Utilization of aminophosphonates in the Petasis boronic acid Mannich reaction.

Michael V. Shevchuk, Alexander E. Sorochinsky, Volodymyr P. Khilya, Vadim D. Romanenko and Valery P. Kukhar

Department of Fine Organic Synthesis, Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, Murmanska 1, Kyiv-94, 02660, Ukraine

Department of Organic Chemistry, Faculty of Chemistry, Taras Shevchenko National University of Kyiv, Volodymyrska 62A, Kyiv-33, 01033, Ukraine

E-mail: kukahr@bpci.kiev.ua

Supporting information

Table of contents

General information 1

Procedures an characterization data for compounds 2a-2h, 4a-4d, 7a, 7b 2

(E)-2-(((Diethoxyphosphoryl)(4-methoxyphenyl)methylamino)-4-phenylbut-3-enoic acid (2a). 2

2-((Diethoxyphosphoryl)(4-methoxyphenyl)methylamino)-2-(4-methoxyphenyl)acetic acid (2b). 3

2-(Benzo[d][1,3]dioxol-5-yl)-2-((diethoxyphosphoryl)(4-methoxyphenyl)methylamino)acetic acid (2c) (major diastereomer). 3

2-((Diethoxyphosphoryl)(4-methoxyphenyl)methylamino)-2-(thiophen-2-yl)acetic acid (2d) (major diastereomer). 4

(E)-2-(Benzyl((diethoxyphosphoryl)(phenyl)methyl)amino)-4-phenylbut-3-enoic acid (2e). 4

2-(Benzyl((diethoxyphosphoryl)(phenyl)methyl)amino)-2-(4-methoxyphenyl)acetic acid (2f). 4

2-(Benzo[d][1,3]dioxol-5-yl)-2-(benzyl((diethoxyphosphoryl)(phenyl)methyl)amino)acetic acid (2g). 5

2-(Benzyl((diethoxyphosphoryl)(phenyl)methyl)amino)-2-(thiophen-2-yl)acetic acid (2h). 5

(E)-2-(2,2-Bis(diethoxyphosphoryl)pyrrolidin-1-yl)-4-phenylbut-3-enoic acid (4a). 6

2-(2,2-Bis(diethoxyphosphoryl)pyrrolidin-1-yl)-2-(4-methoxyphenyl)acetic acid (4b). 6

2-(Benzo[d][1,3]dioxol-5-yl)-2-(2,2-bis(diethoxyphosphoryl)pyrrolidin-1-yl)acetic acid (4c). 7

2-(2,2-Bis(diethoxyphosphoryl)pyrrolidin-1-yl)-2-(thiophen-2-yl)acetic acid (4d). 7

(E)-2-((R)-2-((Diethoxyphosphoryl)-2,2-difluoro-1-phenylethylamino)-4-phenylbut-3-enoic acid (4a). 8

(E)-2-((R)-2-((Diethoxyphosphoryl)-2,2-difluoro-1-phenylethylamino)-4-phenylbut-3-enoic acid (4b). 8

(E)-2-((R)-2-((Diethoxyphosphoryl)-2,2-difluoro-1-phenylethylamino)-2-methyl-4-phenylbut-3-enoic acid (4b). 8

References 9

General information

All the reagents were purchased from commercial sources or were prepared according to the appropriate literature methods. All reactions were carried out under an argon atmosphere. Hexane, dichloromethane, chloroform, toluene, diethyl ether, dioxane and acetonitrile were distilled from P2O5. Methanol was distilled from Mg(OMe)$_2$, ethanol was distilled from CaO followed by distillation from NaOEt and diethyl phtalate, ethyl acetate was washed
with NaHCO₃ and CaCl₂, dried over CaCl₂ and distilled, THF was distilled from Na and benzophenone. Reactions were monitored by TLC using precoated aluminium-backed silica gel plates 0.2 mm thick with fluorescent indicator 254 nm (Fluka) as well as with NMR spectroscopy. Flash chromatography was performed on Merck 60 silica gel for flash chromatography using 250 mm height 15 mm diameter column (~20g of sorbent). Spots were visualized with UV light or were developed with a solution of anisaldehyde and sulfuric acid in ethanol followed by heating. ¹H NMR spectra were recorded on a Varian VXR-300 or Varian 400 MHz spectrometer. ¹³C NMR spectra were recorded at 100 MHz on the Varian 400 MHz spectrometer. ¹⁹F and ³¹P spectra were recorded on the Varian 400 MHz spectrometer at 376 and 162 MHz respectively or on a Gemini-200 spectrometer at 188 and 81 MHz respectively. Chemical shifts are reported relative to those of internal chloroform (δ = 7.26 ppm) or internal hexamethyldisiloxane (δ = 0.05 ppm) for ¹H NMR, internal chloroform (δ = 77.16 ppm) for ¹³C NMR, external CFCI₃ (δ = 0.0 ppm) for ¹⁹F NMR, external 85% H₃PO₄ (δ = 0.0 ppm) for ³¹P NMR. Signals are abbreviated as follows: s = singlet; d = doublet; dd = doublet of doublets; ddd = doublet of doublets of doublets; t = triplet; m = multiplet; bs = broad singlet. Mass spectra were obtained at an Agilent 1100 LC MSD SL instrument (chemical ionization, positive and negative ion detection modes).

