An Efficient and Highly Selective Synthesis of (*Z*)-Fluoroenol Phosphates from Hydroxy Difluorophosphonates

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Abstract: Substituted 2-aryl-2-hydroxy-1,1-difluorophosphonates undergo a reaction with potassium *tert*-butoxide to provide selectively (*Z*)-2-fluoro-1-arylvinyl phosphates in high yields.

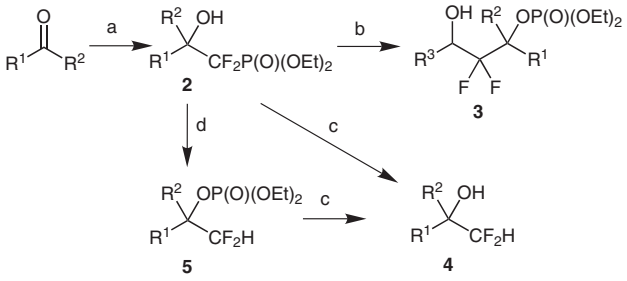
Key words: phosphonates, phosphates, rearrangements, eliminations, enols

Enol phosphates represent an important class of compounds. In living organisms, phosphoenolpyruvate (PEP) plays a vital role in a number of biological processes. Some enol phosphates have also been reported to exhibit interesting biological activity.[1,2] In organic synthesis, enol phosphates are versatile substrates that can be converted into many functional groups and undergo a variety of metal-catalyzed cross-coupling reactions.[3] Typically, such compounds are prepared by the reaction of metal enolates with $ClP(O)(OR)_2$,[4] or by the Perkow reaction[1,5] of α-halogenated carbonyl compounds with $P(OR)_3$, or by other methods.[6] The Perkow reaction often suffers from a competing Arbuzov reaction, yielding acyl phosphonates instead of the desired enol phosphates.

The presence of fluorine substituents often leads to dramatic changes in the physicochemical properties and improved biological activity.[7] Some fluorinated enol phosphates have been reported. Fluorinated ketones have been used for their preparation through reactions with trialkylphosphites (Perkow reaction),[8] which led to fluoro-PEP and its derivatives,[9] and with dialkylphosphites.[10] Reactions of perfluoroalkanoic acid chlorides with trialkylphosphites resulted in double addition to give fluorinated phosphono enol phosphates.[11] Recently, Demir and co-workers have used trifluoromethyltrimethylsilane ($TMSCF_3$) in the reaction with benzoyl phosphonates to form the alcoholate which underwent phosphonate–phosphate rearrangement to form the acyl anion, followed by fluoride elimination to give 1-aryldifluoroethenyl phosphates.[12]

New approaches to the synthesis of fluorinated enol phosphates are valuable both because of the potential biological activity of the products, and because such compounds constitute valuable intermediates for the synthesis of other fluorine-containing compounds. Here, we present a convenient route to fluorinated enol phosphates from easily accessible difluorophosphonates. Moreover, conditions have been developed for selective formation of the *Z*-isomer of the product.

Previously, we have investigated the use of diethyl difluoromethylphoshonate (**1**) for $[CF_2H]^-$ and $[CF_2]^{2-}$ transfer in nucleophilic reactions with carbonyl compounds.[13,14] Common precursors for these transformations are difluorophosphonates **2**, which are prepared from **1** and aldehydes.[15] In the presence of a base, under various conditions, phosphonates **2** were transformed into a range of products containing difluoromethyl or difluoromethylene groups (Scheme 1). Thus, in the presence of an aldehyde and potassium *tert*-butoxide in aprotic solvent (DMF), hydroxyphosphates **3** were formed. Such compounds could be easily transformed into 2,2-difluoro-1,3-diols.[14] Sodium methoxide, in the presence of a protic solvent (MeOH) gave rise to difluoromethyl-containing alcohols **4**.[14] A mild base (K_2CO_3) facilitated the efficient rearrangement of phosphonates into phosphates **5** (Scheme 1).[13]



Scheme 1 Preparation and reactions of difluorophosphonates **2**. *Reagents and conditions*: (a) $(EtO)_2(O)PCF_2H$ (**1**), LDA, THF, –74 °C, 0.5–6 h; (b) R^3CHO, *t*-BuOK, DMF, –60 °C, 0.5–2 h; (c) MeONa, MeOH, THF, 20–40 °C, 1–3 h; (d) K_2CO_3, DMF, r.t., 24 h.

It can be expected that reactions leading to compounds **3**–**5** proceed through the putative difluoromethyl carbanion **6** (Figure 1) – an intermediate that further reacts with a proton source or other electrophile.

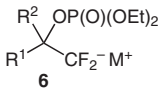


Figure 1 Difluoromethyl carbanion **6** – a crucial intermediate in the formation of compounds **3**–**5** from phosphonates **2**

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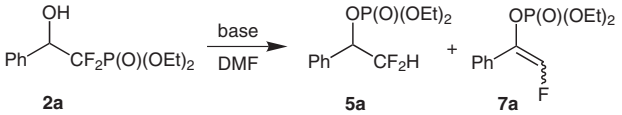
In order to gain an insight into the stability and reactivity of anion **6** in *N*,*N*-dimethylformamide (DMF), we initially focused on the base-induced rearrangement of the phosphorus moiety from carbon to oxygen using **2a** (R^1 = phenyl, R^2 = H) as a model starting phosphonate. The results are summarized in Table 1. It is known that clean formation of **5a** is observed using potassium carbonate (entry 1).[13] Other bases (Et_3N, LiHMDS, MeONa or 0.3 equiv of *t*-BuOK) gave either no reaction or little conversion into **5a** (entries 2–5). However, with one equivalent of potassium *tert*-butoxide, even after one minute at –60 °C, almost complete disappearance of the starting phosphonate was observed. Some phosphate **5a** was formed but the main product was identified as a new compound which, after isolation, was characterized as a mixture of the *E*- and *Z*-isomers of the fluorinated enol phosphates **7a** (entry 6).

