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Organocatalytic Biomimetic Approach to α-Aminophosphonates

by

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Supporting Information

1. General methods

NMR spectra were acquired on a Bruker Ultra Shield 700 instrument, running at 700 MHz for ^{1}H and 176 MHz for ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$: 7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR). ^{31}P NMR spectra were recorded on a Bruker Avance DPX 250 spectrometer at room temperature in $CDCl_3$ as a solvent using 85% H_3PO_4 as external standard. Mass spectra were recorded on a Bruker Maxis Impact spectrometer using electrospray (ES+) ionization (referenced to the mass of the charged species, due to the acidic conditions of the analysis in the mass spectra of the products **7** only the molecular peaks of the corresponding free amines **3** were observed and therefore are reported). Optical rotations were measured on a Perkin-Elmer 241 polarimeter and $[\alpha]_D$ values are given in $deg \cdot cm \cdot g^{-1} \cdot dm^{-1}$; concentration *c* is listed in $g \cdot (100\ mL)^{-1}$. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or I_2 stain. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak IC column). Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. For flash chromatography (FC) silica gel (Silica gel 60, 230-400 mesh, Fluka). Acylphosphonates **1** were prepared according to literature procedures.[1] Cinchona-alkaloid-derived catalysts **10d**[2] and **10e**-**f**[3] were synthesized following the literature procedures.

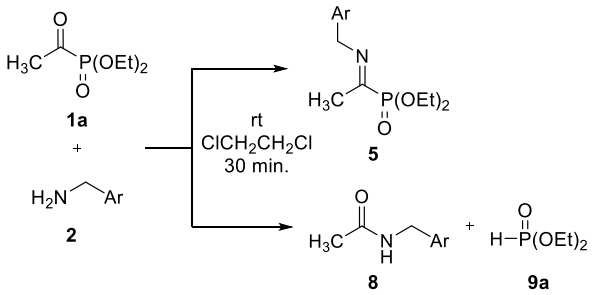
[1] (a) J. Zon, *Synthesis* 1984, **4**, 324; (b) H. Maeda, K. Takahashi and H. Ohmori, *Tetrahedron* 1998, **54**, 12233; (c) S. M. A. Kedrowski and D. A. Dougherty, *Org. Lett.* 2010, **12**, 3990.

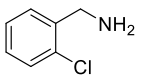
[2] W. Yang and D.-M. Du, *Org. Lett*. 2010, **12**, 5450.

[3] X. Liu, H. Li and L. Deng, *Org. Lett*. 2005, **7**, 167.

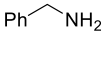
2. Screening results

2.1. Benzylamine screening[a]





2a



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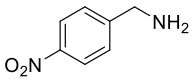

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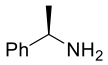
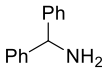


2d

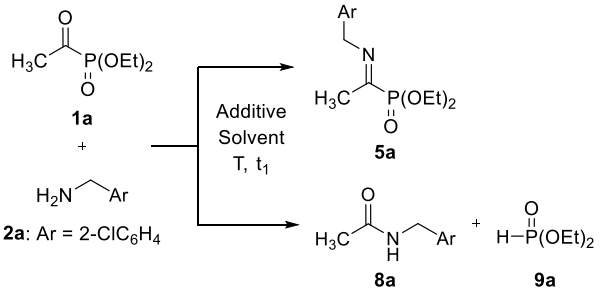


2e

Entry	Amine	**1a**:**5**:**9a** ratio[b]	Conversion [%][c]
1	**2a**	0:1:4	20
2	**2b**	0:0:1	0
3	**2c**	2:2:7	18
4	**2d**	0:2:13	13
5	**2e**	0:1:5	17

[a] Reactions performed on a 0.1 mmol scale. [b] As determined by a ^{31}P NMR of a crude reaction mixture. [c] Conversion into the desired product **5** is given.

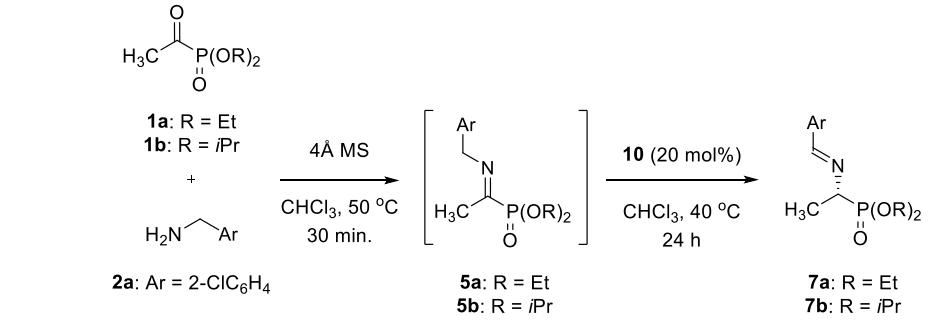
2.2. Condensation reaction conditions screening[a]

