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Short Communication

# Synthesis of *N*-substituted α,α-difluoro-β-aminophosphonates by addition of diethyl lithiodifluoromethylphosphonate to imines

Prabhakar Cherkupally, Petr Beier *

*Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 166 10 Prague, Czech Republic*

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ABSTRACT

Addition of diethyl lithiodifluoromethylphosphonate to *N*-substituted imines provides *N*-substituted α,α-difluoro-β-aminophosphonates. *N*-Alkyl, aryl, or Boc substituted aldimines give good to high yields in these reactions, while in ketimine series, only activated *N*-(2,2,2-trifluoro-1-phenylethylidene)aniline showed high reactivity.



## 1. Introduction

α,α-Difluorophosphonates are important isoelectronic and isosteric analogs of natural phosphates. Many biologically active difluorophosphonates have been made and studied as enzyme inhibitors or probes for the elucidation of biological processes involving phophates [1]. The synthesis and transformations of difluoromethylphosphonates has been widely explored and recently reviewed [2]. Methods for the introduction of the difluoromethylphosphonate moiety include reactions of organometallic reagents $MCF_2P(O)(OEt)_2$ (**1**-M), where M can be Li, CdBr, ZnBr or $SiR_3$ [2] (**1**-Li can also be generated from **1**-MeS and *t*-BuLi [3]) with aldehydes and ketones [4], primary alkyl halides or triflates [4a,5], *N*-sulfinylimines [6], esters [7], oxetanes, epoxides and cyclic sulfates [8], DMF [7a,7b,9], aryl halides [10], 1-haloalkynes [11], and some Michael acceptors [12], or reactions of phosphonodifluoromethyl radical generated from **1**-X, where X = Br, I, SMe, SePh with alkenes or alkynes [13]. Radical additions of diethylphosphite to difluoroalkenes [14] and fluorinations of phosphonates [15] are also known.

Fluorine-containing aminophosphonates and aminophosphonic acids display a broad range of biological properties such as antiviral, antifungal and antitumor effects, as well as enzyme-inhibitory activity [1a,2]. In particular, amino-α,α-difluorophosphonic acids are known as hydrolytically stable isosteric and isopolar phosphoamino acids mimetics and have found application in the design of protein phosphatases, glycosyltransferases, and L-aspartate-β-semialdehyde dehydrogenase inhibitors [16].

Known methods for the synthesis of α,α-difluoro-β-aminophosphonates are based on the coupling of phosphonodifluoromethyl organometallic reagents with electrophiles. Thus, for example, (difluoromethylene)phosphonate-containing azasugars were prepared by nucleophilic opening of arabino-, ribo- and xylofuranosylamines with diethyl lithiodifluoromethylphosphonate (**1**-Li) followed by cyclization of the amino phosphonate intermediates [17]. Addition of **1**-Li to enantiopure sulfinimines afforded the corresponding *N*-sulfinyl α,α-difluoro-β-amino phosphonates with good selectivity and good yields for *N*-sulfinyl aldimines [6]. In case of *N*-sulfinyl ketimines, the yields were only moderate; however, diastereoselectivities were still high. Diisopropyl lithiodifluoromethylphosphonate available by the reaction of $(i\text{PrO})_2(O)PCF_2SMe$ with *t*-BuLi added to benzylidene-phenylamine in 70% yield [3]. A very recent report by Dilman and coworkers described addition of difluoro(trimethylsilyl)methylphosphonate (**1**-TMS) to benzylidine-methyl-amine in only 30% yield [18]. The reaction was carried out in the presence of in situ formed HF, which activated the imine as iminium, and the resulting fluoride activated **1**-TMS to form the nucleophilic species. On the other hand, good yields of coupling products were observed with enamines using **1**-TMS under the same acidic conditions [18]. Building upon our previous studies of reactivity of **1**-Li [4f,12d,19], **1**-TMS [20] and other fluorinated phosphonates [21] with various electrophiles, we became interested in exploring the addition of **1**-Li to various unactivated imines.

* Corresponding author. Tel.: +420 220 183 409; fax: +420 233 331 733.
*E-mail address:* beier@uochb.cas.cz (P. Beier).

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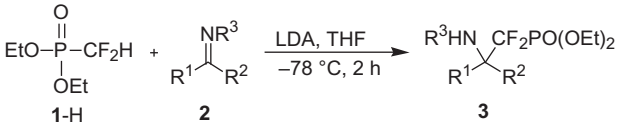
**Table 1**
Synthesis of *N*-substituted α,α-difluoro-β-aminophosphonates **3**.




| Entry | 2 | $R^1$ | $R^2$ | $R^3$ | 3 | Yield (%)[a] |
|---|---|---|---|---|---|---|
| 1 | **2a** | Ph | H | Ph | **3a** | 89 |
| 2 | **2b** | Ph | H | *n*-Bu | **3b** | 72 |
| 3 | **2c** | 4-$MeOC_6H_4$ | H | Ph | **3c** | 87 |
| 4 | **2d** | 4-$MeOC_6H_4$ | H | *n*-Bu | **3d** | 69 |
| 5 | **2e** | 4-$ClC_6H_4$ | H | Ph | **3e** | 84 |
| 6 | **2f** | 4-$ClC_6H_4$ | H | *n*-Bu | **3f** | 82 |
| 7 | **2g** | 2-Furyl | H | Ph | **3g** | 84 |
| 8 | **2h** | 2-Furyl | H | *n*-Bu | **3h** | 73 |
| 9 | **2i** | 3-Pyridyl | H | Ph | **3i** | 86 |
| 10 | **2j** | 3-Pyridyl | H | *n*-Bu | **3j** | 84 |
| 11 | **2k** | 2-Naphthyl | H | Ph | **3k** | 82 |
| 12 | **2l** | 2-Naphthyl | H | *n*-Bu | **3l** | 78 |
| 13 | **2m** | (*E*)-PhCH = CH | H | Ph | **3m** | 86 |
| 14 | **2n** | (*E*)-PhCH = CH | H | *n*-Bu | **3n** | 84 |
| 15 | **2o** | *i*-Pr | H | $PhCH_2$ | **3o** | 68 |
| 16 | **2p** | Ph | H | Boc | **3p** | 88 |
| 17 | **2q** | Ph | Me | Ph | **3q** | 0 |
| 18 | **2r** | Ph | Me | *n*-Bu | **3r** | 0 |
| 19 | **2s** | Ph | $CF_3$ | Ph | **3s** | 95 |
| 20 | **2t** | Ph | $CF_3$ | *n*-Bu | **3t** | 27 |
| 21 | **2u** | Ph | Ph | Ph | **3u** | 0 |
| 22 | **2v** | $-(CH_2)_5-$ | | Ph | **3v** | 0 |

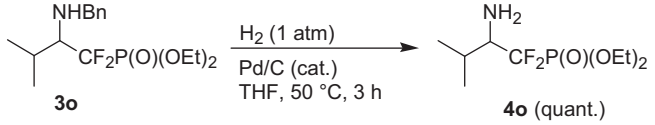
[a] Isolated yield.

## 2. Results and discussion

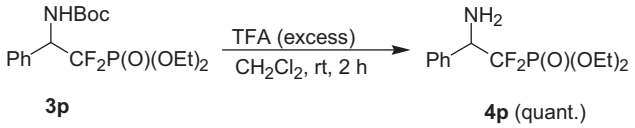
Initially, addition of **1**-TMS to benzylidene-aniline (**2a**) in the presence of fluoride initiators such as CsF, TBAT or TBAF hydrate in THF or DMF was investigated. Under various conditions (temperature, amount of initiator) at best only traces of expected diethyl (1,1-difluoro-2-methylamino-2-phenylethyl)phosphonate (**3a**) were observed by GCMS analysis in accordance to Dilman's observation where dual activation with HF gave low yields [18].