Table 1 Reactions of Difluorophosphonate **2a** with Various Bases[a]



2a **5a** **7a**

Entry	Base (equiv)	Temp (°C)	Time (min)	Conv[b] **5a** (%)	Conv[b] **7a** (%)	*Z*/*E* [b] **7a**
1[13]	K_2CO_3 (4)	r.t.	24 h	>98[c]	–	–
2	Et_3N (2)	60[d]	1 h	–	–	–
3	LiHMDS (2)	–60	10	–	–	–
4	MeONa (2)	–60	10	7	–	–
5	*t*-BuOK (0.3)	–60	10	–	–	–
6	*t*-BuOK (1)	–60	1	11	87	84:16
7	*t*-BuOK (1)	–60	10	22	78	87:13
8	*t*-BuOK (1)	–60	30	3	97	86:14
9	*t*-BuOK (2)	–60	1	–	83	92:8
10	*t*-BuOK (2)	–60	30	–	>98	93:7
11	*t*-BuOK (4)	–60	30	–	>98	97:3

[a] Reagents and conditions: **2a** (0.3 mmol), base (0.3–4 equiv), anhyd DMF (3 mL).
[b] Determined using GC–MS.
[c] **5a** was isolated in 96% yield.[13]
[d] No conversion into **5a** or **7a** at either r.t. or –60 °C.

Increasing the amount of base to two and four equivalents lead to clean conversion of **2a** into **7a**, without formation of the side product **5a** (entries 9–11). Furthermore, the presence of an excess of base dramatically increased the product *Z*/*E* ratio. The best result, in terms of efficiency and selectivity of the formation of **7a**, was achieved using four equivalents of potassium *tert*-butoxide (entry 11). The *E*- and *Z*-isomers of **7a** were distinguished either chromatographically (TLC, GC–MS) or spectroscopically (NMR). Each isomer was isolated and characterized; DPFGSE-NOE was used to identify the *E*- and *Z*-isomers of **7a** (Figure 2). The *E*-isomer was found to be less polar on silica gel than the *Z*-isomer, due to its lower molecular dipole. A comparison of the ^{13}C NMR spectra showed a clear difference between the coupling constants of (*Z*)-**7a** ($^3J_{C-F}$ = 1.8 Hz) and (*E*)-**7a** ($^3J_{C-F}$ = 5.8 Hz); the difference in coupling constants between phosphorus and fluorine atoms was found to be relatively small [$^4J_{P-F}$ = 6.8 Hz for (*Z*)-**7a** and $^4J_{P-F}$ = 7.1 Hz for (*E*)-**7a**].

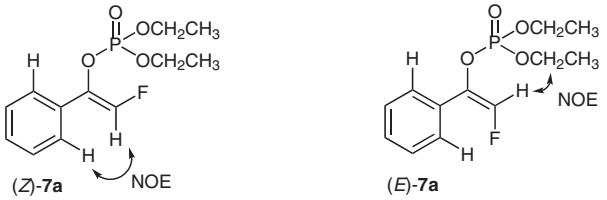
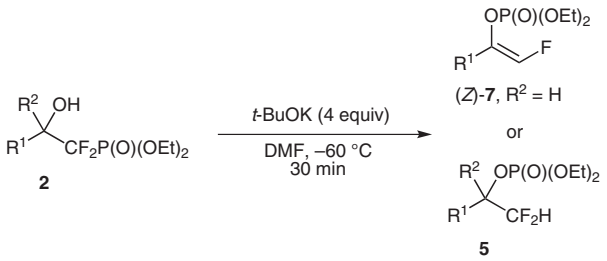


Figure 2 DPFGSE-NOE identification of *E*- and *Z*-isomers of diethyl 2-fluoro-1-phenylvinyl phosphate (**7a**)

UV light affects isomerization of the *Z*-isomer into the *E*-isomer of **7a**. Thus, when compound **7a** (*Z*/*E* = 97:3) was exposed to UV light in a quartz tube, conversion of the *Z*-isomer into the *E*-isomer was observed using GC–MS. After four hours, the resulting mixture contained **7a** in an *Z*/*E* ratio of 58:42; however, during the process, 40% of **7a** decomposed into unidentified compounds. Nevertheless, the *E*-isomer of **7a** was isolated in 23% yield from the resulting mixture.

In order to probe the general utility of this newly developed cascade reaction, a variety of phosphonates **2** were examined; the results are summarized in Table 2.