Procedures and characterization data for compounds 2a-2h, 4a-4d, 7a, 7b

(E)-2-(((Diethoxyphosphoryl)(4-methoxyphenyl)methylamino)-4-phenylbut-3-enoic acid (2a). To a stirred suspension of glyoxylic acid monohydrate (97 mg, 1.05 mmol) in ethyl acetate (5 mL) aminophosphonate 1a (273 mg, 1.00 mmol) was added dropwise, after 5 min (E)-2-phenylethenyl boronic acid (155 mg, 1.05 mmol) was added in one portion and the reaction mixture was refluxed over 2 - 2.5 h while monitored by TLC (5% methanol in chloroform). After the completion of the reaction and cooling the reaction mixture to ambient temperature ethyl acetate (10-15 ml) was added. Mixture was washed with brine (2 x 3 ml) and dried over sodium sulphate. The solvent was evaporated yielding the crude product as yellow oil which tended to solidify. Recrystallization from ethyl acetate/hexane (4/1 v/v) afforded 325 mg (75%) of compound 2a. White solid. ¹H NMR (400 MHz, CDCl₃) δ = 1.14 (t, 3H, OCH₂CH₃), 1.20 (t, 3H, OCH₂CH₃), 3.71 (s, 3H, OCH₃), 3.81 - 4.09 (m, 5H, OCH₂CH₃, CHCOOH), 4.17 (d, JHP = 18.4 Hz, 1H, ArCHP), 6.12 (dd, JHH = 16.0 Hz, JHH = 6.4 Hz, 1H, PhCH=CH), 6.58 (d, JHH = 16.0 Hz, 1H, PhCH=CH), 6.70 (bs, 2H, NH₂⁺), 6.80 (d, JHH = 8Hz, 2H, H₃A), 7.14 - 7.34 (m, 7H, H₃A); ¹³C NMR (100 MHz, CDCl₃) δ = 16.3 (s, OCH₂CH₃), 55.3 (s, OCH₃), 58.2 (d, JCP = 154.8 Hz, ArCHP), 61.2 (d, JCP = 16.8Hz, CHCOOH), 63.3 (d, JCP = 7.4 Hz, OCH₂CH₃), 63.7 (d, JCP = 7.4 Hz, OCH₂CH₃), 114.2, 125.6, 126.6 (d, J = 5.5Hz), 126.8, 128.1, 128.7, 130.1, 133.2, 136.5, 159.9, 174.5 (s, COOH); ³¹P NMR (162 MHz, CDCl₃) δ = 23.2; CI MS, m/z (%) pos 434 [M⁺+H, 45], 296 [100]. Anal. Calcd for C₂₂H₂₉NO₆P: C 60.96; H, 6.51; N, 3.23. Found: C, 60.80; H, 6.45; N, 3.19.
2-((Diethoxyphosphoryl)(4-methoxyphenyl)methylamino)-2-(4-methoxyphenyl)acetic acid (2b). Prepared similarly to 2a, 4-methoxyphenylboronic acid (160 mg, 1.05 mmol) was used instead of (E)-styrylboronic acid. Yield 332 mg (76%). White solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 1.15 (t, 3H, OCH$_2$C$_6$H$_5$), 1.27 (t, 3H, OCH$_2$CH$_3$), 3.77 (s, 3H, OCH$_3$), 3.80 (s, 3H, OCH$_3$), 3.82 - 4.20 (m, 5H, OCH$_2$CH$_3$, ArC$_6$H$_4$P), 4.28 (s, 1H, CHCOOH), 6.82 (d, $J_{HH}$ = 8.9 Hz, 2H, $H_{Ar}$), 6.82 (d, $J_{HH}$ = 8.6 Hz, 2H, $H_{Ar}$), 7.19 (d, $J_{HH}$ = 8.6 Hz, 2H, $H_{Ar}$), 7.30 (d, $J_{HH}$ = 8.9 Hz, 2H, $H_{Ar}$); $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ = 22.8; CI MS, m/z (%)$^+$ 438 (70) [M+H]$^+$, 300 (100); $^-$ 436 (100) [M-H]$^-$. Anal. Calcd for C$_{21}$H$_{28}$NO$_7$P: C, 57.66; H, 6.45; N, 3.20. Found: C, 58.01; H, 6.68; N, 3.25.

