; $CDCl_3$) −115.3 (1F, ddd, $^3J_{HF}$ 4.9, $^2J_{FP}$ 101.8, $^2J_{FF}$ 304.4), −123.9 (1F, ddd, $^3J_{HF}$ 22.2, $^2J_{FP}$ 107.3, $^2J_{FF}$ 304.4); ν_{max}(film)/cm^{-1} 3362, 2982, 2926, 2854, 1452, 1386, 1254 (P=O), 1000 (C–F); *m*/*z* (CI, CH_4) 329.167 (MH^+, $C_{14}H_{28}F_2O_4P$ requires 329.169), 245 (32%), 161 (84), 132 (100).

Diisopropyl 1,1-difluoro-2-hydroxydecylphosphonate (8e)

From 270 µL of nonaldehyde (1.49 mmol), 637 mg of crude oil were obtained. By bulb-to-bulb distillation (140 °C/9.10^{-2} mbar), 354 mg of **8e** (86%) were isolated as a colorless oil δ_H (250 MHz; $CDCl_3$) 0.87 (3H, t, $^3J_{HH}$ 7.0, CH_3), 1.23 (10H, m, CH_2), 1.37 (12H, dd, $^3J_{HH}$ 6.2, $^4J_{HP}$ 2.8, *i*Pr), 1.60–1.95 (4H, m, CH_2), 3.03 (1H, br s, OH), 3.66–3.88 (1H, m, CH(OH)), 4.85 (2H, dsept, $^3J_{HH}$ and $^3J_{HP}$ 6.2, *i*Pr); δ_C (100.6 MHz; $CDCl_3$) 14.1 (s, CH_3), 22.7 (s, CH_2), 23.7 (d, $^3J_{CP}$ 5.1, *i*Pr), 23.8 (d, $^3J_{CP}$ 5.0, *i*Pr), 24.2, 24.3, 25.4, 28.8, 29.3, 29.4, 31.9 (s, CH_2), 71.8 (ddd, $^2J_{CF}$ 33.6, $^2J_{CF}$ 24.7, $^2J_{CP}$ 13.9, CH(OH)), 74.1 (d, $^2J_{CP}$ 7.2, *i*Pr), 74.2 (d, $^2J_{CP}$ 7.1, *i*Pr), 118.6 (dt, $^1J_{CP}$ 207.0, $^1J_{CF}$ 268.5, CF_2P); δ_P (101.2 MHz; $CDCl_3$) 6.7 (dd, $^2J_{FP}$ 101.2, $^2J_{FP}$ 105.9); δ_F (235.2 MHz; $CDCl_3$) −118.4 (1F, ddd, $^3J_{HF}$ 7.1, $^2J_{FP}$ 101.2, $^2J_{FF}$ 301.3), −126.7 (1F, ddd, $^3J_{HF}$ 18.8, $^2J_{FP}$ 105.9, $^2J_{FF}$ 303.6); ν_{max}(film)/cm^{-1} 3852, 3744, 2928, 2858, 2360, 1696, 1508, 1458, 1256 (P=O), 1000 (C–F); *m*/*z* (CI, CH_4) 359.207 (MH^+, $C_{16}H_{34}F_2O_4P$ requires 359.2163), 161 (28%), 132 (100), 110 (24), 41 (16).

Diisopropyl difluoro(1-hydroxycyclohexyl)methylphosphonate (8f)