In contrast, **1**-Li prepared by the treatment of **1**-H with LDA according to Obayashi and Kondo [22] was found to add efficiently to imines (**2**) to provide α,α-difluoro-β-amino phosphonates (**3**) (Table 1). In spite of its relatively weak nucleophilicity and limited thermal stability, **1**-Li added to unactivated imines which are considerable less electrophilic than aldehydes or ketones.

In aldimine series it was found that good to high yields of products **3** can be obtained with imines derived from aromatic aldehydes substituted with both electron-acceptor or electron-donor groups as well as imines derived from heteroaromatic, alkenyl or alkyl aldehydes. *N*-phenyl or *N*-Boc imines gave higher yields than *N*-alkyl imines.




**Scheme 1.** Synthesis of α,α-difluoro-β-aminophosphonate **4o** from **3o**.




**Scheme 2.** Synthesis of α,α-difluoro-β-aminophosphonate **4p** from **3p**.

In ketimine series, it was found that imines derived from ketones such as acetophenone, benzophenone or cyclohexanone were completely unreactive [23]. These results are not surprising since Röschenthaler found that strongly activated sulfinyl ketimines gave only moderate yields with the same nucleophile [6]. Indeed, ketimine activation with strongly electron-withdrawing trifluoromethyl group (e.g. **2s**) restored the reactivity and provided **3s** in excellent yield. On the other hand, the yield dropped when *N*-butyl derivative **2t** was used. This time the product mixture contained **3t, 2t** but no **1**-H. No other fluorinated products were observed by $^{19}F$ NMR of the crude product mixture.

The benzyl or Boc group removal from **3o** and **3p**, respectively, was easily accomplished to provide the corresponding α,α-difluoro-β-aminophosphonates in quantitative yields (Schemes 1 and 2).

## 3. Conclusions

*N*-Alkyl, aryl or Boc substituted aldimines react with high efficiency with diethyl lithiodifluoromethylphosphonate to provide corresponding *N*-substituted α,α-difluoro-β-aminophosphonates. The benzyl or Boc groups were quantitatively removed providing α,α-difluoro-β-aminophosphonates. In contrast, *N*-substituted ketimines were unreactive except for activated imines derived from trifluoroacetophenone.

## 4. Experimental

### 4.1. General

NMR spectra were measured on a 400 or 500 MHz instruments in $CDCl_3$. The chemical shifts ($\delta$) are reported in parts per million (ppm) relative to $Me_4Si$ (0 ppm, for $^1H$ NMR), residual $CHCl_3$ peak (7.26 ppm for $^1H$ NMR), $CDCl_3$ (77.0 ppm for $^{13}C$ NMR), internal $CFCl_3$ (0 ppm for $^{19}F$ NMR), and external $H_3PO_4$ in water (0 ppm for $^{31}P$ NMR). Coupling constants ($J$) are given in Hertz. $^{13}C$ and $^{31}P$

NMR spectra were proton decoupled. GCMS 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). Infrared spectra were measured on a FTIR instrument. Reactions requiring anhydrous conditions were conducted under the atmosphere of dry argon. Dry THF was obtained by distillation from Na/benzophenone immediately before use and $CH_2Cl_2$ was dried using activated molecular sieves (3 Å). All other chemicals obtained from commercial suppliers and were used without further purification. Purifications of products were performed by flash chromatography using silica gel 60. TLC plates were visualized with ultraviolet light (254 nm) and/or in $KMnO_4$ staining solution. Yields refer to isolated material judged to be more than 95% pure by $^1$H NMR spectroscopy and GC/MS analysis.

### 4.2. Synthesis imines 2

Imines **2** were synthesized from the corresponding aldehydes or ketones and amines following literature procedures [24]. All imines except **2t** are known compounds.

#### 4.2.1. N-(2,2,2-Trifluoro-1-phenylethylidene)butan-1-amine (2t)

To a mixture of trifluoroacetophenone (703 mg, 4 mmol) and the *n*-butylamine (1.0 mL, 10 mmol) in toluene (20 mL) was added *p*-toluenesulfonyl acid (15 mg, 0.08 mmol). The resulting mixture was refluxed overnight using a Dean-Stark apparatus until complete disappearance of the ketone (18 h, GCMS monitoring). The mixture was filtered through celite, and washed with hexanes (20 mL). Solvents were evaporated under reduced pressure and the product was obtained by distillation as a colorless oil (740 mg, 80%). Bp 86–90 °C (6 torr); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.86 (t, $^3J_{HH}$ = 7.4 Hz, 3H), 1.25–1.34 (m, 2H), 1.60–1.67 (m, 2H), 3.36–3.41 (m, 2H), 7.22–7.24 (m, 2H), 7.45–7.49 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 13.7, 20.4, 32.3, 53.1, 119.7 (q, $^1J_{CF}$ = 278.5 Hz), 127.7, 128.7, 129.9, 130.6, 158.0 (q, $^2J_{CF}$ = 33.5 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −71.6 (s); FTIR (film): $\nu_{max}$ ($cm^{-1}$) 3086, 3065, 3028, 2961, 2936, 2875, 1668, 1603, 1578, 1493, 1197; MS (EI): *m*/*z* (rel. int.) 200 (3), 186 (31), 160 (66), 104 (100), 91 (24), 77 (13); HRMS (ESI): *m*/*z* calcd for $C_{12}H_{15}F_3N$ $[MH]^+$ 230.11511, found 230.11490.

### 4.3. Synthesis of compounds 3, representative procedure

To a solution of diisopropylamine (0.13 mL, 0.92 mmol, 1.2 equiv.) in dry THF (3 mL) cooled to −78 °C was added a solution of *n*-BuLi (2 M, 0.46 mL, 0.92 mmol, 1.2 equiv.) in cyclohexane. The resulting mixture was stirred at 0 °C for 10 min and then cooled to −78 °C. A solution of **1**-H (144.4 mg, 0.77 mmol) in dry THF (1.5 mL) was added dropwise, followed by stirring at −78 °C for 45 min and addition of **2a** (209.8 mg, 1.15 mmol, 1.5 equiv.) in THF (1.5 mL). The reaction mixture was stirred at −78 °C for 2 h followed by the addition saturated aqueous $NH_4Cl$ (10 mL). The product was extracted into $Et_2O$ (3× 15 mL), the combined organic phase was washed with water (20 mL), brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by silica gel flash chromatography afforded **3a** as a white solid (251 mg, 89%).

#### 4.3.1. Diethyl 1,1-difluoro-2-phenyl-2-phenylaminoethylphosphonate (3a)

White solid (251 mg, 89%). $R_f$ = 0.24 (EtOAc–hexane, 20:80); mp 121–122 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.25 (dt, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.7 Hz, 3H), 1.27 (dt, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.6 Hz, 3H), 4.07–4.26 (m, 4H), 4.95–5.04 (m, 2H), 6.60–6.62 (m, 2H), 6.68–6.72 (m, 1H), 7.08–7.12 (m, 2H), 7.29–7.37 (m, 3H), 7.45–7.48 (m, 2H); $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ 16.2 (d, $^3J_{CP}$ = 6.6 Hz), 16.3 (d, $^3J_{CP}$ = 6.3 Hz), 60.7 (ddd, $^2J_{CF}$ = 24.4, 21.3 Hz, $^2J_{CP}$ = 14.8 Hz), 64.7 (d, $^2J_{CP}$ = 7.3 Hz), 64.8 (d, $^2J_{CP}$ = 7.6 Hz), 113.8, 118.4 (dt, $^1J_{CF}$ = 268.0 Hz, $^1J_{CP}$ = 209.2 Hz), 118.5, 128.4, 128.6, 128.7, 129.2, 134.3 (d, $^3J_{CF}$ = 4.8 Hz), 145.7; $^{19}$F NMR (470.4 MHz, $CDCl_3$): $\delta$ −111.1 (ddd, $^2J_{FF}$ = 304.4 Hz, $^2J_{FP}$ = 101.8 Hz, $^3J_{FH}$ = 8.2 Hz, 1F), −120.6 (ddd, $^2J_{FF}$ = 304.4 Hz, $^2J_{FP}$ = 104.4 Hz, $^3J_{FH}$ = 20.1 Hz, 1F); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 6.72 (dd, $^2J_{PF}$ = 104.4, 101.8 Hz); FTIR (film): $\nu_{max}$ ($cm^{-1}$) 3299, 3118, 3088, 3045, 3034, 1603, 1531, 1501, 1251, 1016; MS (EI): *m*/*z* (rel. int.) 369 (4) $[M]^+$, 183 (15), 182 (100), 140 (4), 104 (8), 77 (10); HRMS (ESI): *m*/*z* calcd for $C_{18}H_{23}F_2NO_3P$ $[MH]^+$ 370.13781, found 365.13794.