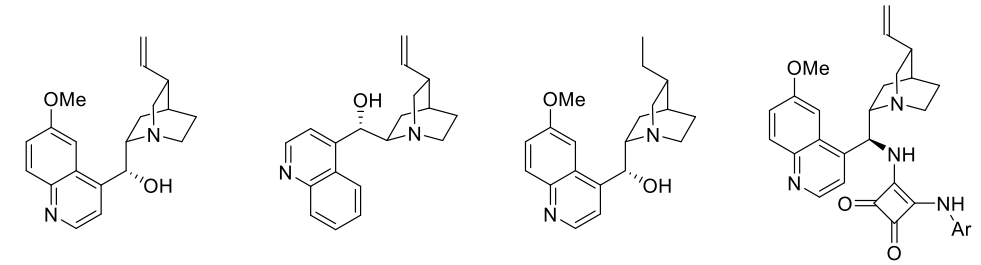


Entry	Solvent	T [°C]	Additive	t_1 [min]	**1a**:**5a**:**9a** ratio[b]	Conversion [%][c]
1	$ClCH_2CH_2Cl$	-40	-	30	0:0:1	0
2	$ClCH_2CH_2Cl$	0	-	30	0:0:1	0
3	$ClCH_2CH_2Cl$	rt	-	30	0:1:5	20
4	$ClCH_2CH_2Cl$	40	-	30	0:1:3	25
5	$ClCH_2CH_2Cl$	50	-	30	0:1:2	33
6	$ClCH_2CH_2Cl$	60	-	30	0:1:3	25
7	CH_2Cl_2	50	-	30	0:2:3	40
8	$CHCl_3$	50	-	30	0:1:1	50
9	THF	50	-	30	0:1:3	25
10	Toluene	50	-	30	0:1:3	25
11	Benzene	50	-	30	0:1:5	17
12	$CHCl_3$	50	MS 4Å	30	0:3:1	75
13	$CHCl_3$	50	$MgSO_4$	30	0:2:1	67
14	$CHCl_3$	50	MS 4Å	1	13:4:1	22
15	$CHCl_3$	50	MS 4Å	10	5:4:1	40
16	$CHCl_3$	50	MS 4Å	60	0:2:8	18

[a] Reactions performed on a 0.1 mmol scale. [b] As determined by a ^{31}P NMR of a crude reaction mixture.
[c] Conversion into the desired product **5a** is given.

2.3. Isomerization reaction catalyst screening



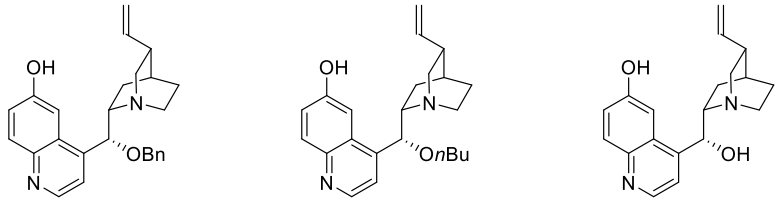


10a
7a: n.d. yield, 48% ee
7b: 42% yield, 59% ee

10b
7b: 45% yield, -69% ee

10c
7b: 40% yield, 10% ee

10d
Ar: $(CF_3)_2C_6H_3$
7b: 40% yield, 95% ee



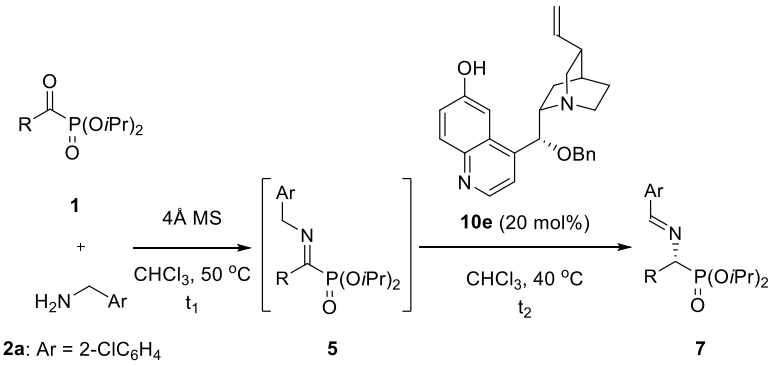
10e
7b: 55% yield, 96% ee

10f
7b: 48% yield, 94% ee

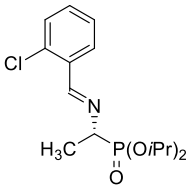
10g
7b: 50% yield, 72% ee

Reactions performed on a 0.1 mmol scale. Isolated yields over two steps are given. Enantiomeric excesses as determined by the chiral stationary phase HPLC.