From 112 µL of cyclohexanone (1.49 mmol), 423 mg of crude oil were obtained. By flash chromatography using petroleum ether–ethyl acetate (8 : 2), 249 mg of **8f** (69%) were isolated as a white solid (mp 60–61 °C/hexane–acetone (8 : 2)) δ_H (250 MHz; $CDCl_3$) 1.36 (12H, dd, $^4J_{HP}$ 2.3, $^3J_{HH}$ 6.2, *i*Pr), 1.46–1.87 (10H, m, CH_2), 3.17 (1H, br s, OH), 4.84 (2H, dsept, $^3J_{HP}$ and $^3J_{HH}$ 6.2, *i*Pr); δ_C (100.6 MHz; $CDCl_3$) 20.5 (s, CH_2), 23.7 (d, $^3J_{CP}$ 5.1, *i*Pr), 24.1 (d, $^3J_{CP}$ 3.3, *i*Pr), 25.4 (s, $CH_2(CH_2C(OH))$), 29.9 (td, $^3J_{CF}$ and $^3J_{CP}$ 2.8, $CH_2(C(OH))$), 73.9 (dt, $^2J_{CP}$ 13.7, $^2J_{CF}$ 21.1, C(OH)), 74.2 (d, $^2J_{CP}$ 7.5, *i*Pr), 119.7 (dt, $^1J_{CP}$ 201.5, $^1J_{CF}$ 270.7, CF_2); δ_P (101.2 MHz; $CDCl_3$) 7.2 (t, $^2J_{FP}$ 105.9); δ_F (235.2 MHz; $CDCl_3$) −122.5 (d, $^2J_{FP}$ 105.9); ν_{max}(KBr)/cm^{-1} 3394, 2986, 2942, 1448, 1388, 1376, 1252 (P=O), 1128, 1046, 1014 (C–F); *m*/*z* (EI) 314 (M^+, 1%), 210 (20), 174 (20), 132 (100), 110 (22), 81 (18); Anal. Calcd for $C_{13}H_{25}F_2O_4P$: C, 49.68; H, 8.02; Found: C, 49.64; H, 8.05%.

Diisopropyl 1,1-difluoro-2-phenyl-2-phenylaminoethylphosphonate (9a)

From 270 mg of *N*-phenylbenzylimine (1.49 mmol), 570 mg of crude oil were obtained. By flash chromatography using petroleum ether–ethyl acetate (8 : 2), 319 mg of **9a** (70%) were isolated as a white solid (mp 123–125 °C/hexane–acetone (7 : 3)) δ_H (250 MHz; $CDCl_3$) 1.24 (3H, d, $^3J_{HH}$ 6.1, *i*Pr), 1.29 (3H, d, $^3J_{HH}$ 6.2, *i*Pr), 1.30 (3H, d, $^3J_{HH}$ 6.2, *i*Pr), 1.35 (3H, d, $^3J_{HH}$ 6.2, *i*Pr), 4.80 (2H, dsept, $^3J_{HP}$ and $^3J_{HH}$ 6.2, *i*Pr), 4.95 (1H, dddd, $^3J_{HF}$ 20.6, $^3J_{HF}$ and $^3J_{HP}$ and $^3J_{HH}$ 7.6, CH(NH)), 5.10 (1H, d, $^3J_{HH}$ 7.6, NH), 7.07–7.14 (2H, m, Ph), 6.58–6.73 (3H, m, Ph), 7.31–7.51 (5H, m, Ph); δ_C (100.6 MHz; $CDCl_3$) 23.5 (d, $^3J_{CP}$ 5.7, *i*Pr), 23.6 (d, $^3J_{CP}$ 5.5, *i*Pr), 24.1 (d, $^3J_{CP}$ 4.2, *i*Pr), 24.2 (d, $^3J_{CP}$ 5.9, *i*Pr), 60.9 (ddd, $^2J_{CF}$ 25.3, $^2J_{CF}$ 21.2, $^2J_{CP}$14.4), 74.1 (d, $^2J_{CP}$ 7.2, *i*Pr), 74.2 (d, $^2J_{CP}$ 7.3, *i*Pr), 118.0 (td, $^1J_{CF}$ 267.4, $^1J_{CP}$ 211.1, CF_2), 113.7, 118.3, 128.4, 128.6, 128.8, 129.2, 134.6, 145.9 (s, Ph); δ_P (101.2 MHz; $CDCl_3$) 6.2 (dd, $^2J_{FP}$ 101.2, $^2J_{FP}$ 105.9); δ_F (235.2 MHz; $CDCl_3$) −111.1 (1F, ddd, $^3J_{HF}$ 7.6, $^2J_{FP}$ 101.2, $^2J_{FF}$ 303.6), −121.85 (1F, ddd, $^3J_{HF}$ 20.6, $^2J_{FP}$ 105.9, $^2J_{FF}$ 303.6); ν_{max}(KBr)/cm^{-1} 3318, 2984, 1604, 1500, 1252 (P=O), 1180, 1050, 1010 (C–F), 698; *m*/*z* (EI) 397 (M^+, 17%), 182 (100), 104 (9), 77 (9); Anal. Calcd for $C_{20}H_{26}F_2NO_3P$: C, 60.45; H, 6.59. Found: C, 60.47; H, 6.68%.