#### 4.3.2. Diethyl 1,1-difluoro-2-phenyl-2-butylaminoethylphosphonate (3b)

Colourless oil (185 mg, 72%). $R_f$ = 0.28 (EtOAc–hexane, 20:80); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 0.85 (t, $^3J_{HH}$ = 7.3 Hz, 3H), 1.26–1.36 (m, 8H), 1.38–1.50 (m, 2H), 1.79 (br s, 1H), 2.45–2.53 (m, 2H), 4.06–4.33 (m, 5H), 7.32–7.40 (m, 5H); $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ 13.9, 16.2 (d, $^3J_{CP}$ = 5.8 Hz), 16.3 (d, $^3J_{CP}$ = 5.8 Hz), 20.2, 32.0, 47.2, 64.1 (d, $^2J_{CP}$ = 6.7 Hz), 64.5 (d, $^2J_{CP}$ = 6.7 Hz), 64.6 (ddd, $^2J_{CF}$ = 23.1, 19.2 Hz, $^2J_{CP}$ = 15.6 Hz), 119.4 (ddd, $^1J_{CF}$ = 268.8, 265.8 Hz, $^1J_{CP}$ = 210.2 Hz), 128.2, 128.3, 129.1, 135.1 (d, $^3J_{CF}$ = 5.8 Hz); $^{19}$F NMR (470.4 MHz, $CDCl_3$): $\delta$ −111.6 (ddd, $^2J_{FF}$ = 301.9 Hz, $^2J_{FP}$ = 102.5 Hz, $^3J_{FH}$ = 8.6 Hz, 1F), −122.3 (ddd, $^2J_{FF}$ = 301.9 Hz, $^2J_{FP}$ = 104.8 Hz, $^3J_{FH}$ = 21.7 Hz, 1F); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 7.52 (dd, $^2J_{PF}$ = 104.8, 102.5 Hz); FTIR (film): $\nu_{max}$ ($cm^{-1}$) 3317, 3090, 3064, 3031, 2960, 2932, 2873, 1604, 1590, 1496, 1267, 1032; MS (EI): *m*/*z* (rel. int.) 306 (3), 163 (13), 162 (100), 140 (6), 106 (8), 91 (6), 72 (6); HRMS (ESI): *m*/*z* calcd for $C_{16}H_{27}F_2NO_3P$ $[MH]^+$ 350.16911, found 350.16925.

#### 4.3.3. Diethyl 2-(4-methoxyphenyl)-1,1-difluoro-2-phenylaminoethylphosphonate (3c)

White solid (241 mg, 87%). $R_f$ = 0.17 (EtOAc–hexane, 20:80); mp 117–118 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.27 (t, 3H, $^3J_{HH}$ = 7.1 Hz), 1.28 (t, 3H, $^3J_{HH}$ = 7.1 Hz), 3.77 (s, 3H), 4.08–4.27 (m, 4H), 4.89–5.00 (m, 2H), 6.59–6.62 (m, 2H), 6.68–6.71 (m, 1H), 6.86–6.89 (m, 2H), 7.08–7.12 (m, 2H), 7.36–7.39 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 16.2 (d, $^3J_{CP}$ = 5.6 Hz), 16.3 (d, $^3J_{CP}$ = 5.5 Hz), 55.2, 60.2 (ddd, $^2J_{CF}$ = 24.9, 21.1 Hz, $^2J_{CP}$ = 14.8 Hz), 64.6 (d, $^2J_{CP}$ = 6.6 Hz), 64.7 (d, $^2J_{CP}$ = 6.6 Hz), 113.8, 113.9, 118.5 (ddd, $^1J_{CF}$ = 268.1, 266.0 Hz, $^1J_{CP}$ = 208.6 Hz), 118.4, 126.2 (d, $^3J_{CF}$ = 5.1 Hz), 129.1, 129.8, 145.8, 159.8; $^{19}$F NMR (470.4 MHz, $CDCl_3$): $\delta$ −111.1 (ddd, $^2J_{FF}$ = 302.5 Hz, $^2J_{FP}$ = 101.9 Hz, $^3J_{FH}$ = 8.1 Hz, 1F), −121.0 (ddd, $^2J_{FF}$ = 302.5 Hz, $^2J_{FP}$ = 104.4 Hz, $^3J_{FH}$ = 20.3 Hz, 1F); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 6.92 (dd, $^2J_{PF}$ = 104.4, 101.9 Hz); FTIR (film): $\nu_{max}$ ($cm^{-1}$) 3299, 3120, 3055, 3039, 2843, 1612, 1603, 1553, 1513, 1501, 1252, 1178, 1030, 1019; MS (EI): *m*/*z* (rel. int.) 399 (4) $[M]^+$, 213 (15), 212 (100), 170 (5), 104 (8), 77 (8); HRMS (ESI): *m*/*z* calcd for $C_{19}H_{25}F_2NO_4P$ $[MH]^+$ 400.14838, found 400.14828.

#### 4.3.4. Diethyl 2-(4-methoxyphenyl)-1,1-difluoro-2-butylaminoethylphosphonate (3d)

Colourless oil (169 mg, 69%). $R_f$ = 0.11 (EtOAc–hexane, 20:80); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.86 (t, $^3J_{HH}$ = 7.3 Hz, 3H), 1.26–1.36 (m, 8H), 1.38–1.51 (m, 2H), 1.74 (br s, 1H), 2.43–2.54 (m, 2H), 3.81 (s, 3H), 4.06–4.35 (m, 5H), 6.89–6.92 (m, 2H), 7.28–7.32 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 13.8, 16.2 (d, $^3J_{CP}$ = 6.1 Hz), 16.3 (d, $^3J_{CP}$ = 6.0 Hz), 20.2, 32.0, 47.1, 55.2, 63.9 (ddd, $^2J_{CF}$ = 23.5, 19.4 Hz, $^2J_{CP}$ = 15.5 Hz), 64.1 (d, $^2J_{CP}$ = 7.2 Hz), 64.4 (d, $^2J_{CP}$ = 6.5 Hz), 113.6, 119.4 (ddd, $^1J_{CF}$ = 268.7, 265.0 Hz, $^1J_{CP}$ = 209.7 Hz), 127.0 (dd, $^3J_{CF}$ = 6.2 Hz, $^3J_{CF}$ = 1.9 Hz), 130.2, 159.6; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −111.6 (ddd, $^2J_{FF}$ = 301.2 Hz, $^2J_{FP}$ = 103.1 Hz, $^3J_{FH}$ = 8.8 Hz, 1F), −122.4 (ddd, $^2J_{FF}$ = 301.2 Hz, $^2J_{FP}$ = 105.3 Hz, $^3J_{FH}$ = 21.5 Hz,

1F); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 7.65 (dd, $^2J_{PF}$ = 105.3, 103.1 Hz); FTIR (film): $\nu_{max}$ ($cm^{-1}$) 3320, 3068, 2839, 1611, 1586, 1514, 1265, 1252, 1178, 1032; MS (EI): *m*/*z* (rel. int.) 288 (2), 193 (13), 192 (100), 170 (5), 136 (5), 109 (6); HRMS (ESI): *m*/*z* calcd for $C_{17}H_{29}F_2NO_4P$ $[MH]^+$ 380.17968, found 380.17932.