2-(Benzo[d][1,3]dioxol-5-yl)-2-((diethoxyphosphoryl)(4-methoxyphenyl)methylamino)acetic acid (2c) (major diastereomer). To a stirred suspension of glyoxylic acid monohydrate (200 mg, 2.17 mmol) in ethyl acetate (5 mL) aminophosphonate 1a (590 mg, 2.16 mmol) was added dropwise, after 5 min 3,4-methylenedioxyphenylboronic acid (348 mg, 2.10 mmol) was added in one portion and the reaction mixture was refluxed over 3 - 4 h while monitored by TLC (5% methanol in chloroform). After the completion of the reaction and cooling the reaction mixture to an ambient temperature ethyl acetate (10-15 ml) was added. Mixture was washed with brine (2 x 3 ml) and dried over sodium sulphate. The solvent was evaporated yielding the crude product as yellow oil. Flash chromatography using chloroform/ethyl acetate/methanol (35/55/10 v/v/v) afforded 500 mg (53%) of compound 2c as colorless oil. LC-MS and $^1$H NMR showed diastereomeric ratio in purified product equal to 82:18. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 1.14 (t, 3H, OCH$_2$C$_6$H$_5$), 1.23 (t, 3H, OCH$_2$CH$_3$), 3.77 (s, 3H, OCH$_3$), 3.81 - 3.90 (m, 1H, OCH$_2$C$_6$H$_5$), 3.92 - 4.11 (m, 3H, OCH$_2$CH$_3$), 4.10 (d, $J_{HP}$ = 18.2 Hz, 1H, ArC$_6$H$_4$P), 4.23 (s, 1H, CHCOOH), 5.89 (s, 2H, OCH$_2$O), 6.68 - 6.84 (m, 5H, $H_{Ar}$), 7.27 (d, $J_{HH}$ = 8.4 Hz, 2H, $H_{Ar}$); $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ = 22.8; CI MS, m/z (%)$^+$ 452 (20) [M+H]$^+$, 314 (100); $^-$ 450 (100) [M-H]$^-$. Anal. Calcd for C$_{21}$H$_{26}$NO$_8$P: C, 55.88; H, 5.81; N, 3.10. Found: C, 55.95; H, 5.80; N, 3.18.
2-((Diethoxyphosphoryl)(4-methoxyphenyl)methylamino)-2-(thiophen-2-yl)acetic acid (2d) (major diastereomer). Prepared similarly to compound 2c from aminophosphonate 1a (300 mg, 1.10 mmol), 2-thiopheneboronic acid (140 mg, 1.10 mmol) and glyoxylic acid (101 mg, 1.10 mmol). LC-MS of the purified product showed only one pick, though $^1$H NMR spectroscopy indicated 68:32 mixture of diastereomers. For this reason interpretation and referencing of the „aromatic” area of $^{13}$C spectrum was not possible. Yield 178 mg (43%). White solid. $^1$H NMR (400 MHz, CDCl$_3$) δ = 1.05 (t, 3H, OCH$_2$CH$_3$), 1.25 (t, 3H, OCH$_2$CH$_3$), 3.66 - 3.81 (m, 1H, OCH$_2$CH$_3$), 3.77 (s, 3H, OCH$_3$), 3.84 - 4.19 (m, 3H, OCH$_2$CH$_3$), 4.49 (d, $J_{HP}$ = 16.8 Hz, 1H, ArCHP), 5.26 (s, 1H, COOH), 6.83 (d, $J_{HH}$ = 8.0 Hz, 2H, C$_6$H$_4$meta), 6.90 (m, 1H, Hthiophene), 7.17 - 7.35 (m, 4H, C$_6$H$_4$ortho, Hthiophene); $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 16.2 (d, $J_{CP}$ = 6.0 Hz, OCH$_2$CH$_3$), δ = 16.5 (d, $J_{CP}$ = 6.0 Hz, OCH$_2$CH$_3$), 55.3 (s, OCH$_3$), 56.7 (d, $J_{CP}$ = 159.0 Hz, ArCHP), 57.8 (d, $J_{CP}$ = 18.7Hz, CCOOH), 63.3 (d, $J_{CP}$ = 7.0 Hz, OCH$_2$CH$_3$), 63.9 (d, $J_{CP}$ = 7.0 Hz, OCH$_2$CH$_3$), 64.6 (d, J$_{CP}$ = 2.0 Hz, CCOOH); $^{31}$P NMR (162 MHz, CDCl$_3$) δ = 23.0; CI MS, m/z (%) pos 414 (20) [M+H]$^+$, 276 (100); neg 412 (100) [M-H]$^-$.

(E)-2-(Benzyl((diethoxyphosphoryl)(phenyl)methyl)amino)-4-phenylbut-3-enoic acid (2e). Prepared similarly to 2a from aminophosphonate 1b (333 mg, 1.00 mmol). Yield 394 mg (80%). White solid. $^1$H NMR (400 MHz, CDCl$_3$) δ = 1.02 (t, 3H, OCH$_2$CH$_3$), 1.24 (t, 3H, OCH$_2$CH$_3$), 3.73 (d, J$_{HH}$ = 13.0 Hz, 1H, PhCH$_2$N), 4.20 (d, J$_{HH}$ = 13.0 Hz, 1H, PhCH$_2$N), 3.74 - 4.07 (m, 4H, OCH$_2$CH$_3$), 4.22 (d, J$_{HP}$ = 25.0 Hz, 1H, PhCHP), 4.67 (d, J$_{HH}$ = 8.0Hz, 1H, CCOOH), 5.75 (d, J$_{HH}$ = 16.0 Hz, 1H, PhCH=CH), 5.94 (dd, J$_{HH}$ = 16.0 Hz, J$_{HH}$ = 8Hz, 1H, PhCH=CH), 6.96 - 7.47 (m, 15H, H$_{Ar}$); $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 16.2 (d, J$_{CP}$ = 6.1 Hz, OCH$_2$CH$_3$), 16.5 (d, J$_{CP}$ = 6.1 Hz, OCH$_2$CH$_3$), 53.8 (d, J$_{CP}$ = 9.9 Hz, PhCH$_2$N), 59.5 (d, J$_{CP}$ = 164.8 Hz, PhCHP), 63.1 (d, J$_{CP}$ = 7.0 Hz, OCH$_2$CH$_3$), 63.1 (s, CCOOH), 63.4 (d, J$_{CP}$ = 8.0 Hz, OCH$_2$CH$_3$), 122.4, 126.6, 127.9, 128.0, 128.4, 128.8, 129.0, 129.8, 130.9, 130.95, 135.3, 136.5, 137.7; $^{31}$P NMR (162 MHz, CDCl$_3$) δ = 23.9.