3. Biomimetic asymmetric synthesis of α-aminophosphonates 7 – general procedure

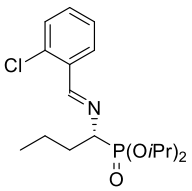


An ordinary screw-cap vial was charged with a magnetic stirring bar, the corresponding acylphosphonate **1** (0.2 mmol, 1 equiv), $CHCl_3$ (0.4 mL), 2-chlorobenzylamine **2a** (0.2 mmol, 1 equiv) and powdered molecular sieves 4Å (100 mg). The resulting mixture was heated at 50 °C for a given time (t_1 - reaction progress was monitored by ^{31}P NMR spectroscopy). After cooling the reaction mixture to room temperature, catalyst **10e** (0.02 mmol, 0.2 equiv) was added. Subsequent heating of the reaction at 40 °C for a given time (t_2 - reaction progress was monitored by ^{31}P NMR spectroscopy) resulted in a complete consumption of the *N*-benzylimine **5**. The crude reaction mixture was directly purified by FC on silica gel to afford target product **7**.



7b (*R*,*E*)-Diisopropyl (1-((2-chlorobenzylidene)amino)ethyl)phosphonate (Table 2, entry 1)

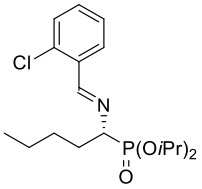
Following the general procedure, **7b** was isolated by FC on silica (hexane/EtOAc 3:1) in 55% yield as a pale-yellow oil (t_1 = 30 min; t_2 = 24 h). ^1H NMR (700 MHz, $CDCl_3$) δ 8.67 (d, *J* = 4.9 Hz, 1H), 7.97 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.37 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.34 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.28 (dt, *J* = 7.8, 0.9 Hz, 1H), 4.74 (ddt, *J* = 12.5, 7.4, 6.2 Hz, 2H), 3.87 (dq, *J* = 13.5, 6.8 Hz, 1H), 1.56 (dd, *J* = 17.9, 6.9 Hz, 3H), 1.37 (d, *J* = 6.2 Hz, 3H), 1.34 (d, *J* = 6.2 Hz, 3H), 1.32 (d, *J* = 6.2 Hz, 3H), 1.27 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 160.0 (d, *J* = 16.9 Hz), 135.5, 133.1 (d, *J* = 3.2 Hz), 131.9, 129.9, 128.7, 127.1, 71.1 (d, *J* = 7.2 Hz, 2C), 64.5(d, *J* = 158.7 Hz), 24.4 (d, *J* = 3.4 Hz), 24.3 (d, *J* = 3.4 Hz), 24.1 (d, *J* = 5.0 Hz, 2C), 17.0 (d, *J* = 5.6 Hz).^{31}P NMR (101 MHz, $CDCl_3$) δ 22.6. HRMS calculated for $[C_{15}H_{23}ClNO_3P\text{-}C_7H_3Cl+H]^+$: 210.1259; found: 210.1255. The ee was determined by HPLC using a Chiralpak IC column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 9.0 min, τ_{minor} = 7.5 min (96% *ee*). $[\alpha]^{20}_D$ = -1.2 (*c* = 1.23, $CHCl_3$).



7c (*R*,*E*)-Diisopropyl (1-((2-chlorobenzylidene)amino)butyl)phosphonate (Table 2, entry 2)

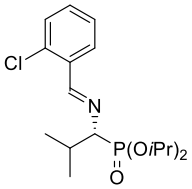
Following the general procedure, **7c** was isolated by FC on silica (hexane/EtOAc 3:1) in 59% yield as a pale-yellow oil (t_1 = 120 min; t_2 = 30 h). ^1H NMR (700 MHz, $CDCl_3$) δ 8.70 (d, *J* = 5.1 Hz, 1H), 8.06 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.36 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.33 (dt, *J* = 8.1, 1.8 Hz, 1H), 7.28 (dt, *J* = 7.2, 1.0 Hz, 1H), 4.71 - 4.74 (m, 2H), 3.65 (ddd, *J* = 13.4, 10.5, 3.0 Hz, 1H), 2.05 – 1.88 (m, 2H), 1.41 – 1.36 (m, 1H), 1.35 (d, *J* = 6.2 Hz, 3H), 1.33 (d, *J* = 6.2 Hz, 3H), 1.31 (d, *J* = 6.2 Hz, 3H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.23 – 1.16 (m, 1H), 0.91 (t, *J* = 7.4 Hz, 3H).^{13}C NMR (176