#### 4.3.5. Diethyl 2-(4-chlorophenyl)-1,1-difluoro-2-phenylaminoethylphosphonate (3e)

White solid (198 mg, 84%). $R_f$ = 0.24 (EtOAc–hexane, 20:80); mp 128–129 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.27 (dt, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.6 Hz, 3H), 1.29 (dt, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.6 Hz, 3H), 4.09–4.29 (m, 4H), 4.90–5.01 (m, 2H), 6.56–6.58 (m, 2H), 6.69–6.74 (m, 1H), 7.08–7.14 (m, 2H), 7.31–7.34 (m, 2H), 7.40–7.43 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 16.2 (d, $^3J_{CP}$ = 5.6 Hz), 16.3 (d, $^3J_{CP}$ = 5.4 Hz), 60.3 (ddd, $^2J_{CF}$ = 24.9, 21.3 Hz, $^2J_{CP}$ = 14.8 Hz), 64.8 (d, $^2J_{CP}$ = 6.4 Hz), 64.9 (d, $^2J_{CP}$ = 6.4 Hz), 113.8, 118.2 (ddd, $^1J_{CF}$ = 268.6, 266.5 Hz, $^1J_{CP}$ = 209.5 Hz), 118.8, 128.6, 129.2, 130.1, 133.0 (d, $^3J_{CF}$ = 5.3 Hz), 134.5, 145.4; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −111.1 (ddd, $^2J_{FF}$ = 305.6 Hz, $^2J_{FP}$ = 101.2, $^3J_{FH}$ = 7.8 Hz, 1F), −121.1 (ddd, $^2J_{FF}$ = 305.6 Hz, $^2J_{FP}$ = 104.6 Hz, $^3J_{FH}$ = 20.2 Hz, 1F); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 6.45 (dd, $^2J_{PF}$ = 104.6, 101.2 Hz); FTIR (film): $\nu_{max}$ ($cm^{-1}$) 3305, 3118, 3053, 3036, 1603, 1579, 1526, 1500, 1492, 1253, 1180, 1030, 1017; MS (EI): *m*/*z* (rel. int.) 403 (2) $[M]^+$, 218 (33), 216 (100), 174 (5), 104 (8), 77 (12); HRMS (ESI): *m*/*z* calcd for $C_{18}H_{22}ClF_2NO_3P$ $[MH]^+$ 404.09884, found 404.09878.

#### 4.3.6. Diethyl 2-(4-chlorophenyl)-1,1-difluoro-2-butylaminoethylphosphonate (3f)

Colourless oil (223 mg, 82%). $R_f$ = 0.19 (EtOAc–hexane, 20:80); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.86 (t, $^3J_{HH}$ = 7.3 Hz, 3H), 1.26–1.36 (m, 8H), 1.38–1.50 (m, 2H), 1.81 (br s, 1H), 2.47 (t, $^3J_{HH}$ = 7.1 Hz, 2H), 4.09–4.35 (m, 5H), 7.32–7.37 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 13.8, 16.2 (d, $^3J_{CP}$ = 6.1 Hz), 16.3 (d, $^3J_{CP}$ = 6.3 Hz), 20.2, 32.0, 47.1, 64.2 (ddd, $^2J_{CF}$ = 23.4, 19.6 Hz, $^2J_{CP}$ = 15.6 Hz), 64.3 (d, $^2J_{CP}$ = 7.4 Hz), 64.6 (d, $^2J_{CP}$ = 6.6 Hz), 119.1 (ddd, $^1J_{CF}$ = 269.1, 265.5 Hz, $^1J_{CP}$ = 210.3 Hz), 128.4, 130.5, 133.7 (dd, $^3J_{CF}$ = 6.3, 1.3 Hz), 134.3; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −111.8 (ddd, $^2J_{FF}$ = 302.5 Hz, $^2J_{FP}$ = 101.9 Hz, $^3J_{FH}$ = 8.5 Hz, 1F), −122.5 (ddd, $^2J_{FF}$ = 302.5 Hz, $^2J_{FP}$ = 104.6 Hz, $^3J_{FH}$ = 21.1 Hz, 1F); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 7.15 (dd, $^2J_{PF}$ = 104.6, 101.9 Hz); FTIR (film): $\nu_{max}$ ($cm^{-1}$) 3319, 2960, 2931, 2873, 1596, 1492, 1269, 1165, 1033; MS (EI): *m*/*z* (rel. int.) 340 (2), 198 (33), 196 (100), 174 (6), 140 (9), 109 (7), 72 (9); HRMS (ESI): *m*/*z* calcd for $C_{16}H_{25}ClF_2NO_3P$ $[MH]^+$ 384.13014, found 384.13016.

#### 4.3.7. Diethyl 2-(2-furyl)-1,1-difluoro-2-phenylaminoethylphosphonate (3g)

Pale brown solid (106 mg, 84%). $R_f$ = 0.16 (EtOAc–hexane, 20:80); mp 118–119 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.29 (dt, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.6 Hz, 3H), 1.31 (dt, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.5 Hz, 3H), 4.09–4.29 (m, 4H), 4.56 (d, $^3J_{HH}$ = 10.0 Hz, 1H), 5.11–5.22 (m, 1H), 6.34 (dd, $^3J_{HH}$ = 3.3, 1.8 Hz, 1H), 6.42 (d, $^3J_{HH}$ = 3.3 Hz, 1H), 6.71–6.79 (m, 3H), 7.14–7.19 (m, 2H), 7.41 (dd, $^3J_{HH}$ = 1.8 Hz, $^4J_{HH}$ = 0.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 16.3 (d, $^3J_{CP}$ = 5.7 Hz), 55.4 (ddd, $^2J_{CF}$ = 26.0, 22.2 Hz, $^2J_{CP}$ = 16.6 Hz), 64.7 (d, $^2J_{CP}$ = 6.7 Hz), 110.1, 110.5, 114.3, 118.2 (ddd, $^1J_{CF}$ = 270.4, 267.3 Hz, $^1J_{CP}$ = 209.5 Hz), 119.3, 129.3, 143.0, 145.6, 148.0 (dd, $^3J_{CF}$ = 3.7, 1.6 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −112.3 (ddd, $^2J_{FF}$ = 302.1 Hz, $^2J_{FP}$ = 101.5 Hz, $^3J_{FH}$ = 8.4 Hz, 1F), −119.8 (ddd, $^2J_{FF}$ = 302.1 Hz, $^2J_{FP}$ = 100.3 Hz, $^3J_{FH}$ = 19.0 Hz, 1F); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 6.35 (dd, $^2J_{PF}$ = 101.5, 100.3 Hz); FTIR (film): $\nu_{max}$ ($cm^{-1}$) 3304, 3187, 3134, 3114, 3059, 1601, 1533, 1515, 1500, 1493, 1256, 1182, 1042, 1029; MS (EI): *m*/*z* (rel. int.) 359 (4) $[M]^+$, 173 (13), 172 (100), 130 (4), 104 (5), 77 (6); HRMS (ESI): *m*/*z* calcd for $C_{16}H_{21}F_2NO_4P$ $[MH]^+$ 360.11708, found 360.11676.