2-(Benzyl((diethoxyphosphoryl)(phenyl)methyl)amino)-2-(4-methoxyphenyl)acetic acid (2f). Prepared similarly to 2a from aminophosphonate 1b (333 mg, 1.00 mmol), 4-methoxyphenylboronic acid (152 mg, 1.00 mmol) and glyoxylic acid (92 mg, 1.00 mmol). Crude product gave satisfactory spectral data. Yield 472 mg (95%). White solid. $^1$H NMR (400 MHz, CDCl$_3$) δ = 1.01 (t, 3H, OCH$_2$CH$_3$), 1.41 (t, 3H, OCH$_2$CH$_3$), 3.64 - 3.75 (m, 1H,
P(O)(OEt)₂ (88%). White solid. 1H NMR (400 MHz, CDCl₃) 1.00 mmol) and glyoxylic acid (92 mg, 1.00 mmol). Crude product gave satisfactory spectral data. Yield 450 mg

Prepared

C
H
131.5, 135.2 (d, JCP = 4.0 Hz, PhC₃), 62.5 (d, JCP = 7.6 Hz, OCH₂CH₃), 63.1 (d, JCP = 7.6 Hz, OCH₂CH₃), 64.1 (s, CHCOOH), 113.7, 127.5, 128.3, 128.4, 128.7, 129.6, 130.7, 130.7 (d, JCP = 9.0 Hz), 135.1 (d, JCP = 9.0 Hz), 159.2, 174.73 (d, JCP = 3.8 Hz, COOH); ³¹P NMR (162 MHz, CDCl₃) δ = 24.1; CI MS, m/z (%) pos 498 (70) [M+H]+, 360 (100), 196 (45), 165 (10). Anal. Caled for C₂₇H₃₂NO₆P: C, 65.18; H, 6.48; N, 2.82. Found: C, 64.95; H, 6.43; N, 2.78.

2-(Benzol[d][1,3]dioxol-5-yl)-2-(benzyl(diethoxyphosphoryl)(phenyl)methyl)amino)acetic acid (2g). Prepared simillarity to 2a from aminophosphonate 1b (333 mg, 1.00 mmol), 3,4-methylenedioxyphenylboric acid (166 mg, 1.00 mmol) and glyoxylic acid (92 mg, 1.00 mmol). Crude product gave satisfactory spectral data. Yield 450 mg (88%). White solid. ¹H NMR (400 MHz, CDCl₃) δ = 1.00 (t, 3H, OCH₂CH₃), 1.43 (t, 3H, OCH₂CH₃), 3.66 - 3.75 (m, 1H, OCH₂CH₃), 3.85 - 3.94 (m, 1H, OCH₂CH₃), 3.99 (d, JHH = 14.2 Hz, 1H, PhC₃H₂N), 4.18 - 4.27 (m, 1H, OCH₂CH₃), 4.28 (d, JHP = 20.0 Hz, 1H, PhCHP), 4.35 - 4.45 (m, 1H, OCH₂CH₃), 4.49 (d, JHH = 14.2 Hz, JHP = 4.9 Hz, 1H, PhC₃H₂N), 5.04 (s, 1H, CHCOOH), 5.85 (d, JHH = 7.0 Hz, 2H, OCH₂O), 6.32 (s, 1H, H₃), 6.46 (d, JHH = 7.9 Hz, 1H, H₃), 6.62 (d, JHH = 7.9 Hz, 1H, H₃), 7.14 (d, JHH = 7.2 Hz, 2H, H₃), 7.16 - 7.33 (m, 8H, H₃), 11.00 (bs, COOH); ¹³C NMR (100 MHz, CDCl₃) δ = 16.3 (d, JCP = 5.0 Hz, OCH₂CH₃), 16.7 (d, JCP = 8.0 Hz, OCH₂CH₃), 52.9 (s, PhC₃H₂N), 58.8 (d, JCP = 150.0, PhCHP), 62.5 (d, JCP = 7.0 Hz, OCH₂CH₃), 63.1 (d, JCP = 7.0 Hz, OCH₂CH₃), 64.0 (s, CHCOOH), 101.1 (s, OCH₂O), 108.0, 110.0, 122.8, 127.5, 128.4, 128.5, 128.7, 129.6, 130.7 (d, JCP = 9.0 Hz), 131.5, 135.2 (d, JCP = 9.0 Hz), 139.6, 147.2, 147.6, 174.4 (d, JCP = 3.0Hz, COOH); ³¹P NMR (162 MHz, CDCl₃) δ = 23.8; CI MS, m/z (%) pos 512 (55) [M+H]+, 374 (100), 334 (10), 196 (35); neg 510 (100) [M-H]-, 227 (10), 85 (10). Anal. Caled for C₂₇H₃₂NO₆P: C, 63.40; H, 5.91; N, 2.74. Found: C, 63.71; H, 5.99; N, 2.79.