Diisopropyl 1,1-difluoro-2-oxo-2-phenylethylphosphonate (9b)

From 190 µL of methyl benzoate ester (1.49 mmol), 468 mg of crude oil were obtained. By flash chromatography using petroleum ether–ethyl acetate (8 : 2), 268 mg of **9b** (73%) were isolated as a colorless oil δ_H (250 MHz; $CDCl_3$) 1.33 (6H, d, $^3J_{HH}$ 6.2, *i*Pr), 1.37 (6H, d, $^3J_{HH}$ 6.2, *i*Pr), 4.89 (2H, dsept, $^3J_{HP}$ and $^3J_{HH}$ 6.2, *i*Pr), 7.45–7.50 (2H, m, Ph), 7.58–7.65 (1H, m, Ph), 8.12–8.16 (2H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) 23.9 (d, $^3J_{CP}$ 5.3, *i*Pr), 24.5 (d, $^3J_{CP}$ 3.3, *i*Pr), 75.2 (d, $^2J_{CP}$ 7.0, *i*Pr), 115.2 (dt, $^1J_{CP}$ 200.9, $^1J_{CF}$ 273.9, CF_2), 128.9, 130.8 (t, $^3J_{CF}$ 3.1, Ph), 132.6, 134.9, 188.4 (dt, $^2J_{CF}$ 24.3, $^2J_{CP}$ 14.8, C(=O)); δ_P (101.2 MHz; $CDCl_3$) 1.0 (t, $^2J_{FP}$ 96.5); δ_F (235.2 MHz; $CDCl_3$) −110.2 (d, $^2J_{FP}$ 96.5); ν_{max}(film)/cm^{-1} 3748, 2986, 2360, 1700 (C=O), 1290

(P=O), 1010 (C–F); *m/z* (CI, CH_4) 321.112 (MH^+,$C_{14}H_{20}F_2O_4P$ requires 321.107), 219 (19%), 105 (100), 77 (21).

Methyl(diisopropoxyphosphonyl)difluoroethane dithioate (9c)

To the lithiated anion 345 μL of carbon disulfide (5.70 mmol) were added, and 30 minutes later 355 μL of methylene iodide (5.70 mmol). By usual work-up 428 mg of crude oil were obtained. By flash chromatography using petroleum ether–ethyl acetate (6 : 4), 207 mg of **9c** (59%) were isolated as a red oil δ_H (250 MHz; $CDCl_3$) 1.36 (12H, dd, $^3J_{HH}$ 6.3, $^4J_{HP}$ 3.2, *i*Pr), 2.66 (3H, s, SCH_3), 4.85 (2H, dsept, $^3J_{HP}$ and $^3J_{HH}$ 6.3, *i*Pr); δ_C (62.9 MHz; $CDCl_3$) 19.5 (s, SCH_3), 23.5 (d, $^3J_{CP}$ 5.3, *i*Pr), 24.1 (d, $^3J_{CP}$ 2.5, *i*Pr), 75.0 (d, $^2J_{CP}$ 7.1, *i*Pr), 117.0 (dt, $^1J_{CP}$ 212.2, $^1J_{CF}$ 270.8, CF_2), 220.0 (dt, $^3J_{CP}$ 17.3, $^3J_{CF}$ 22.1, C(=S)); δ_P (101.2 MHz; $CDCl_3$) 3.6 (t, $^2J_{FP}$ 104.5); δ_F (235.2 MHz; $CDCl_3$) −99.3 (d, $^2J_{FP}$ 104.5); ν_{max}(film)/cm^{-1}2982, 2936, 1466, 1454, 1386, 1276 (P=O), 1182, 1142, 1102, 1052, 998 (C–F) cm^{-1}; *m/z* (EI) 306.035 (M^+, $C_9H_{17}F_2O_3PS_2$ requires: 306.032), 286 (22%), 224 (23), 205 (76), 202 (34), 142 (27), 123 (16), 91 (100), 41 (25).