#### 4.3.8. Diethyl 2-(2-furyl)-1,1-difluoro-2-butylaminoethylphosphonate (3h)

Pale yellow oil (146 mg, 73%). $R_f$ = 0.20 (EtOAc–hexane, 20:80); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 0.87 (t, $^3J_{HH}$ = 7.3 Hz, 3H), 1.28–1.37 (m, 8H), 1.38–1.50 (m, 2H), 1.71 (br s, 1H), 2.51–2.61 (m, 2H), 4.15–4.35 (m, 5H), 6.38–6.40 (m, 2H), 7.43–7.44 (m, 1H); $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ 13.8, 16.2 (d, $^3J_{CP}$ = 5.4 Hz), 16.3 (d, $^3J_{CP}$ = 5.6 Hz), 20.2, 31.9, 47.4, 58.6 (ddd, $^2J_{CF}$ = 24.4, 20.4 Hz, $^2J_{CP}$ = 16.9 Hz), 64.2 (d, $^2J_{CP}$ = 6.7 Hz), 64.6 (d, $^2J_{CP}$ = 6.3 Hz), 110.1, 110.3, 118.8 (ddd, $^1J_{CF}$ = 270.6, 265.8 Hz, $^1J_{CP}$ = 210.9 Hz), 142.8, 149.0 (d, $^3J_{CF}$ = 6.0 Hz); $^{19}$F NMR (470.4 MHz, $CDCl_3$): $\delta$ −111.2 (ddd, $^2J_{FF}$ = 300.1 Hz, $^2J_{FP}$ = 102.2 Hz, $^3J_{FH}$ = 7.8 Hz, 1F), −121.8 (ddd, $^2J_{FF}$ = 300.1 Hz, $^2J_{FP}$ = 101.2 Hz, $^3J_{FH}$ = 21.8 Hz, 1F); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 7.16 (dd, $^2J_{PF}$ = 102.2, 101.2 Hz); FTIR (film): $\nu_{max}$ ($cm^{-1}$) 3314, 3117, 2960, 2933, 2873, 1601, 1502, 1270, 1165, 1034; MS (EI): *m*/*z* (rel. int.) 267 (3), 153 (10), 152 (100), 130 (6), 109 (7), 96 (11), 81 (6); HRMS (ESI): *m*/*z* calcd for $C_{14}H_{25}F_2NO_4P$ $[MH]^+$ 340.14838, found 340.14841.

#### 4.3.9. Diethyl 2-(3-pyridyl)-1,1-difluoro-2-phenylaminoethylphosphonate (3i)

Pale yellow solid (217 mg, 86%). $R_f$ = 0.07 (EtOAc–hexane, 50:50); mp 107–108 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.27 (dt, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.5 Hz, 3H), 1.29 (dt, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.4 Hz, 3H), 4.11–4.30 (m, 4H), 4.98–5.09 (m, 2H), 6.58–6.61 (m, 2H), 6.71–6.75 (m, 1H), 7.09–7.14 (m, 2H), 7.27–7.30 (m, 1H), 7.79–7.83 (m, 1H), 8.58 (dd, $^3J_{HH}$ = 4.8 Hz, $^4J_{HH}$ = 1.4 Hz, 1H), 8.73 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 16.1 (d, $^3J_{CP}$ = 5.8 Hz), 16.2 (d, $^3J_{CP}$ = 5.6 Hz), 59.0 (ddd, $^2J_{CF}$ = 25.3, 21.5 Hz, $^2J_{CP}$ = 14.9 Hz), 64.8 (d, $^2J_{CP}$ = 6.5 Hz), 64.9 (d, $^2J_{CP}$ = 6.4 Hz), 113.8, 118.1 (ddd, $^1J_{CF}$ = 268.8, 266.7 Hz, $^1J_{CP}$ = 209.9 Hz), 119.0, 123.4, 129.3, 130.4 (d, $^3J_{CF}$ = 5.3 Hz), 136.2, 145.2, 149.8, 150.3; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −110.8 (ddd, $^2J_{FF}$ = 304.7 Hz, $^2J_{FP}$ = 100.3 Hz, $^3J_{FH}$ = 7.8 Hz, 1F), −121.2 (ddd, $^2J_{FF}$ = 304.7 Hz, $^2J_{FP}$ = 102.9 Hz, $^3J_{FH}$ = 21.2 Hz, 1F); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 6.19 (dd, $^2J_{PF}$ = 102.9, 100.3 Hz); FTIR (film): $\nu_{max}$ ($cm^{-1}$) 3261, 3118, 3052, 2981, 2929, 2871, 1634, 1603, 1524, 1500, 1259, 1162, 1052; MS (EI): *m*/*z* (rel. int.) 370 (4) $[M]^+$, 184 (14), 183 (100), 166 (3), 142 (3), 104 (3), 77 (7); HRMS (ESI): *m*/*z* calcd for $C_{17}H_{22}O_3F_2N_2P$ $[MH]^+$ 371.13306, found 371.13300.

#### 4.3.10. Diethyl 2-(3-pyridyl)-1,1-difluoro-2-butylaminoethylphosphonate (3j)

Pale yellow oil (205 mg, 84%). $R_f$ = 0.16 (EtOAc–hexane, 50:50); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.86 (t, $^3J_{HH}$ = 7.3 Hz, 3H), 1.26–1.37 (m, 8H), 1.41–1.50 (m, 2H), 1.96 (br s, 1H), 2.45–2.55 (m, 2H), 4.13–4.36 (m, 5H), 7.31–7.35 (m, 1H), 7.77–7.78 (m, 1H), 8.59–8.63 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 13.5, 16.0 (d, $^3J_{CP}$ = 5.1 Hz), 16.1 (d, $^3J_{CP}$ = 5.3 Hz), 19.9, 31.7, 47.0, 62.6 (ddd, $^2J_{CF}$ = 23.5, 19.8 Hz, $^2J_{CP}$ = 15.6 Hz), 64.1 (d, $^2J_{CP}$ = 6.9 Hz), 64.4 (d, $^2J_{CP}$ = 6.6 Hz), 118.8 (ddd, $^1J_{CF}$ = 269.3, 265.4 Hz, $^1J_{CP}$ = 210.6 Hz), 123.0, 130.8 (d, $^3J_{CF}$ = 6.1 Hz), 136.3, 149.5, 150.5; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −111.5 (ddd, $^2J_{FF}$ = 303.5 Hz, $^2J_{FP}$ = 101.2 Hz, $^3J_{FH}$ = 8.4 Hz, 1F), −122.3 (ddd, $^2J_{FF}$ = 303.5 Hz, $^2J_{FP}$ = 104.1 Hz, $^3J_{FH}$ = 21.1 Hz, 1F); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 6.77 (dd, $^2J_{PF}$ = 104.1, 101.2 Hz); FTIR (film): $\nu_{max}$ ($cm^{-1}$) 3307, 3032, 2959, 2932, 2873, 1637, 1591, 1578, 1266, 1165, 1033; MS (EI): *m*/*z* (rel. int.) 307 (6), 279 (4), 164 (16), 163 (100), 142 (19), 107 (16); HRMS (ESI): *m*/*z* calcd for $C_{15}H_{26}F_2N_2O_3P$ $[MH]^+$ 351.16436, found 351.16445.