2-(Benzyl(diethoxyphosphoryl)(phenyl)methyl)amino)-2-(thiophen-2-yl)acetic acid (2h). Prepared simillarity to 2c, from aminophosphonate 1b (397 mg, 1.19 mmol), 2-thiopheneboronic acid (153 mg, 1.20 mmol) and glyoxylic acid (110 mg, 1.20 mmol). Chloroform/ethanol acetate/methanol 35/55/5 v/v/v was used for flash chromatography. Yield 390 mg (69%) Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ = 1.04 (t, 3H, OCH₂CH₃), 1.42 (t, 3H, OCH₂CH₃), 3.74 - 3.85 (m, 1H, OCH₂CH₃), 3.93 (m, 1H, OCH₂CH₃), 4.00 (d, JHH = 14.2 Hz, 1H, PhC₃H₂N), 4.21 (m, 1H, OCH₂CH₃), 4.31 (d, JHP = 22.0 Hz, 1H, PhCHP), 4.35 (m, 1H, OCH₂CH₃), 4.47 (d, JHH = 14.2 Hz, JHP = 3.5 Hz, 1H, PhC₃H₂N), 5.43 (s, 1H, CHCOOH), 6.74 (s, 1H, H₃), 6.82 (s, 1H, H₃), 7.13 (s, 1H, H₃), 7.28 - 7.50 (m, 10H, H₃), 11.00 (bs, COOH); ¹³C NMR (100 MHz, CDCl₃) δ = 16.4 (d, JCP = 6.0 Hz, OCH₂CH₃), 16.74 (d, JCP = 6.0 Hz, OCH₂CH₃), 53.3 (d, JCP = 4.0 Hz, PhC₃H₂N), 58.3 (d, JCP = 152.0 Hz, PhCHP), 59.8 (s, CHCOOH),
62.8 (d, JCP = 8.0 Hz, OCH2CH3), 63.3 (d, JCP = 8.0 Hz, OCH2CH3), 126.1, 126.3, 127.6, 127.8, 128.6, 128.9, 130.0, 130.6 (d, JCP = 9.0 Hz), 134.4 (d, JCP = 8.0 Hz), 138.9, 140.1, 172.8 (s, COOH); 31P NMR (162 MHz, CDCl3) δ = 24.1; CI MS, m/z (%) pos 474 (35) [M+H]+, 336 (100), 196 (35); neg 472 (100) [M-H], 227 (15), 85 (10). Anal. Calcd for C24H28NO5PS: C, 60.88; H, 5.96; S, 6.77. Found: C, 61.68; H, 5.95; S, 7.09.

(E)-2-(2,2-Bis(diethoxophosphoryl)pyrrolidin-1-yl)-4-phenylbut-3-enolic acid (4a). To a stirred suspension of glyoxylic acid monohydrate (138 mg, 1.50 mmol) in ethyl acetate (5 mL) tetraethyl pyrrolidine-2,2-diylidiphosphonate 3 (515 mg, 1.50 mmol) was added dropwise, after 5 min 2-(E)-styrylboronic acid (222 mg, 1.50 mmol) was added in one portion and the reaction mixture was refluxed over 4 h while monitored by TLC (5% methanol in chloroform). After the completion of the reaction the solvent was evaporated yielding the crude product as yellow oil. Flash chromatography using 5% of methanol in dichloromethane afforded 360 mg (47%) of 4a as yellow oil. 1H NMR (400 MHz, CDCl3) δ = 1.14 (t, 3H, OCH2CH3), 1.23 (t, 3H, OCH2CH3), 1.34 (t, 3H, OCH2CH3), 1.37 (t, 3H, OCH2CH3), 1.77 - 1.95 (m, 2H, CH2), 2.32 - 2.51 (m, 2H, CH2), 3.04 - 3.15 (m, 2H, CH2), 3.93 - 4.34 (m, 8H, OCH2), 5.15 (d, JHH = 8.1 Hz, 1H, CHCOOH), 6.44 (dd, JHH = 8.1Hz, JHH = 16.0 Hz, 1H, PhCH=CH2), 6.64 (d, JHH = 16.0 Hz, 1H, PhCH=CH2), 7.19 (t, JHH = 7.0 Hz, 1H, Hα), 7.27 (t, JHH = 7.0 Hz, 2H, Hα), 7.39 (d, JHH = 7.0 Hz, 2H, Hα); 13C NMR (100 MHz, CDCl3) δ = 16.2 (d, JCP = 6.5 Hz, OCH2CH3), 16.4 (d, JCP = 5.3Hz, OCH2CH3), 16.5 (d, JCP = 6.1Hz, OCH2CH3), 16.5 (d, JCP = 5.7 Hz, OCH2CH3), 24.0 (t, JCP = 3.1 Hz, CH2), 32.1 (t, JCP = 4.2 Hz, CH2), 47.4 (d, JCP = 6.9 Hz, CH2), 61.9 (s, CHCOOH), 62.1 (d, JCP = 7.6 Hz, OCH2CH3), 63.4 (d, JCP = 7.6 Hz, OCH2CH3), 64.9 (d, JCP = 7.6 Hz, OCH2CH3), 122.6, 126.7, 127.7, 128.5, 135.0, 136.8, 172.9 (s, COOH); 31P NMR (162 MHz, CDCl3) δ = 21.4 (d, JPP = 92.0 Hz, 1P), 23.6 (d, JPP = 92.0 Hz, 1P).