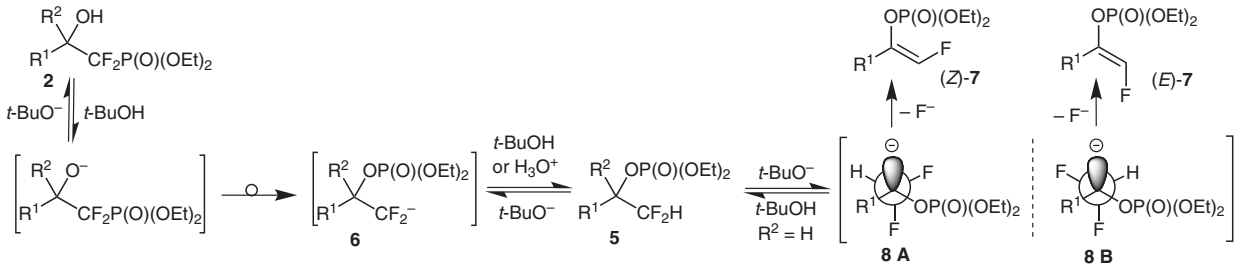
Table 2 Preparation of (*Z*)-Fluoroenol Phosphates (*Z*)-**7** and Difluoromethyl Phosphates **5**[a]



2 **5**

Entry	Phosphonate **2**	R^1	R^2	Product	Yield (%)[b]	*Z*/*E*[c]
1	**2a**	Ph	H	(*Z*)-**7a**	88	97:3
2	**2b**	4-ClC_6H_4	H	(*Z*)-**7b**	90	98:2
3	**2c**	4-$MeOC_6H_4$	H	(*Z*)-**7c**	79	84:16
4	**2d**	2-naphthyl	H	(*Z*)-**7d**	83	95:5
5	**2e**	$Ph(CH_2)_2$	H	**5e**	85	–
6	**2f**	Ph	Me	**5f**	89	–

[a] Reagents and conditions: phosphonate **2** (1 mmol), *t*-BuOK (4 mmol), anhyd DMF (7 mL), 30 min, –60 °C.
[b] Isolated yields.
[c] *Z*/*E* ratios were determined using GC–MS of the crude reaction mixture.



Scheme 2 Proposed mechanism for formation of phosphates **5** and **7**

Phosphonates **2a–d**, which were prepared from the corresponding aromatic aldehydes, reacted cleanly to form enol phosphates **7a–d** in high yields and selectivities for the *Z*-isomers (entries 1–4). An electron-withdrawing group on the aromatic ring (4-chloro) had a beneficial effect on both the yield and the selectivity (entry 2). The presence of an electron-donating group (4-methoxy) presented no problem, however the yield and *Z*/*E* selectivity were slightly reduced (entry 3). In the case of phosphonate **2e**, which was prepared from the corresponding alkyl aldehyde, the sole product was the difluoromethyl-containing phosphate **5e** (entry 5). The same type of product was also obtained through reaction of phosphonate **2f**, which was derived from acetophenone (entry 6).

From these observations a plausible mechanism can be envisaged (Scheme 2). After base-induced deprotonation of phosphonate **2**, rearrangement to the phosphate carboanion **6** occurs. Proton capture gives the difluoromethyl-containing phosphate **5**, which is the final product in cases when $R^2 \neq H$. When $R^2 = H$ and R^1 = aryl, another route is opened: deprotonation with excess base to give the anion **8** (this does not occur when R^1 = alkyl). Anion **8** can exist in two relatively stable conformations (**A** and **B**), both with a fluorine atom *antiperiplanar* to the lone electron pair. Conformation **A** is expected to have lower energy than conformation **B**, both because of the two favorable *gauche* interactions between the phosphate oxygen and fluorine atoms and because of the lower vicinal steric interactions between the R^1 group and hydrogen. Therefore, fluoride elimination gives preferentially (*Z*)-**7**. This mechanism is supported by results from a control experiment in which **5a** was reacted with potassium *tert*-butoxide under the optimized reaction conditions, to give **7a** quantitatively in an *Z*/*E* ratio of 97:3.

In summary, a facile and efficient synthesis of (*Z*)-2-fluoro-1-arylvinyl phosphates, starting from 2-aryl-2-hydroxy-1,1-difluorophosphonates, is described. The reaction involves phosphonate–phosphate rearrangement to give the intermediate difluoromethyl phosphates followed by HF elimination. With both 2-alkyl-2-hydroxy-1,1-difluorophosphonates and 2-aryl-2-alkyl-2-hydroxy-1,1-difluorophosphonates, the reaction terminates at the difluoromethyl phosphate stage. The simple execution, readily available substrates, high yields and high *Z*/*E* selectivities make this protocol very attractive.

NMR spectra were recorded at r.t. in $CDCl_3$ on a Bruker Avance 400 MHz or 500 MHz instrument. Chemical shifts (δ) are reported in ppm and coupling constants (*J* values) are given in Hz. GC–MS spectra were recorded on an Agilent 7890A gas chromatograph coupled with a 5975C quadrupole mass-selective electron impact (EI) detector (70 eV). High-resolution mass spectra (HRMS) were recorded on a LTQ Orbitrap XL instrument using electrospray ionization (ESI). Elemental analyses were obtained using a Perkin–Elmer PE 2400 Series II CHNS analyzer. Reactions were conducted under Ar. Solvents were dried either by using activated 3 Å molecular sieves (DMF, MeOH) or by distillation over Na/benzophenone (THF). All other chemicals were used as received. Purification of the products was performed by flash chromatography using silica gel 60.