#### 4.3.11. Diethyl 2-(2-naphthyl)-1,1-difluoro-2-phenylaminoethylphosphonate (3k)

Colourless solid (234 mg, 82%). $R_f$ = 0.24 (EtOAc–hexane, 20:80); mp 143–144 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.19 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.24 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 4.05–4.27 (m, 4H), 5.09–5.22 (m, 2H), 6.64–6.70 (m, 3H), 7.06–7.11 (m, 2H), 7.44–7.48

(m, 2H), 7.58 (d, $^3J_{HH}$ = 8.5 Hz, 1H), 7.78–7.84 (m, 3H), 7.96 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 16.1 (d, $^3J_{CP}$ = 5.6 Hz), 16.2 (d, $^3J_{CP}$ = 5.6 Hz), 61.0 (ddd, $^2J_{CF}$ = 24.8, 21.1 Hz, $^2J_{CP}$ = 14.7 Hz), 64.7 (d, $^2J_{CP}$ = 6.3 Hz), 64.8 (d, $^2J_{CP}$ = 6.2 Hz), 113.9, 118.5 (ddd, $^1J_{CF}$ = 268.6, 266.6 Hz, $^1J_{CP}$ = 209.2 Hz), 118.6, 126.0, 126.1, 126.3, 127.6, 128.0, 128.1, 128.4, 129.2, 131.9 (d, $^3J_{CF}$ = 5.1 Hz), 133.1, 133.4, 145.7; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −110.8 (ddd, $^2J_{FF}$ = 304.5 Hz, $^2J_{FP}$ = 101.7 Hz, $^3J_{FH}$ = 8.2 Hz, 1F), −120.6 (ddd, $^2J_{FF}$ = 304.5 Hz, $^2J_{FP}$ = 104.4 Hz, $^3J_{FH}$ = 20.2 Hz, 1F); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 6.80 (dd, $^2J_{PF}$ = 104.4, 101.7 Hz); FTIR (film): $\nu_{max}$ ($cm^{-1}$) 3311, 3117, 3057, 3015, 1603, 1524, 1501, 1258, 1176, 1030, 1020; MS (EI): *m*/*z* (rel. int.) 419 (6) $[M]^+$, 233 (20), 232 (100), 190 (5), 104 (11), 77 (8); HRMS (ESI): *m*/*z* calcd for $C_{22}H_{25}F_2NO_3P$ $[MH]^+$ 420.15346, found 420.15339.

#### 4.3.12. Diethyl 2-(2-naphthyl)-1,1-difluoro-2-butylaminoethylphosphonate (3l)

Colourless oil (202 mg, 78%). $R_f$ = 0.22 (EtOAc–hexane, 20:80); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.84 (t, $^3J_{HH}$ = 7.3 Hz, 3H), 1.21–1.36 (m, 8H), 1.38–1.53 (m, 2H), 1.92 (br s, 1H), 2.52 (t, $^3J_{HH}$ = 7.2 Hz, 2H), 4.03–4.36 (m, 4H), 4.42 (ddd, $^3J_{HF}$ = 21.5, 8.6 Hz, $^3J_{HP}$ = 2.9 Hz, 1H), 7.45–7.54 (m, 3H), 7.82–7.87 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 13.8, 16.2 (d, $^3J_{CP}$ = 5.7 Hz), 16.3 (d, $^3J_{CP}$ = 5.8 Hz), 20.2, 32.0, 47.2, 64.1 (d, $^2J_{CP}$ = 6.9 Hz), 64.5 (d, $^2J_{CP}$ = 6.5 Hz), 64.8 (ddd, $^2J_{CF}$ = 23.4, 19.2 Hz, $^2J_{CP}$ = 15.4 Hz), 119.5 (ddd, $^1J_{CF}$ = 269.1, 265.5 Hz, $^1J_{CP}$ = 210.1 Hz), 126.0, 126.1, 126.2, 127.6, 127.9, 128.9, 132.6 (dd, $^3J_{CF}$ = 6.1, 1.4 Hz), 133.0, 133.3; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −111.4 (ddd, $^2J_{FF}$ = 302.1 Hz, $^2J_{FP}$ = 102.3 Hz, $^3J_{FH}$ = 8.6 Hz, 1F), −122.0 (ddd, $^2J_{FF}$ = 302.1 Hz, $^2J_{FP}$ = 104.9 Hz, $^3J_{FH}$ = 21.5 Hz, 1F); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 7.50 (dd, $^2J_{PF}$ = 104.9, 102.3 Hz); FTIR (film): $\nu_{max}$ ($cm^{-1}$) 3317, 3057, 2959, 2930, 2872, 1601, 1509, 1268, 1165, 1031; MS (EI): *m*/*z* (rel. int.) 308 (2), 213 (17), 212 (100), 190 (8), 156 (4), 129 (6), 109 (3); HRMS (ESI): *m*/*z* calcd for $C_{20}H_{29}F_2NO_3P$ $[MH]^+$ 400.18476, found 400.18478.

#### 4.3.13. (E)-Diethyl 1,1-difluoro-4-phenyl-2-phenylamino-3-butenylphosphonate (3m)

Light yellow solid (249 mg, 86%). $R_f$ = 0.24 (EtOAc–hexane, 20:80); mp 110–111 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.29 (dt, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.5 Hz, 3H), 1.31 (dt, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.5 Hz, 3H), 4.09–4.31 (m, 4H), 4.38 (d, $^3J_{HH}$ = 9.3 Hz, 1H), 4.63–4.75 (m, 1H), 6.24 (dd, $^3J_{HH}$ = 15.9, 6.3 Hz, 1H), 6.72–6.78 (m, 4H), 7.16–7.31 (m, 5H), 7.35–7.38 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 16.3 (d, $^3J_{CP}$ = 5.7 Hz), 59.3 (ddd, $^2J_{CF}$ = 24.2, 22.4 Hz, $^2J_{CP}$ = 15.2 Hz), 64.6 (d, $^2J_{CP}$ = 6.7 Hz), 64.7 (d, $^2J_{CP}$ = 7.0 Hz), 113.9, 118.7, 119.1 (ddd, $^1J_{CF}$ = 268.4, 267.4 Hz, $^1J_{CP}$ = 208.5 Hz), 121.9–122.0 (m), 126.7, 128.1, 128.5, 129.3, 134.8, 136.1, 146.1; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −112.8 (ddd, $^2J_{FF}$ = 301.7 Hz, $^2J_{FP}$ = 103.4 Hz, $^3J_{FH}$ = 9.6 Hz, 1F), −119.1 (ddd, $^2J_{FF}$ = 301.7 Hz, $^2J_{FP}$ = 101.7 Hz, $^3J_{FH}$ = 17.4 Hz, 1F); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 6.77 (dd, $^2J_{PF}$ = 103.4, 101.7 Hz); FTIR (film): $\nu_{max}$ ($cm^{-1}$) 3302, 3119, 3057, 3031, 3005, 1600, 1578, 1533, 1498, 1255, 1189, 1051, 1035; MS (EI): *m*/*z* (rel. int.) 395 (4) $[M]^+$, 209 (17), 208 (100), 130 (8), 115 (11), 91 (9), 77 (10); HRMS (ESI): *m*/*z* calcd for $C_{20}H_{26}F_2NO_3P$ $[MH]^+$ 396.15346, found 396.15368.