2-(2,2-Bis(diethoxophosphoryl)pyrrolidin-1-yl)-2-(4-methoxyphenyl)acetic acid (4b). Prepared similarly to 4a from tetraethyl pyrrolidine-2,2-diylidiphosphonate 3 (394 mg, 1.15 mmol), 4-methoxyphenylboronic acid (182 mg, 1.20 mmol) and glyoxylic acid (110 mg, 1.20 mmol). Yield 380 mg (65%). Colorless oil. 1H NMR (400 MHz, CDCl3) δ = 1.00 (t, 3H, OCH2CH3), 1.20 (t, 3H, OCH2CH3), 1.34 (t, 3H, OCH2CH3), 1.35 (t, 3H, OCH2CH3), 1.81 - 1.89 (m, 2H, CH2), 2.27 - 2.52 (m, 2H, CH2), 2.75 - 2.80 (m, 1H, CH2), 3.13 - 3.20 (m, 1H, CH2), 3.76 (s, 3H, OCH3), 3.77 - 3.98 (m, 2H, OCH2CH3), 4.03 - 4.32 (m, 6H, OCH2CH3), 5.57 (s, 1H, CHCOOH), 6.81 (d, JHH = 8.6 Hz, CδHmeth), 7.36 (d, JHH = 8.6 Hz, CαHmeth); 13C NMR (100 MHz, CDCl3) δ = 16.1 (d, JCP = 6.0 Hz, OCH2CH3), 16.5 (d, JCP = 6.0 Hz, OCH2CH3), 16.6 (d, JCP = 6.0 Hz, OCH2CH3), 23.9 (t, JCP = 3.0 Hz, CH2), 32.1 (t, JCP = 4.5 Hz, CH2), 48.7 (d, JCP = 5.0 Hz, CH2), 55.4 (s, OCH3), 61.9 (d, JCP = 8.0 Hz, OCH2CH3), 63.1 (d, JCP = 8.0 Hz, OCH2CH3), 63.5 (d, JCP = 8.0 Hz, OCH2CH3), 63.8 (s, CHCOOH), 64.0 (dd, JCP = 148.0 Hz, JCP = 154.0 Hz, PCP), 64.7 (d, JCP = 8.0 Hz, OCH2CH3), 113.2, 128.2, 131.5, 159.1, 174.1 (s, COOH); 31P NMR (162 MHz, CDCl3) δ = 21.6 (d, JPP = 92.0 Hz, 1P), 23.5 (d, JPP = 92.0 Hz, 1P); CI MS, m/z (%) pos 370 (100), 206 (10), 165 (10).
2-(Benzo[d][1,3]dioxol-5-yl)-2-(2,2-bis(diethoxyphosphoryl)pyrrolidin-1-yl)acetic acid (4c). Prepared similarly to 4a from tetraethyl pyrrrolidine-2,2-diylidiphosphonate 3 (412 mg, 1.20 mmol), 3,4-methylene dioxyphenylboronic acid (210 mg, 1.25 mmol) and glyoxylic acid (112 mg, 0.73 mmol). Yield 460 mg (73%). Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 1.06 (t, 3H, OCH$_2$CH$_3$), 1.24 (t, 3H, OCH$_2$CH$_3$), 1.35 (t, 3H, OCH$_2$CH$_3$), 1.36 (t, 3H, OCH$_2$CH$_3$), 1.79 - 1.92 (m, 2H, CH$_2$), 2.29 - 2.53 (m, 2H, CH$_2$), 2.78 - 2.87 (m, 1H, CH$_2$), 3.11 - 3.22 (m, 1H, CH$_2$), 3.87 - 4.02 (m, 2H, OCH$_2$CH$_3$), 4.03 - 4.33 (m, 6H, OCH$_2$CH$_3$), 5.54 (s, 1H, CHCOOH), 5.90 (d, $J_{HH}$ = 2.0 Hz, OCH$_2$O), 6.73 (d, $J_{HH}$ = 8.0 Hz, 1H, 5-H$_{ax}$), 6.93 (dd, $J_{HH}$ = 8.0 Hz, $J_{HH}$ = 1.6 Hz, 1H, 6-H$_{ax}$), 6.95 (s, 2-H$_{eq}$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 16.1 (d, $J_{CP}$ = 6.0 Hz, OCH$_2$CH$_3$), 16.5 (d, $J_{CP}$ = 6.0 Hz, OCH$_2$CH$_3$), 16.6 (d, $J_{CP}$ = 6.0 Hz, OCH$_2$CH$_3$), 23.9 (t, $J_{CP}$ = 3.5 Hz, CH$_2$), 32.1 (t, $J_{CP}$ = 3.5 Hz, CH$_3$), 48.7 (d, $J_{CP}$ = 5.0 Hz, CH$_2$), 82.0 (d, $J_{CP}$ = 8.0 Hz, OCH$_2$CH$_3$), 83.2 (d, $J_{CP}$ = 8.0 Hz, OCH$_2$CH$_3$), 101.1 (s, OCH$_2$O), 107.7, 110.6, 123.8, 130.0, 147.1, 147.2, 174.0 (s, COOH); $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ = 21.5 (d, $J_{PP}$ = 80.0 Hz, 1P), 23.6 (d, $J_{PP}$ = 92.0 Hz, 1P); CI MS, m/z (%) pos 384 (100), 206 (10); neg 520 (100) [M-H], 382 (20), 338 (10), 271 (15), 125 (15), 101 (40).