(*Z*)-Fluoroenol Phosphates (*Z*)-7; General Procedure

A solution of *t*-BuOK (4 mmol) in DMF (4 mL) was added to a stirred solution of substituted diethyl difluoro hydroxyphosphonate **2** (1 mmol) in DMF (3 mL) cooled to –60 °C. After stirring for 30 min, the reaction mixture was quenched with sat. aq NH_4Cl (20 mL), and extracted with *tert*-butyl methyl ether (3 × 15 mL). The combined organic phase was washed with distilled H_2O (20 mL) and brine (15 mL), dried (anhyd $MgSO_4$), filtered through glass wool, and the solvent was removed to give the crude product. Flash column chromatography afforded the pure (*Z*)-fluoroenol phosphates.

Diethyl (*Z*)-2-Fluoro-1-phenylvinyl Phosphate [(*Z*)-7a]

Purified by chromatography (EtOAc–hexanes, 25:75).

Yield: 241 mg (88%); colorless liquid; R_f = 0.30 (EtOAc–hexanes, 40:60).

^{1}H NMR (500 MHz): δ = 1.29 (dt, $^3J_{H-H}$ = 7.1 Hz, $^4J_{H-P}$ = 1.2 Hz, 6 H, 2 × CH_3), 4.06–4.24 (m, 4 H, 2 × CH_2), 6.98 (dd, $^2J_{H-F}$ = 75.2 Hz, $^4J_{H-P}$ = 2.9 Hz, 1 H, CHF), 7.34–7.39 (m, 3 H, ArH), 7.44–7.48 (m, 2 H, ArH).

^{13}C NMR (125 MHz): δ = 15.9 (d, $^3J_{C-P}$ = 7.1 Hz, CH_3), 64.6 (d, $^2J_{C-P}$ = 5.9 Hz, CH_2), 125.3 (d, J_{C-F} = 3.5 Hz, Ar), 128.5, 129.1 (d, J_{C-F} = 1.3 Hz, Ar), 131.0 (t, $^3J_{C-F}$ = $^3J_{C-P}$ = 1.8 Hz, C_{Ar}CO), 135.9 (t, $^2J_{C-F}$ = $^2J_{C-P}$ = 9.0 Hz, CO), 138.9 (dd, $^1J_{C-F}$ = 262.4 Hz, $^3J_{C-P}$ = 6.9 Hz, CHF).

^{19}F NMR (470 MHz): δ = –148.2 (dd, $^2J_{F-H}$ = 75.2 Hz, $^4J_{F-P}$ = 6.8 Hz).

^{31}P NMR (202 MHz): δ = –5.38 (d, $^4J_{P-F}$ = 6.8 Hz).

GC–MS (t_R = 11.1 min): *m*/*z* (%) = 274 (30) $[M]^+$, 226 (30), 217 (15), 198 (100), 137 (20), 109 (25), 105 (20), 101 (15), 81 (20), 78 (20), 77 (15) $[C_6H_5]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{16}O_4FNaP$: 297.0662; found: 297.0663.

Anal. Calcd for $C_{12}H_{16}FO_4P$: C, 52.56; H, 5.88. Found: C, 52.54; H, 5.92.

Diethyl (*Z*)-2-Fluoro-1-(4-clorophenyl)vinyl Phosphate [(*Z*)-7b]
Purified by chromatography (EtOAc–hexanes, 30:70).

Yield: 277 mg (90%); colorless liquid; R_f = 0.41 (EtOAc–hexanes, 40:60).

^{1}H NMR (400 MHz): δ = 1.31 (dt, $^3J_{H–H}$ = 7.1 Hz, $^4J_{H–P}$ = 1.2 Hz, 6 H, 2 × CH_3), 4.10–4.25 (m, 4 H, 2 × CH_2), 6.98 (dd, $^2J_{H–F}$ = 74.8 Hz, $^4J_{H–P}$ = 2.9 Hz, 1 H, CHF), 7.32–7.33 (m, 2 H, ArH), 7.38–7.42 (m, 2 H, ArH).

^{13}C NMR (100 MHz): δ = 15.9 (d, $^3J_{C–P}$ = 7.0 Hz, CH_3), 64.7 (d, $^2J_{C–P}$ = 6.0 Hz, CH_2), 126.6 (d, $J_{C–F}$ = 3.6 Hz, Ar), 128.8, 129.7, 135.0, 135.2, 139.0 (dd, $^1J_{C–F}$ = 263.5 Hz, $^3J_{C–P}$ = 6.8 Hz, CHF).

^{19}F NMR (376 MHz): δ = –147.1 (dd, $^2J_{F–H}$ = 74.8 Hz, $^4J_{F–P}$ = 6.9 Hz).

^{31}P NMR (162 MHz): δ = –5.66 (d, $^4J_{P–F}$ = 6.9 Hz).

GC–MS (t_R = 12.0 min): *m*/*z* (%) = 310 (10) $[M]^+$, 308 (30) $[M]^+$, 279 (10), 262 (12), 260 (36), 251 (15), 234 (30), 232 (100), 171 (15), 143 (15), 139 (15), 120 (15), 109 (10), 81 (20).

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{15}O_4ClFNaP$: 331.0274; found: 331.0273.

Anal. Calcd for $C_{12}H_{15}ClFO_4P$: C, 46.69; H, 4.90. Found: C, 46.71; H, 4.98.

Diethyl (*Z*)-2-Fluoro-1-(4-methoxyphenyl)vinyl Phosphate [(*Z*)-7c]
Purified by chromatography (EtOAc–hexanes, 25:75).

Yield: 240 mg (79%); colorless liquid; R_f = 0.28 (EtOAc–hexanes, 40:60).