#### 4.3.14. (E)-Diethyl 1,1-difluoro-4-phenyl-2-butylamino-3-butenylphosphonate (3n)

Pale yellow oil (183 mg, 84%). $R_f$ = 0.16 (EtOAc–hexane, 20:80); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.90 (t, $^3J_{HH}$ = 7.3 Hz, 3H), 1.29–1.56 (m, 11H), 1.41–1.56 (m, 2H), 2.54–2.61 (m, 1H), 2.71–2.77 (m, 1H), 3.72–3.83 (m, 1H), 4.18–4.34 (m, 4H), 6.10 (dd, $^3J_{HH}$ = 15.9, 8.6 Hz), 6.64 (d, $^3J_{HH}$ = 15.9 Hz), 7.23–7.35 (m, 3H), 7.40–7.43 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 13.9, 16.2 (d, $^3J_{CP}$ = 5.7 Hz), 16.3 (d, $^3J_{CP}$ = 5.8 Hz), 20.3, 32.1, 47.0, 63.6 (ddd, $^2J_{CF}$ = 23.4, 20.5 Hz, $^2J_{CP}$ = 15.4 Hz), 64.1 (d, $^2J_{CP}$ = 6.8 Hz), 64.4 (d, $^2J_{CP}$ = 6.5 Hz), 119.8 (ddd, $^1J_{CF}$ = 267.6, 266.0 Hz, $^1J_{CP}$ = 209.4 Hz), 123.0–123.1 (m), 126.6, 127.9, 128.5, 135.5, 136.2; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −112.4 (ddd, $^2J_{FF}$ = 301.0 Hz, $^2J_{FP}$ = 102.8 Hz, $^3J_{FH}$ = 9.9 Hz, 1F), −120.6 (ddd, $^2J_{FF}$ = 301.0 Hz, $^2J_{FP}$ = 103.9 Hz, $^3J_{FH}$ = 18.1 Hz, 1F); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 7.44 (dd, $^2J_{PF}$ = 103.9, 102.8 Hz); FTIR (film): $\nu_{max}$ ($cm^{-1}$) 3316, 3083, 3060, 3027, 2982, 2959, 2931, 2872, 1651, 1599, 1578, 1496, 1270, 1165, 1030; MS (EI): *m*/*z* (rel. int.) 189 (15), 188 (100), 165 (2), 132 (4), 115 (8); HRMS (ESI): *m*/*z* calcd for $C_{18}H_{29}F_2NO_3P$ $[MH]^+$ 376.18476, found 376.18481.

#### 4.3.15. Diethyl 1,1-difluoro-2-benzylamino-3-methylbutylphosphonate (3o)

Colourless oil (161 mg, 68%). $R_f$ = 0.29 (EtOAc–hexane, 20:80); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 0.97 (d, $^3J_{HH}$ = 6.8 Hz, 3H), 1.05 (d, $^3J_{HH}$ = 6.9 Hz, 3H), 1.33 (dt, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.6 Hz, 3H), 1.37 (dt, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.6 Hz, 3H), 1.50 (br s, 1H), 2.21–2.30 (m, 1H), 3.04–3.12 (m, 1H), 3.90 (d, $^2J_{HH}$ = 12.7 Hz, 1H), 4.08 (d, $^2J_{HH}$ = 12.7 Hz, 1H), 4.18–4.32 (m, 4H), 7.22–7.26 (m, 1H), 7.29–7.33 (m, 2H), 7.38–7.40 (m, 2H); $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ 16.3 (d, $^3J_{CP}$ = 5.1 Hz), 16.4 (d, $^3J_{CP}$ = 5.0 Hz), 17.0, 21.4, 28.0, 54.1, 63.9 (ddd, $^2J_{CF}$ = 20.2, 18.6 Hz, $^2J_{CP}$ = 14.7 Hz), 64.1 (d, $^2J_{CP}$ = 6.7 Hz), 64.2 (d, $^2J_{CP}$ = 6.9 Hz), 122.6 (dt, $^1J_{CF}$ = 267.1 Hz, $^1J_{CP}$ = 206.7 Hz), 127.0, 128.2, 128.3, 140.5; $^{19}$F NMR (470.4 MHz, $CDCl_3$): $\delta$ −112.3 (ddd, $^2J_{FF}$ = 301.9 Hz, $^2J_{FP}$ = 107.7 Hz, $^3J_{FH}$ = 13.7 Hz, 1F), −114.9 (ddd, $^2J_{FF}$ = 301.9 Hz, $^2J_{FP}$ = 106.9 Hz, $^3J_{FH}$ = 19.4 Hz, 1F); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 7.83 (dd, $^2J_{PF}$ = 107.7, 106.9 Hz); FTIR (film): $\nu_{max}$ ($cm^{-1}$) 3350, 3087, 3064, 3029, 2988, 2966, 2934, 2914, 2876, 1605, 1585, 1496, 1269, 1164, 1030; MS (EI): *m*/*z* (rel. int.) 306 (12), 162 (51), 106 (49), 91 (100), 65 (6); HRMS (ESI): *m*/*z* calcd for $C_{16}H_{27}F_2NO_3P$ $[MH]^+$ 350.16911, found 350.16837.

#### 4.3.16. t-Butyl [2-(diethoxyphosphoryl)-2,2-difluoro-1-phenylethyl] carbamate (3p)

Colourless oil (247 mg, 88%). $R_f$ = 0.13 (EtOAc–hexane, 20:80); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.13 (t, $^3J_{HH}$ = 6.6 Hz, 3H), 1.31 (t, $^3J_{HH}$ = 6.9 Hz, 3H), 1.43 (s, 9H), 3.90–4.25 (m, 4H), 5.28–5.40 (m, 1H), 5.91 (d, $^3J_{HH}$ = 8.9 Hz, 1H), 7.33–7.42 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 15.9 (d, $^3J_{CP}$ = 5.8 Hz), 16.2 (d, $^3J_{CP}$ = 5.6 Hz), 28.2, 56.7–57.5 (m), 64.4 (d, $^2J_{CP}$ = 7.0 Hz), 64.7 (d, $^2J_{CP}$ = 6.8 Hz), 80.1, 118.3 (dt, $^1J_{CF}$ = 266.5 Hz, $^1J_{CP}$ = 207.7 Hz), 128.2, 128.4, 128.5, 134.2, 154.7; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −112.8 (ddd, $^2J_{FF}$ = 303.7 Hz, $^2J_{FP}$ = 103.3 Hz, $^3J_{FH}$ = 10.9 Hz, 1F), −116.5 (ddd, $^2J_{FF}$ = 303.7 Hz, $^2J_{FP}$ = 102.7 Hz, $^3J_{FH}$ = 17.3 Hz, 1F); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 5.53 (dd, $^2J_{PF}$ = 103.3, 102.7 Hz); FTIR (film): $\nu_{max}$ ($cm^{-1}$) 3301, 3066, 3035, 2981, 2933, 2872, 1720, 1270, 1167, 1021; MS (EI): *m*/*z* (rel. int.) 320 (4), 206 (19), 150 (56), 132 (29), 106 (100), 57 (28); HRMS (ESI): *m*/*z* calcd for $C_{17}H_{26}F_2NNaO_5P$ $[MNa]^+$ 416.14089, found 416.14053.

#### 4.3.17. Diethyl 1,1,3,3,3-pentafluoro-2-phenyl-2-phenylaminopropylphosphonate (3s)

Colourless oil (244 mg, 95%). $R_f$ = 0.44 (EtOAc–hexane, 20:80); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.32 (dt, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.8 Hz, 3H), 1.42 (dt, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 0.7 Hz, 3H), 4.21–4.39 (m, 4H), 6.15 (br s, 1H), 6.45 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 6.71–6.75 (m), 6.98–7.04 (m, 2H), 7.39–7.48 (m, 3H), 7.73 (d, $^3J_{HH}$ = 7.4 Hz, 2H); $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ 16.1 (d, $^3J_{CP}$ = 5.9 Hz), 16.2 (d, $^3J_{CP}$ = 5.6 Hz), 65.7 (d, $^2J_{CP}$ = 7.9 Hz), 66.0 (d, $^2J_{CP}$ = 7.1 Hz), 71.9–72.3 (m), 116.0 (ddd, $^1J_{CF}$ = 275.8, 273.1 Hz, $^1J_{CP}$ = 202.8 Hz), 117.1, 119.4, 124.9 (q, $^1J_{CF}$ = 293.9 Hz), 128.0, 128.3, 128.4–128.5 (m), 129.5, 130.1, 143.2; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −62.0 (dd, $^4J_{FF}$ = 11.3, 10.2 Hz, 3F), −112.7 to −113.1 (m, 2F); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 4.25 (dd, $^2J_{PF}$ = 102.7, 98.8 Hz); FTIR (film): $\nu\nu_{max}$ ($cm^{-1}$) 3337, 3061, 3015, 1603, 1552, 1500, 1267, 1167, 1026; MS (EI): *m*/*z* (rel. int.) 437 (8) $[M]^+$, 251 (16), 250 (100), 180 (11), 77 (12); HRMS (ESI): *m*/*z* calcd for $C_{19}H_{21}F_5NNaO_3P$ $[MNa]^+$ 460.10714, found 460.10698.