2-(2,2-Bis(diethoxyphosphoryl)pyrrolidin-1-yl)-2-(thiophen-2-yl)acetic acid (4d). Prepared similarly to 4a from tetraethyl pyrrrolidine-2,2-diylidiphosphonate 3 (343 mg, 1.00 mmol), 2-thiopheneboronic acid (128 mg, 1.00 mmol) and glyoxylic acid (92 mg, 1.00 mmol). Yield 390 mg (80%). Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 1.05 (t, 3H, OCH$_2$CH$_3$), 1.15 (t, 3H, OCH$_2$CH$_3$), 1.30 (t, 3H, OCH$_2$CH$_3$), 1.31 (t, 3H, OCH$_2$CH$_3$), 1.77 - 1.84 (m, 2H, CH$_2$), 2.19 (m, 2H, CH$_2$), 3.01 - 3.07 (m, 1H, CH$_2$), 3.17 - 3.23 (m, 1H, CH$_2$), 3.78 - 3.88 (m, 1H, OCH$_2$CH$_3$), 3.90 - 4.10 (m, 3H, OCH$_2$CH$_3$), 4.14 - 4.26 (m, 4H, OCH$_2$CH$_3$), 5.83 (s, 1H, CHCOOH), 6.87 (d, $J_{HH}$ = 3.7 Hz, 1H, 1H, $H_{\text{thiophene}}$), 7.08 (dd, $J_{HH}$ = 1.0Hz, $J_{HH}$ = 3.7Hz, 1H, $H_{\text{thiophene}}$), 7.20 (dd, $J_{HH}$ = 1.0Hz, $J_{HH}$ = 5.1Hz, 1H, $H_{\text{thiophene}}$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 16.2 (d, $J_{CP}$ = 6.0 Hz, OCH$_2$CH$_3$), 16.5 (d, $J_{CP}$ = 6.0 Hz, OCH$_2$CH$_3$), 16.5 (d, $J_{CP}$ = 6.0 Hz, OCH$_2$CH$_3$), 16.6 (d, $J_{CP}$ = 6.0 Hz, OCH$_2$CH$_3$), 24.0 (t, $J_{CP}$ = 3.0 Hz, CH$_2$), 32.3 (t, $J_{CP}$ = 4.0 Hz, CH$_2$), 48.1 (d, $J_{CP}$ = 4.0 Hz, CH$_2$), 59.8 (s, CHCOOH), 62.3 (d, $J_{CP}$ = 7.0 Hz, OCH$_2$CH$_3$), 63.2 (d, $J_{CP}$ = 7.0 Hz, OCH$_2$CH$_3$), 63.5 (d, $J_{CP}$ = 7.0 Hz, OCH$_2$CH$_3$), 65.3 (d, $J_{CP}$ = 150.0 Hz, $J_{CP}$ = 150.0 Hz, PCP), 64.6 (d, $J_{CP}$ = 7.0 Hz, OCH$_2$CH$_3$), 125.9, 125.9, 128.7, 138.3, 172.5 (s, COOH); $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ = 20.8 (d, $J_{PP}$ = 92.3Hz, 1P), 23.3 (d, $J_{CP}$ = 92.3Hz, 1P); CI MS, m/z (%) pos 346 (100), 206 (15); neg 482 (100) [M-H], 438 (10), 328 (10), 233 (40), 138 (10), 103 (30), 85 (45). Anal. Calcd for C$_{14}$H$_{15}$NO$_3$P$_2$: C, 44.72; H, 6.46, N, 2.90, S, 6.63. Found: C, 44.61; H, 6.41; N, 2.87; S, 6.68.
(E)-2-((R)-2-(Diethoxyphosphoryl)-2,2-difluoro-1-phenylethylamino)-4-phenylbut-3-enoic acid (7a) (major diastereomer). To a stirred suspension of glyoxylic acid monohydrate (47 mg, 0.51 mmol) in dichloromethane (3 mL) aminophosphonate 6 (147 mg, 0.50 mmol) was added dropwise, after 5 min (E)-2-phenylethenyl boronic acid (74 mg, 0.50 mmol) was added in one portion and the reaction mixture was stirred for 24 h while monitored by TLC (5% methanol in chloroform). The solvent was evaporated and the residual oil was chromatographed using gradient of isopropanol (7-13%) in dichloromethane to yield 7a in 55% summary yield. Yield 79 mg (35%). Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 1.25 (t, 3H, OCH$_2$C$_6$H$_3$), 1.31 (t, 3H, OCH$_2$C$_6$H$_3$), 3.93 (d, $J_{HH}$ = 7.3 Hz 1H, PhCOOH), 4.02 - 4.31 (m, 4H, OC$_2$H$_2$CH$_3$), 4.35 (ddd, $J_{HF}$ = 20.6 Hz, $J_{HP}$ = 7.6 Hz, 1H, CF$_2$CH), 6.03 (dd, $J_{HH}$ = 15.9 Hz, 1H, PhCH=CH), 6.52 (d, $J_{HH}$ = 15.9 Hz, 1H, PhCH=CH), 7.16 - 7.39 (m, 10H, H$_7$Ph); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = -122.53 (ddd, $J_{FF}$ = 304.0 Hz, $J_{FP}$ = 108.0 Hz, $J_{FH}$ = 20.6 Hz, 1F), -112.51 (ddd, $J_{FF}$ = 304.0 Hz, $J_{FP}$ = 104.0 Hz, $J_{FH}$ = 7.6 Hz, 1F); $^{19}$P NMR (162 MHz, CDCl$_3$) $\delta$ = 7.6 (dd, $J_{PF}$ = 108.0 Hz, $J_{PP}$ = 104.0 Hz).

(E)-2-((R)-2-(Diethoxyphosphoryl)-2,2-difluoro-1-phenylethylamino)-4-phenylbut-3-enoic acid (7a) (minor diastereomer). Yield 45 mg (20%). Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 1.19 (t, OCH$_2$C$_6$H$_3$), 1.29 (t, $J_{HH}$ = 7.0Hz, 3H, OCH$_2$C$_6$H$_3$), 3.81 (d, $J_{HH}$ = 8.1Hz, 1H, CHCOOH), 4.03 - 4.31 (m, 4H, OCH$_2$C$_6$H$_3$), 4.35 (ddd, $J_{HH}$ = 22.6Hz, $J_{HP}$ = 23.0 Hz, 1H, CF$_2$CH), 6.15 (dd, $J_{HH}$ = 15.8 Hz, $J_{HH}$ = 8.1 Hz, 1H, PhCH=CH), 6.53 (d, $J_{HH}$ = 15.8 Hz, 1H, PhCH=CH), 7.18 - 7.39 (m, 10H, H$_7$Ph); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = -121.1 (ddd, $J_{FF}$ = 304.0 Hz, $J_{FP}$ = 108.0 Hz, $J_{FH}$ = 22.6 Hz, 1F), -110.2 (ddd, $J_{FF}$ = 304.0 Hz, $J_{FP}$ = 100.0 Hz, $J_{FH}$ = 7.6 Hz, 1F); $^{19}$P NMR (162 MHz, CDCl$_3$) $\delta$ = 7.3 (dd, $J_{PF}$ = 108.0 Hz, $J_{PP}$ = 100.0 Hz).