^{1}H NMR (400 MHz): δ = 1.30 (dt, $^3J_{H–H}$ = 7.1 Hz, $^4J_{H–P}$ = 1.2 Hz, 6 H, 2 × CH_3), 3.81 (s, 3 H, OCH_3), 4.07–4.24 (m, 4 H, 2 × CH_2), 6.88 (dd, $^2J_{H–F}$ = 75.8 Hz, $^4J_{H–P}$ = 2.9 Hz, 1 H, CHF), 6.87–6.91 (m, 2 H, ArH), 7.37–7.41 (m, 2 H, ArH).

^{13}C NMR (100 MHz): δ = 16.0 (d, $^3J_{C–P}$ = 7.1 Hz, CH_3), 55.3 (OCH_3), 64.5 (d, $^2J_{C–P}$ = 6.1 Hz, CH_2), 114.0, 123.4, 127.1 (d, $J_{C–F}$ = 3.4 Hz, Ar), 135.8 (t, $^2J_{C–F}$ = $^2J_{C–P}$ = 9.1 Hz, CO), 137.9 (dd, $^1J_{C–F}$ = 260.7 Hz, $^3J_{C–P}$ = 7.0 Hz, CHF), 160.3.

^{19}F NMR (376 MHz): δ = –150.1 (dd, $^2J_{F–H}$ = 75.8 Hz, $^4J_{F–P}$ = 6.8 Hz).

^{31}P NMR (162 MHz): δ = –5.66 (d, $^4J_{P–F}$ = 6.8 Hz).

GC–MS (t_R = 12.4 min): *m*/*z* (%) = 304 (80) $[M]^+$, 275 (30), 247 (60), 228 (100), 167 (30), 135 (50), 108 (25), 81 (25).

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{18}O_5FNaP$: 327.0768; found: 327.0767.

Anal. Calcd for $C_{13}H_{18}FO_5P$: C, 51.32; H, 5.96. Found: C, 51.46; H, 6.08.

Diethyl (*Z*)-2-Fluoro-1-(naphthalene-2-yl)vinyl Phosphate [(*Z*)-7d]
Purified by chromatography (EtOAc–hexanes, 25:75).

Yield: 269 mg (83%); colorless liquid; R_f = 0.25 (EtOAc–hexanes, 30:70).

^{1}H NMR (400 MHz): δ = 1.30 (dt, $^3J_{H–H}$ = 7.1 Hz, $^4J_{H–P}$ = 1.2 Hz, 6 H, 2 × CH_3), 4.11–4.25 (m, 4 H, 2 × CH_2), 7.12 (dd, $^2J_{H–F}$ = 75.2 Hz, $^4J_{H–P}$ = 2.9 Hz, 1 H, CHF), 7.46–7.51 (m, 3 H, ArH), 7.79–7.87 (m, 3 H, ArH), 7.95–7.98 (m, 1 H, ArH).

^{13}C NMR (100 MHz): δ = 15.9 (d, $^3J_{C–P}$ = 7.0 Hz, CH_3), 64.6 (d, $^2J_{C–P}$ = 5.9 Hz, CH_2), 122.4 (d, $J_{C–F}$ = 2.3 Hz, Ar), 124.9 (d, $J_{C–F}$ = 5.0 Hz, Ar), 126.6, 126.7, 127.6, 128.2, 128.4, 130.0, 133.0, 133.4, 136.1 (t, $^2J_{C–F}$ = $^2J_{C–P}$ = 9.1 Hz, CO), 139.3 (dd, $^1J_{C–F}$ = 262.9 Hz, $^3J_{C–P}$ = 6.8 Hz, CHF).

^{19}F NMR (376 MHz): δ = –147.4 (dd, $^2J_{F–H}$ = 75.2 Hz, $^4J_{F–P}$ = 6.9 Hz).

^{31}P NMR (162 MHz): δ = –5.55 (d, $^4J_{P–F}$ = 6.9 Hz).

GC–MS (t_R = 13.8 min): *m*/*z* (%) = 324 (70) $[M]^+$, 295 (20), 276 (20), 267 (30), 248 (100), 187 (30), 170 (35), 159 (40), 155 (30), 128 (35), 127 (30), 81 (25).

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{18}O_4FNaP$: 347.0819; found: 347.0814.

Anal. Calcd for $C_{16}H_{18}FO_4P$: C, 59.26; H, 5.59. Found: C, 59.60; H, 5.52.

Diethyl (*E*)-2-Fluoro-1-phenylvinyl Phosphate [(*E*)-7a]
A solution of *t*-BuOK (448.9 mg, 4 mmol) in DMF (4 mL) was added to a stirred solution of diethyl 1,1-difluoro-2-hydroxy-2-phenylethylphosphonate (**2a**; 294.2 mg, 1 mmol) in DMF (3 mL) cooled to –60 °C. After 30 min of stirring, the reaction mixture was quenched with sat. aq NH_4Cl (20 mL) and extracted with *tert*-butyl methyl ether (3 × 15 mL). The combined organic phase was washed with distilled H_2O (20 mL) and brine (15 mL), dried (anhyd $MgSO_4$), filtered through glass wool, and the solvent was removed to give the crude mixture of isomers (*Z*/*E* = 97:3). This mixture was dissolved in THF (4 mL) and transferred into a quartz tube equipped with a stirring bar and a septum. Isomerization under UV light (50 W Hg lamp) was followed by GC–MS. After 4 h, the temperature of the mixture was raised to 50 °C and the solvent was removed. The pure product was isolated by flash column chromatography (EtOAc–hexanes, 25:75).