*4.3.18. Diethyl 1,1,3,3,3-pentafluoro-2-phenyl-2-butylaminopropylphosphonate (**3t**)*

Colourless oil (78 mg, 27%). $R_f$ = 0.46 (EtOAc–hexane, 20:80); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.92 (t, $^3J_{HH}$ = 7.3 Hz, 3H), 1.26 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.35–1.44 (m, 5H), 1.49–1.60 (m, 2H), 2.44–2.54 (m, 1H), 2.61 (br s, 1H), 2.94–2.98 (m, 1H), 4.09–4.19 (m, 2H), 4.21–4.35 (m, 2H), 7.38–7.42 (m, 3H), 7.71–7.73 (m, 2H); $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ 13.9, 16.1 (d, $^3J_{CP}$ = 5.7 Hz), 16.2 (d, $^3J_{CP}$ = 5.6 Hz), 20.1, 33.0, 42.4, 65.0 (d, $^2J_{CP}$ = 7.5 Hz), 65.3 (d, $^2J_{CP}$ = 7.0 Hz), 71.9–72.6 (m), 117.1 (dt, $^1J_{CF}$ = 274.0 Hz, $^1J_{CP}$ = 206.2 Hz), 124.9 (dq, $^1J_{CF}$ = 294.3 Hz, $^3J_{CF}$ = 3.3 Hz), 127.8, 129.0, 129.6–129.7 (m), 129.8; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −63.1 (t, $^4J_{FF}$ = 10.7 Hz, 3F), −111.8 to −112.1 (m, 2F); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 4.28 (dd, $^2J_{PF}$ = 104.1, 100.1 Hz); FTIR (film): $\nu_{max}$ ($cm^{-1}$) 3332, 3103, 3063, 3034, 2961, 2934, 2874, 1586, 1499, 1267, 1165, 1026; MS (EI): *m*/*z* (rel. int.) 374 (3), 318 (6), 231 (14), 230 (100), 174 (30), 72 (37); HRMS (ESI): *m*/*z* calcd for $C_{17}H_{26}NF_5O_3P$ $[MH]^+$ 418.15650, found 418.15643.

*4.4. Synthesis of diethyl (2-amino-1,1-difluoro-3-methylbutyl)phosphonate (**4o**)*

To a solution of **3o** (176 mg, 0.50 mmol) in THF (3.0 mL), 10% Pd/C (5 mg, cat.) was added, a balloon with hydrogen was attached and the mixture was stirred at 50 °C for 3 h. The catalyst was filtered off through a Celite pad, the solid on the filter was washed with $Et_2O$ (20 mL), and volatiles were removed under reduced pressure giving **4o** as a colorless oil (134 mg, quant., >98% purity by $^1$H NMR). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.94 (d, $^3J_{HH}$ = 6.8 Hz, 3H), 1.05 (d, $^3J_{HH}$ = 6.9 Hz, 3H), 1.34–1.41 (m, 8H), 2.19–2.28 (m, 1H), 3.10 (ddt, $^3J_{HF}$ = 21.3, 10.8 Hz, $^3J_{HH}$ = 3.2 Hz, 1H), 4.24–4.34 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 16.0 (t, $^4J_{CF}$ = 2.0 Hz), 16.2 (d, $^3J_{CP}$ = 5.5 Hz), 16.3 (d, $^3J_{CP}$ = 5.6 Hz), 21.1, 27.0–27.1 (m), 58.0 (ddd, $^2J_{CF}$ = 20.9, 19.9 Hz, $^2J_{CP}$ = 14.3 Hz), 64.2 (d, $^2J_{CP}$ = 7.0 Hz), 64.4 (d, $^2J_{CP}$ = 6.8 Hz), 121.3 (ddd, $^1J_{CF}$ = 267.0, 264.8 Hz, $^1J_{CP}$ = 207.0 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −116.1 (ddd, $^2J_{FF}$ = 299.4 Hz, $^2J_{FP}$ = 106.6 Hz, $^3J_{FH}$ = 10.8 Hz, 1F), −120.1 (ddd, $^2J_{FF}$ = 299.4 Hz, $^2J_{FP}$ = 109.1 Hz, $^3J_{FH}$ = 21.3 Hz, 1F); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 7.77 (dd, $^2J_{PF}$ = 106.6, 109.1 Hz); FTIR (film): $\nu_{max}$ ($cm^{-1}$) 3402, 3336, 2984, 2966, 2935, 2917, 1471, 1446, 1393, 1370, 1268, 1165, 1028; MS (EI): *m*/*z* (rel. int.) 216 (14), 188 (7), 160 (13), 132 (6), 72 (100); HRMS (ESI): *m*/*z* calcd for $C_9H_{21}F_2NO_3P$ $[MH]^+$ 260.12216, found 260.12207.

*4.5. Synthesis of diethyl 2-amino-1,1-difluoro-2-phenylethylphosphonate (**4p**)*

To a solution of **3p** (114 mg, 0.29 mmol) in $CH_2Cl_2$ (1.5 mL), TFA (1.5 mL) was added and the mixture was stirred at rt for 2 h (the progress was monitored by TLC). Volatiles were removed under reduced pressure and a solution of $NaHCO_3$ was added to the resulting oil. Product was extracted into $CH_2Cl_2$ (3× 15 mL), the combined organic phase was washed with water (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure giving pure **4p** as white solid (89 mg, quant., >98% purity by $^1$H NMR). mp 68–69 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.21 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.23 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 2.01 (br s, 2H), 3.95–4.21 (m, 4H), 4.36–4.44 (m, 1H), 7.29–7.39 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 16.0 (d, $^3J_{CP}$ = 5.7 Hz), 16.1 (d, $^3J_{CP}$ = 5.7 Hz), 58.3 (ddd, $^2J_{CF}$ = 22.5, 21.0 Hz, $^2J_{CP}$ = 16.0 Hz), 64.1 (d, $^2J_{CP}$ = 6.9 Hz), 64.4 (d, $^2J_{CP}$ = 6.8 Hz), 119.4 (dt, $^1J_{CF}$ = 266.8 Hz, $^1J_{CP}$ = 207.0 Hz), 128.2, 128.3, 128.4, 136.3–136.5 (m); $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −115.5 (ddd, $^2J_{FF}$ = 299.1 Hz, $^2J_{FP}$ = 103.0 Hz, $^3J_{FH}$ = 11.3 Hz, 1F), −120.4 (ddd, $^2J_{FF}$ = 299.1 Hz, $^2J_{FP}$ = 106.0 Hz, $^3J_{FH}$ = 17.6 Hz, 1F); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ 6.69 (dd, $^2J_{PF}$ = 106.0, 103.0 Hz); FTIR (film): $\nu_{max}$ ($cm^{-1}$) 3371, 3307, 3088, 3065, 3034, 2984, 2923, 2870, 1604, 1494, 1249, 1178, 1166, 1018; MS (EI): *m*/*z* (rel. int.) 140 (3), 132 (4), 107 (9), 106 (100), 79 (10); HRMS (ESI): *m*/*z* calcd for $C_{12}H_{18}O_3F_2NNaP$ $[MNa]^+$ 316.08846, found 316.08846.

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