Diisopropyl 1,1-difluoro-2-phenylsulfanylmethylphosphonate (9d)

From 747 mg of diphenyl disulfide (3.44 mmol), 887 mg of crude oil were obtained. By flash chromatography using petroleum ether–ethyl acetate (8 : 2), 182 mg of **9d** (49%) were isolated as a colorless oil. δ_H (250 MHz; $CDCl_3$) 1.32 (12H, dd, $^3J_{HH}$ 6.2, $^4J_{HP}$ 3.7, *i*Pr), 4.82 (2H, dsept, $^3J_{HP}$ 6.4, $^3J_{HH}$ 6.2, *i*Pr), 7.28–7.38 (3H, m, Ph), 7.55–7.58 (2H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) 23.6 (d, $^3J_{CP}$ 5.0, *i*Pr), 24.2 (d, $^3J_{CP}$ 3.0, *i*Pr), 73.7 (d, $^2J_{CP}$ 7.0, *i*Pr), 124.6 (dt, $^1J_{CP}$ 218.4, $^1J_{CF}$ 299.2, CF_2P), 129.1, 130.2, 136.9 (s, Ph); δ_P (101.2 MHz; $CDCl_3$) 3.1 (t, $^2J_{FP}$ 99.8); δ_F (235.2 MHz; $CDCl_3$) −84.2 (d, $^2J_{FP}$ 99.8); ν_{max}(film)/cm^{-1}2984, 2338, 1472, 1388, 1274 (P=O), 1116, 1000 (C–F), 750; *m/z* (EI) 324.078 (M^+, $C_{13}H_{19}F_2O_3PS$ requires 324.076), 282 (30%), 240 (100), 159 (38), 110 (28), 94 (26), 65 (20), 41 (17).

Diisopropyl 1,1-difluoro-2-phenylselenalylmethylphosphonate (9e)

From 1.071 g of diphenyl diselenide (3.44 mmol), 1.270 g of crude oil were obtained. By flash chromatography using petroleum ether–ethyl acetate (8 : 2), 210 mg of **9e** (50%) were isolated as a colorless oil. δ_H (250 MHz; $CDCl_3$) 1.29 (12H, dd, $^3J_{HH}$ 6.3, $^4J_{HP}$ 1.3, *i*Pr), 4.80 (2H, dsept, $^3J_{HP}$ and $^3J_{HH}$ 6.3, *i*Pr), 7.20–7.40 (3H, m, Ph), 7.60–7.70 (2H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) 23.7 (d, $^3J_{CP}$ 5.0, *i*Pr), 24.2 (d, $^3J_{CP}$ 3.1, *i*Pr), 74.6 (d, $^2J_{CP}$ 6.9, *i*Pr), 124.6 (dt, $^1J_{CP}$ 211.7, $^1J_{CF}$ 311.7, CF_2), 129.1, 129.8, 137.7 (s, Ph); δ_P (101.2 MHz; $CDCl_3$) 3.4 (t, $^2J_{FP}$ 94.5); δ_F (235.2 MHz; $CDCl_3$) −85.3 (d, $^2J_{FP}$ 94.5); ν_{max}(film)/cm^{-1}2984, 2938, 1468, 1378, 1272 (P=O), 1040 (C–F); *m/z* (EI) 372.017 (M^+, $C_{13}H_{19}F_2O_3PSe$ requires 372.021), 330 (16%), 288 (100), 158 (19), 127 (15), 94 (19), 77 (15).