Yield: 63 mg (23%); colorless liquid; R_f = 0.38 (EtOAc–hexanes, 40:60).

^{1}H NMR (500 MHz): δ = 1.30 (dt, $^3J_{H–H}$ = 7.1 Hz, $^4J_{H–P}$ = 1.1 Hz, 6 H, 2 × CH_3), 4.08–4.22 (m, 4 H, 2 × CH_2), 7.35 (m, 1 H, ArH), 7.36 (dd, $^2J_{H–F}$ = 76.9 Hz, $^4J_{H–P}$ = 3.2 Hz, 1 H, CHF), 7.41 (m, 2 H, ArH), 7.66 (m, 2 H, ArH).

^{13}C NMR (125 MHz): δ = 16.0 (d, $^3J_{C–P}$ = 6.7 Hz, CH_3), 64.8 (d, $^2J_{C–P}$ = 6.1 Hz, CH_2), 126.5 (d, $J_{C–F}$ = 7.9 Hz, Ar), 128.3, 129.0 (d, $J_{C–F}$ = 1.8 Hz, Ar), 130.7 (dd, $^3J_{C–F}$ = 5.8 Hz, $^3J_{C–P}$ = 3.8 Hz, C_{Ar}CO), 137.9 (dd, $^2J_{C–F}$ = 26.8 Hz, $^2J_{C–P}$ = 9.0 Hz, CO), 144.2 (dd, $^1J_{C–F}$ = 259.9 Hz, $^3J_{C–P}$ = 5.3 Hz, CHF).

^{19}F NMR (470 MHz): δ = –156.1 (dd, $^2J_{F–H}$ = 76.9 Hz, $^4J_{F–P}$ = 7.1 Hz).

^{31}P NMR (202 MHz): δ = –3.79 (d, $^4J_{P–F}$ = 7.1 Hz).

GC–MS (t_R = 10.8 min): *m*/*z* (%) = 274 (30) $[M]^+$, 226 (30), 217 (15), 198 (100), 137 (20), 109 (25), 105 (20), 101 (15), 81 (20), 78 (20), 77 (15) $[C_6H_5]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{17}O_4FP$: 275.0843; found: 275.0843.

Anal. Calcd for $C_{12}H_{16}FO_4P$: C, 52.56; H, 5.88. Found: C, 52.55; H, 6.18.

2,2-Difluoro-1-phenylethyl Diethyl Phosphate (5a)[13]
K_2CO_3 (165.8 mg, 1.2 mol) was added to a solution of 1,1-difluoro-2-hydroxy-2-phenylethylphosphonate (**2a**; 88.2 mg, 0.3 mmol) in DMF (3 mL). After stirring at r.t. for 24 h, H_2O (15 mL) was added and the product was extracted with *tert*-butyl methyl ether (4 × 10 mL). The combined organic phase was washed with H_2O (10 mL), brine (10 mL), dried (anhyd $MgSO_4$), filtered through glass wool, and the solvent was removed to give the crude product. The pure product was isolated by flash column chromatography (EtOAc–hexanes, 30:70).

Yield: 85 mg (96%); colorless liquid; R_f = 0.48 (EtOAc–hexanes, 50:50).

^{1}H NMR (400 MHz): δ = 1.17 (dt, $^3J_{H–H}$ = 7.1 Hz, $^4J_{H–P}$ = 1.1 Hz, 3 H, CH_3), 1.28 (dt, $^3J_{H–H}$ = 7.1 Hz, $^4J_{H–P}$ = 1.1 Hz, 3 H, CH_3), 3.88–4.18 (m, 4 H, 2 × CH_2), 5.39 (ddt, $^3J_{H–F}$ = 10.2, 9.7 Hz, $^3J_{H–H}$ = 4.2 Hz, 1 H, CHO), 5.91 (dt, $^2J_{H–F}$ = 55.2 Hz, $^3J_{H–H}$ = 4.2 Hz, 1 H, CF_2H), 7.39–7.47 (m, 5 H, ArH).

^{13}C NMR (100 MHz): δ = 15.7 (d, $^3J_{C–P}$ = 7.2 Hz, CH_3), 15.8 (d, $^3J_{C–P}$ = 7.2 Hz, CH_3), 64.0 (d, $^2J_{C–P}$ = 5.8 Hz, CH_2), 64.2 (d, $^2J_{C–P}$ = 5.8 Hz, CH_2), 77.4 (ddd, $^2J_{C–F}$ = 25.2, 20.2 Hz, $^2J_{C–P}$ = 5.0 Hz, CHO), 113.8 (ddd, $^1J_{C–F}$ = 254.4, 245.6 Hz, $^3J_{C–P}$ = 8.8 Hz, CF_2H), 127.6, 128.6, 129.5, 132.8–132.9 (m).

^{19}F NMR (470 MHz): δ = –129.0 (ddd, $^2J_{F–F}$ = 286.4 Hz, $^2J_{F–H}$ = 55.2 Hz, $^3J_{F–H}$ = 9.7 Hz, 1 F, C$F_a$$F_b$H), –127.2 (ddd, $^2J_{F–F}$ = 286.4 Hz, $^2J_{F–H}$ = 55.2 Hz, $^3J_{F–H}$ = 10.2 Hz, 1 F, $CF_a$$F_b$H).