(E)-2-((R)-2-(Diethoxyphosphoryl)-2,2-difluoro-1-phenylethylamino)-2-methyl-4-phenylbut-3-enoic acid (7b) (major diastereomer). Prepared similary to 7a from 6 (147 mg, 0.50 mmol), (E)-styrylboronic acid (74 mg, 0.50 mmol) and pyruvic acid (44 mg, 0.50 mmol) in 49% summary yield (110 mg). Only major diastereomer was obtained in individual form, yield 35 mg (15%). White solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 1.26 (t, 3H, OCH$_2$C$_6$H$_3$), 1.32 (t, 3H, OCH$_2$C$_6$H$_3$), 1.50 (s, 3H, CH$_3$), 4.09 - 4.33 (m, 4H, OCH$_2$C$_6$H$_3$), 4.38 (dd, $J_{HH}$ = 23.0 Hz, $J_{HF}$ = 8.0 Hz, 1H, CF$_2$CH), 5.94 (d, $J_{HH}$ = 16.0 Hz, 1H, PhCH=CH), 6.48 (d, $J_{HH}$ = 16.0 Hz, 1H, PhCH=CH), 6.40 (bs, NH), 7.07 (d, $J_{HH}$ = 7.0 Hz, 2H, H$_7$Ph), 7.18 - 7.39 (m, 8H, H$_7$Ph); $^{13}$C NMR (100 MHz, 100 MHZ, CDCl$_3$) $\delta$ = 16.3 (m, OCH$_2$C$_6$H$_3$), 22.2 (s, CH$_3$), 63.5 (s, CHCOOH), 64.7 (d, $J_{CP}$ = 7.0 Hz, OCH$_2$C$_6$H$_3$), 65.2 (d, $J_{CP}$ = 7.0Hz, OCH$_2$C$_6$H$_3$), 126.7, 128.07, 128.5, 128.6, 129.1, 130.9, 131.5, 136.1; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = -121.6 (ddd, $J_{FF}$ = 304.0 Hz, $J_{FP}$ = 108.0 Hz, $J_{FH}$ = 23.0 Hz, 1F), -110.6 (ddd, $J_{FF}$ = 304.0 Hz, $J_{FP}$ = 104.0 Hz, $J_{FH}$ = 8.0 Hz, 1F); $^{19}$P NMR (162 MHz, CDCl$_3$) $\delta$ = 6.7 (dd, $J_{PF}$ = 108.0 Hz, $J_{PP}$ = 104.0 Hz). Anal. Calcd for C$_{23}$H$_{28}$F$_2$NO$_5$P: C, 59.10; H, 6.04. Found: C, 59.06; H, 6.14.
References

1. Diethyl 1-amino-(4-methoxyphenyl)methylphosphonate 1a: Synthesis, 1994, 763-764;
2. Diethyl 1-(N-benzylamino)-1-phenylmethylphosphonate 1b: Solution of benzaldehyde (2.32 mL, 22.87 mmol) and benzylamine (2.50 mL, 22.87 mmol) in dichloromethane (30 mL) was stirred with anhydrous sodium sulfate (5.5 g, 38.73 mmol) overnight. After filtration of inorganic solid and evaporation of solvent the residual oil was distilled (90-92 °C/0.05 mm) to yield (3.53 g, 79%) of imine. The imine (3.53 g, 18.07 mmol) was heated with diethylphosphite (2.5 g, 18.07 mmol) for 8 h at 70-80 °C while monitored by $^{31}$P NMR. After cooling to an ambient temperature the reaction mixture was treated with the solution of oxalic acid (3.26 g, 36.16 mmol) in anhydrous acetone (25 mL). The resulting precipitate was filtered, washed with acetone and dried in vacuum to yield 6.57 g of 1b oxalate. The oxalate was dissolved in water (20 mL) and treated with saturated aqueous solution of sodium carbonate till pH 10. Water layer was extracted with dichloromethane (4 x 15 mL), the extract was washed with brine (10 mL) and dried over anhydrous sodium sulfate. After evaporation of the solvent aminophosphonate 1b was obtained as colorless viscous oil (5.3 g, 85%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.13 (t, 3H, OCH$_2$CH$_3$), 1.27 (t, 3H, OCH$_2$CH$_3$), 2.32 (bs, 1H, NH), 3.54 (d, $J_{HH} = 13.1$ Hz, 1H, PhCH$_2$), 3.81 (d, $J_{HH} = 13.1$ Hz, 1H, PhCH$_2$), 3.91 – 4.13 (m, 4H, OCH$_2$CH$_3$), 4.03 (d, $J_{HH} = 20$ Hz, 1H, PhCHP); $^{31}$P NMR (81 MHz, acetone): $\delta = 24.08$.