Diisopropyl 1,1-difluoro-1-iodomethylphosphonate (9f)

From a THF solution (1 mL) containing 873 mg of sublimed iodine (3.44 mmol), 370 mg of crude oil were obtained. The crude was diluted in dichloromethylene (25 mL) and washed with a saturated solution of NH_4Cl, an aqueous solution of $Na_2S_2O_4$ (1 M), and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuum. By bulb-to-bulb distillation (50 °C/8.10^{-2} mbar), 276 mg of **9f** (70%) were isolated as a yellow oil. δ_H (250 MHz; $CDCl_3$) 1.4 (12H, dd, $^3J_{HH}$ 6.2, $^4J_{HP}$ 3.0, *i*Pr), 4.9 (2H, dsept, $^3J_{HP}$ and $^3J_{HH}$ 6.2, *i*Pr); δ_C (100.6 MHz; $CDCl_3$) 22.6 (d, $^3J_{CP}$ 5.5, *i*Pr), 23.1 (d, $^3J_{CP}$ 3.2, *i*Pr), 74.7 (d, $^2J_{CP}$ 7.1, *i*Pr), 97.2 (dt, $^1J_{CP}$ 220.5, $^1J_{CF}$ 332.8, CF_2); δ_P (101.2 MHz; $CDCl_3$) −3.2 (t, $^2J_{FP}$ 86.4); δ_F (235.2 MHz; $CDCl_3$) −59.8 (d, $^2J_{FP}$ 86.4); ν_{max}(film)/cm^{-1}2984, 2938, 1468, 1388, 1276 (P=O), 1120, 1100, 1066, 1002 (C–F); *m/z* (EI) 301 (15%), 299 (19), 285 (100), 259 (44), 173 (86), 133 (51), 127 (16), 123 (16), 107 (35), 91 (21), 89 (25), 69 (38), 65 (70), 47 (17), 43 (51), 41 (47); *m/z* (CI, CH_4) 342.979 (MH^+, $C_7H_{15}F_2O_3PI$ requires 342.977).

Diisopropyl 1,1-difluoro-2-phenyl-3-nitropropylphosphonate (10a)

From 521 mg of β-nitrostyrene (3.44 mmol), 755 mg of crude oil were obtained. By flash chromatography using petroleum ether–ethyl acetate (7 : 3), 167 mg of **10a** (39%) were isolated as a colorless oil δ_H (400 MHz; $CDCl_3$) 1.28 (12H, d, $^3J_{HH}$ 6.3, *i*Pr), 4.35 (1H, m, CH), 4.68 (1H, dsept, $^3J_{HP}$ and $^3J_{HP}$6.4, *i*Pr), 4.80 (1H, dsept, $^3J_{HP}$ and $^3J_{HH}$ 6.3, *i*Pr), 4.88 (1H, dd, $^3J_{HH}$ 10.2, $^3J_{HH}$ 13.7, CH_2), 5.21 (1H, dd, $^2J_{HH}$ 13.7, $^3J_{HH}$ 4.7, CH_2), 7.35 (5H, m, Ph); δ_C (100.6 MHz; $CDCl_3$) 23.4 (d, $^3J_{CP}$ 5.1, *i*Pr), 23.5 (d, $^3J_{CP}$ 5.3, *i*Pr), 23.9 (d, $^3J_{CP}$ 3.5, *i*Pr), 24.0 (d, $^3J_{CP}$ 3.2, *i*Pr), 48.2 (dt, $^2J_{CP}$ 16.3, $^2J_{CF}$ 20.3, C-2), 74.1 (d, $^2J_{CP}$ 7.3, *i*Pr), 74.3 (dt, $^3J_{CP}$ and $^3J_{CF}$ 5.2, C-1), 74.4 (d, $^2J_{CP}$ 6.9, *i*Pr), 118.5 (dt, $^1J_{CP}$ 215, $^1J_{CF}$ 266.2, CF_2), 128.7, 128.9, 129.7 (s, Ph), 131.3 (br s, Ph); δ_P (101.2 MHz; $CDCl_3$) 2.5 (dd, $^2J_{PF}$ 105.9, $^2J_{PF}$ 101.2); δ_F (235.2 MHz; $CDCl_3$) −112.2 (1F, ddd, $^3J_{FH}$ 14.1, $^2J_{FP}$ 105.9, $^2J_{FF}$ 303.6), −114.6 (1F, ddd, $^3J_{FH}$ 18.8, $^2J_{FP}$ 101.2, $^2J_{FF}$ 303.6); ν_{max}(film)/cm^{-1}2984, 2938, 1560, 1378, 1268 (P=O), 1162, 1102; *m/z* (EI) 365 (M^+, 1%), 264 (29), 235 (100), 214 (66), 153 (29), 131 (31), 103 (31); Anal. Calcd for $C_{15}H_{22}F_2NO_5P$: C, 49.32; H, 6.07. Found: C, 50.18; H, 6.22%.