^{31}P NMR (162 MHz): δ = –1.63 (s).

GC–MS (t_R = 10.5 min): *m*/*z* (%) = 274 (70) [M – HF]$^+$, 243 (45), 226 (50), 198 (90), 141 (50), 109 (60), 91 (100), 77 (40) [C_6H_5]$^+$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}O_4F_2P$: 295.0905; found: 295.0905.

1,1-Difluoro-4-phenylbutan-2-yl Diethyl Phosphate (5e)

Prepared from diethyl 1,1-difluoro-2-hydroxy-4-phenylbutylphosphonate (**2e**) according to the general procedure for the preparation of (*Z*)-**7** and purified by chromatography (EtOAc–hexanes, 25:75), to give **5e**.

Yield: 274 mg (85%); colorless liquid; R_f = 0.32 (EtOAc–hexanes, 30:70).

^{1}H NMR (400 MHz): δ = 1.35 (dt, $^3J_{H–H}$ = 7.1 Hz, $^4J_{H–P}$ = 1.1 Hz, 3 H, CH_3), 1.36 (dt, $^3J_{H–H}$ = 7.1 Hz, $^4J_{H–P}$ = 1.1 Hz, 3 H, CH_3), 2.02–2.09 (m, 2 H, CH_2), 2.71–2.79 (m, 1 H, $CH_2CH_aH_b$), 2.84–2.91 (m, 1 H, $CH_2CH_aH_b$), 4.12–4.20 (m, 4 H, 2 × CH_2CH_3), 4.43–4.55 (m, 1 H, CHO), 5.86 (ddd, $^2J_{H–F}$ = 55.7, 54.7 Hz, $^3J_{H–H}$ = 3.3 Hz, 1 H, CF_2H), 7.19–7.23 (m, 3 H, ArH), 7.28–7.33 (m, 2 H, ArH).

^{13}C NMR (100 MHz): δ = 16.0 (d, $^3J_{C–P}$ = 7.2 Hz, CH_3), 16.1 (d, $^3J_{C–P}$ = 7.2 Hz, CH_3), 30.3–30.4 (m, CH_2), 30.6 (CH_2), 64.2–64.3 (m, CH_2CH_3), 75.5 (dt, $^2J_{C–F}$ = 25.7 Hz, $^2J_{C–P}$ = 5.8 Hz, CHO), 114.0 (dt, $^1J_{C–F}$ = 245.2 Hz, $^3J_{C–P}$ = 4.5 Hz, CF_2H), 126.2, 128.3, 128.5, 140.5.

^{19}F NMR (376 MHz): δ = –128.0 (ddd, $^2J_{F–F}$ = 289.9 Hz, $^2J_{F–H}$ = 54.7 Hz, $^3J_{F–H}$ = 9.0 Hz, 1 F, C$F_a$$F_b$H), –132.3 (ddd, $^2J_{F–F}$ = 289.9 Hz, $^2J_{F–H}$ = 55.7 Hz, $^3J_{F–H}$ = 13.0 Hz, 1 F, $CF_a$$F_b$H).

^{31}P NMR (162 MHz): δ = –1.35 (s).

GC–MS (t_R = 10.9 min): *m*/*z* (%) = 322 (5) [M]$^+$, 168 (30), 155 (30), 127 (20), 117 (100), 99 (25), 91 (30).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{22}O_4F_2P$: 323.1218; found: 323.1219.

Anal. Calcd for $C_{14}H_{21}F_2O_4P$: C, 52.17; H, 6.57. Found: C, 52.49; H, 6.25.

1,1-Difluoro-2-phenylpropan-2-yl Diethyl Phosphate (5f)

Prepared from diethyl 1,1-difluoro-2-hydroxy-2-phenylpropylphosphonate (**2f**) according to the general procedure for the preparation of (*Z*)-**7** and purified by chromatography (EtOAc–hexanes, 30:70) to give **5f**.

Yield: 274 mg (89%); colorless liquid; R_f = 0.33 (EtOAc–hexanes, 40:60).

^{1}H NMR (400 MHz): δ = 1.24–1.30 (m, 6 H, 2 × CH_3), 2.02 (s, 3 H, CH_3C), 3.98–4.15 (m, 4 H, 2 × CH_2), 6.04 (t, $^2J_{H–F}$ = 56.1 Hz, 1 H, CF_2H), 7.35–7.43 (m, 3 H, ArH), 7.50–7.53 (m, 2 H, ArH).

^{13}C NMR (100 MHz): δ = 15.9 (d, $^3J_{C–P}$ = 7.0 Hz, CH_3CH_2), 16.0 (d, $^3J_{C–P}$ = 7.1 Hz, CH_3CH_2), 18.9–19.0 (m, CH_3C), 63.8 (d, $^2J_{C–P}$ = 5.9 Hz, CH_2), 63.9 (d, $^2J_{C–P}$ = 6.0 Hz, CH_2), 82.8 (dt, $^2J_{C–F}$ = 24.0 Hz, $^2J_{C–P}$ = 5.8 Hz, CCH_3), 114.9 (dt, $^1J_{C–F}$ = 249.8 Hz, $^3J_{C–P}$ = 9.0 Hz, CF_2H), 126.5, 128.3, 128.8, 137.4.