Diisopropyl 1,1-difluoro-3-nitro-2-isopropylpropylphosphonate (10b)

From 417 mg of (*E*)-3-methylnitrobutene (3.44 mmol), 674 mg of crude oil were obtained. By flash chromatography using petroleum ether–ethyl acetate (8 : 2), 217 mg of **10b** (57%) were isolated as a colorless oil δ_H (400 MHz; $CDCl_3$) 0.96 (3H, d, $^3J_{HH}$ 7, CH_3), 1.04 (3H, d, $^3J_{HH}$ 7, CH_3), 1.38 (12H, dd, $^3J_{HH}$ 6.2, $^4J_{HP}$ 3.5, *i*Pr), 2.43–2.52 (1H, m, CH), 3.10–3.25 (1H, m, CH), 4.36 (1H, dd, $^2J_{HH}$14.7, $^3J_{HH}$ 5.2, $CH_b(NO_2)$), 4.77–4.89 (3H, m, $CH_a(NO_2)$, *i*Pr); δ_C (100.6 MHz; $CDCl_3$) 17.6 (s, CH_3), 21.2 (s,CH_3), 23.6 (d, $^3J_{CP}$ 4.6, *i*Pr), 23.9 (d, $^3J_{CP}$ 3.5,*i*Pr), 24.0 (d, $^3J_{CP}$ 3.7, *i*Pr), 25.7 (dt, $^3J_{CP}$ and $^3J_{CF}$ 2.8, CH), 46.3 (dt, $^2J_{CP}$ 15.7, $^2J_{CF}$ 18.0, CH), 70.1 (dt, $^3J_{CF}$ and $^3J_{CP}$ 5.2, $CH_2(NO_2)$), 74.2 (d, $^2J_{CP}$ 7.2, *i*Pr), 74.3 (d, $^2J_{CP}$ 7.3, *i*Pr), 120.7 (dt, $^1J_{CP}$ 214.3, $^1J_{CF}$ 267.8, CF_2); δ_P (101.2 MHz; $CDCl_3$) 5.1 (t, $^2J_{PF}$ 114.0); δ_F (235.2 MHz; $CDCl_3$) −109.4 (1F, ddd, $^3J_{FH}$ 20.3, $^2J_{FP}$ 114.0, $^2J_{FF}$ 329.4), −116.4 (1F, ddd, $^3J_{FH}$ 20.3, $^2J_{FP}$ 114.0, $^2J_{FF}$ 329.4); ν_{max}(film)/cm^{-1}2982, 2940, 1562, 1468, 1382, 1270 (P=O), 1180, 1102 (C–O), 998 (C–F); *m/z* (EI) 332 (MH^+, 5%), 331 (M^+, 1), 248 (27), 230 (100), 201 (30), 159 (44), 119 (63), 99 (55), 77 (34); Anal. Calcd for $C_{12}H_{24}F_2O_5PN$: C, 43.50; H, 7.30; Found: C, 43.53; H, 7.39%.