^{19}F NMR (376 MHz): δ = –130.7 (dd, $^2J_{F–F}$ = 278.9 Hz, $^2J_{F–H}$ = 56.0 Hz, 1 F, C$F_a$$F_b$H), –129.8 (ddd, $^2J_{F–F}$ = 278.9 Hz, $^2J_{F–H}$ = 56.2 Hz, $^4J_{F–P}$ = 1.1 Hz, 1 F, $CF_a$$F_b$H).

^{31}P NMR (162 MHz): δ = –5.50 (s).

GC–MS (t_R = 10.9 min): *m*/*z* (%) = 257 (30) [M – CF_2H]$^+$, 155 (100), 154 (30), 127 (35), 103 (30), 99 (25), 77 (15) [C_6H_5]$^+$.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{19}O_4F_2NaP$: 331.0881; found: 331.0879.

Anal. Calcd for $C_{13}H_{19}F_2O_4P$: C, 50.65; H, 6.21. Found: C, 50.96; H, 6.51.

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References

(1) Lichtenthaler, R. W. *Chem. Rev.* **1961**, *61*, 607.
(2) Pomeisl, K.; Kvíčala, J.; Paleta, O.; Klásek, A.; Kafka, S.; Kubelka, V.; Havlíček, J.; Čejka, J. *Tetrahedron* **2007**, *63*, 10549.
(3) Protti, S.; Fagoni, M. *Chem. Commun.* **2008**, 3611.
(4) (a) Sasaki, M.; Honda, S.; Tetsuji, N.; Takakura, H.; Tachibana, K. *Synlett* **2000**, 838. (b) Schroth, W.; Spitzner, R.; Jörg, F. *Synthesis* **1983**, 827. (c) An, J.; Wilson, J. M.; An, Y.-Z.; Wiemer, D. F. *J. Org. Chem.* **1996**, *61*, 4040. (d) Whitehead, A.; Moore, J. D.; Hanson, P. R. *Tetrahedron Lett.* **2003**, *44*, 4275. (e) Miller, J. A. *Tetrahedron Lett.* **2002**, *43*, 7111. (f) Ding, Y.; Huang, X. *Synth. Commun.* **2001**, *31*, 449.
(5) (a) Machleidt, H.; Strehlke, G. U. *Angew. Chem.* **1964**, *76*, 494. (b) Sekine, M.; Okimoto, K.; Yamada, K.; Hata, T. *J. Org. Chem.* **1981**, *46*, 2097. (c) Moorhoff, C. M. *Synth. Commun.* **2003**, *33*, 2069. (d) Onishi, J. Y.; Takuwa, T.; Mukaiyama, T. *Chem. Lett.* **2003**, *32*, 994.
(6) (a) Boyce, C. B. C.; Webb, S. B.; Phillips, L.; Ager, I. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1644. (b) Stowell, J. K.; Widlanski, T. S. *J. Am. Chem. Soc.* **1994**, *116*, 789. (c) Ding, Y.; Wang, W.; Liu, Z. *Phosphorus, Sulfur Silicon Relat. Elem.* **1996**, *118*, 113.
(7) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (b) Boehm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Mueller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637. (c) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3.
(8) (a) Tarasenko, K. V.; Gerus, I. I.; Kukhar, V. P. *J. Fluorine Chem.* **2007**, *128*, 1264. (b) Wiley, D. W.; Simmons, H. E. *J. Org. Chem.* **1964**, *29*, 1876. (c) Seifert, F. U.; Röschenthaler, G.-V. *J. Fluorine Chem.* **1994**, *68*, 169.
(9) (a) Bergmann, E. D.; Shahak, I. *J. Chem. Soc.* **1960**, 462. (b) Stubbe, J. A.; Kenyon, G. L. *Biochemistry* **1972**, *11*, 338. (c) Sundaram, A. K.; Woodard, R. W. *J. Org. Chem.* **2000**, *65*, 5891.
(10) (a) Ishihara, T.; Yamana, M.; Ando, T. *Tetrahedron Lett.* **1983**, *24*, 5657. (b) Ishihara, T.; Okada, Y.; Kuroboshi, M.; Shinozaki, T.; Ando, T. *Chem. Lett.* **1988**, 819.
(11) (a) Ishihara, T.; Maekawa, T.; Ando, T. *Tetrahedron Lett.* **1983**, *24*, 4229. (b) Ishihara, T.; Maekawa, T.; Yamasaki, Y.; Ando, T. *J. Fluorine Chem.* **1986**, *34*, 271. (c) Ishihara, T.; Maekawa, T.; Yamasaki, Y.; Ando, T. *J. Fluorine Chem.* **1987**, *34*, 323.

(12) Demir, A. S.; Eymur, S. *J. Org. Chem.* **2007**, *72*, 8527.
(13) Zibinsky, M.; Beier, P.; Prakash, G. K. S. *Khim. Interesakh Ustoich. Razvit.* **2008**, *16*, 71.
(14) Beier, P.; Alexandrova, A. V.; Zibinsky, M.; Prakash, G. K. S. *Tetrahedron* **2008**, *64*, 10977.
(15) (a) Romanenko, V. D.; Kukhar, V. P. *Chem. Rev.* **2006**, *106*, 3868. (b) Obayashi, M.; Ito, E.; Matsui, K.; Kondo, K. *Tetrahedron Lett.* **1982**, *23*, 2323. (c) Piettre, S. R.; Cabanas, L. *Tetrahedron Lett.* **1996**, *37*, 5881. (d) Piettre, S. R.; Girol, C.; Schelcher, C. G. *Tetrahedron Lett.* **1996**, *37*, 4711.