Diisopropyl 1,1-difluoro-2,2-dihydroxyethylphosphonate (11)

To a solution of lithiophosphonate 116 μL of dimethyl formamide (1.49 mmol) was added. After 1 h of stirring at −78 °C, the mixture was acidified by addition of 3 mL of HCl (1 M) and warmed-up to 0 °C. After extraction with dichloromethylene 300 mg of crude oil were obtained. By flash chromatography using petroleum ether–ethyl acetate (3 : 7), 240 mg of **11** (80%) were isolated as a white solid. Crystallization in pentane–acetone (8 : 2) afforded suitable sample for X-ray analysis (mp 78–80 °C). δ_H (250 MHz; $CDCl_3$) 1.38 (6H, d, $^3J_{HH}$ 5.9, *i*Pr), 1.41 (6H, d, $^3J_{HH}$ 5.9, *i*Pr), 4.91 (2H, dsept, $^3J_{HP}$ and $^3J_{HH}$ 6.1, *i*Pr), 4.5–5.5 (2H, m, OH), 5.15 (1H, dt, $^3J_{PH}$ 11.6, $^3J_{FH}$ 6.7, $CH(OH)_2$); δ_C (100.6 MHz; $CDCl_3$) 23.5 (d, $^3J_{CP}$ 5.6, *i*Pr), 24.2 (d, $^3J_{CP}$ 2.9, *i*Pr), 74.7 (d, $^3J_{CP}$ 7.1, CH*i*Pr), 89.7 (dt, $^2J_{CP}$ 15.2, $^2J_{CF}$ 28.3, $CH(OH)_2$), 115.7 (dt,$^1J_{CP}$ 202.3, $^1J_{CF}$ 268.2, CF_2); δ_P (101.2 MHz; $CDCl_3$) 4.6 (t, $^2J_{PF}$ 97.8); δ_F (235.2 MHz; $CDCl_3$) −122.5 (dd, $^2J_{PF}$ 97.8, $^3J_{HF}$ 6.70); ν_{max}($CHCl_3$)/cm^{-1}3600–3200 (νOH), 2950, 1470, 1390, 1220 (P=O), 1180, 1100, 1000 (C–F); Anal. Calcd for $C_8H_{17}F_2O_5P$: C, 36.65; H, 6.54. Found: C, 36.69; H, 6.54%.

X-Ray analysis ‡ $C_8H_{17}F_2O_5P$, M_r 262.19, monoclinic, $P21/a$, a 6.751(2), b 24.363(9), c 8.091(1) Å, β 101.75(2)°, V 1302.9(6) Å^{-3}, Z 4, D_x 1.337 Mg m^{-3}, λ(Mo-Kα) 0.71073 Å, μ 2.39 cm^{-1}, F(000) 552, T 293 K. The sample (0.52 × 0.42 × 0.37 mm) is studied on an automatic diffractometer CAD4 NONIUS with graphite monochromatized MoKα radiation (Fair, 1990). The cell parameters are obtained by fitting a set of 25 high-theta reflections. The data collection ($2\theta_{max}$ 54°, scan $\omega/2\theta$ 1, t_{max} 60 s, range HKL: H 0,8 K 0,31 L −10,10) gives 2837 unique reflections from which 2167 with $I > 2.0\sigma(I)$. After Lorenz and polarization corrections (Spek, 1997) the structure was solved with SIR-97 (Altomare & al., 1998) which reveals the non hydrogen atoms of the compound. After anisotropic refinement a Fourier Difference reveals many hydrogen atoms. The whole structure was refined with SHELXL97 (Sheldrick, 1997) by the full-matrix least-square techniques (use of F square magnitude; x, y, z, β_{ij} for P, O, F and C atoms, x, y, z in riding mode for H atoms; 146 variables and 2837 observations; calc $w = 1/[\sigma^2(Fo^2) + (0.076P)^2 + 0.33P]$ where $P = (Fo^2 + 2Fc^2)/3$ with the resulting R 0.044, R_w 0.124 and S_w = 1.054 (residual $\Delta\rho \leq 0.28$ eÅ^{-3}).

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‡ CCDC reference numbers CCDC 203879. See http://www.rsc.org/suppdata/ob/b3/b301729j/ for crystallographic data in .cif or other electronic format.

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