MHz, $CDCl_3$) δ 160.6 (d, *J* = 17.2 Hz), 135.3, 133.1 (d, *J* = 3.2 Hz), 131.8, 129.9, 128.8, 127.1, 71.0 (d, *J* = 7.4 Hz), 70.9 (d, *J* = 6.9 Hz),69.7 (d, *J* = 157.2 Hz), 32.2 (d, *J* = 4.6 Hz), 24.3 (d, *J* = 3.4 Hz), 24.2 (d, *J* = 3.4 Hz), 24.1 (d, *J* = 4.5 Hz), 24.1 (d, *J* = 4.5 Hz), 20.0 (d, *J* = 15.5 Hz), 13.6.^{31}P NMR (101 MHz, $CDCl_3$) δ 22.9. HRMS calculated for $[C_{17}H_{27}ClNO_3P\text{-}C_7H_3Cl+H]^+$: 238.1567; found: 238.1568. The ee was determined by HPLC using a Chiralpak IC column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 7.1 min, τ_{minor} = 5.2 min (92% *ee*). $[\alpha]^{20}_D$ = -4.3 (*c* = 0.98, $CHCl_3$).



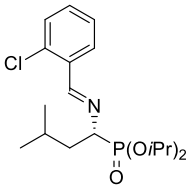
7d (*R*,*E*)-Diisopropyl (1-((2-chlorobenzylidene)amino)pentyl)phosphonate (Table 2, entry 3)

Following the general procedure, **7d** was isolated by FC on silica (hexane/EtOAc 3:1) in 56% yield as a pale-yellow oil (t_1 = 120 min; t_2 = 30 h). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.69 (d, *J* = 4.9 Hz, 1H), 8.06 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.36 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.34 (dt, *J* = 8.0, 1.7 Hz, 1H), 7.28 (dt, *J* = 7.7, 1.6 Hz, 1H), 4.67– 4.79 (m, 2H), 3.63 (dt, *J* = 13.4, 6.7 Hz, 1H), 2.04 – 1.93 (m, 2H), 1.35 (d, *J* = 6.2 Hz, 3H), 1.33 (d, *J* = 6.2 Hz, 3H), 1.30 (d, *J* = 6.2 Hz, 3H), 1.27-1.34 (m, 3H), 1.24 (d, *J* = 6.1 Hz, 3H), 1.17 (dt, *J* = 7.5, 4.1 Hz, 1H), 0.87 (dt, *J* = 7.2, 1.8 Hz, 3H).^{13}C NMR (176 MHz, $CDCl_3$) δ 160.5 (d, *J* = 17.1 Hz), 135.4, 133.1 (d, *J* = 3.3 Hz), 131.8, 129.9, 128.8, 127.1, 71.0 (d, *J* = 7.2 Hz), 70.9 (d, *J* = 6.9 Hz), 70,0 (d, *J* = 157.0 Hz), 29.9 (d, *J* = 4.4 Hz), 29.1 (d, *J* = 15.0 Hz), 24.3 (d, *J* = 3.4 Hz), 24.3 (d, *J*= 3.5 Hz), 24.1 (d, *J* = 4.6 Hz), 24.1 (d, *J* = 4.6 Hz), 22.3, 14.0.^{31}P NMR (101 MHz, $CDCl_3$) δ 22.8. HRMS calculated for $[C_{18}H_{29}ClNO_3P\text{-}C_7H_3Cl+H]^+$: 252.1723; found: 252.1726. The ee was determined by HPLC using a Chiralpak IC column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 6.5 min, τ_{minor} = 5.0 min (90% *ee*). $[\alpha]^{20}_D$ = -2.1 (*c* = 1.33, $CHCl_3$).



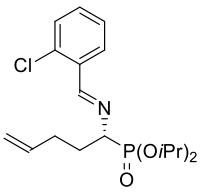
7e (*R*,*E*)-Diisopropyl (1-((2-chlorobenzylidene)amino)-2-methylpropyl)phosphonate (Table 2, entry 4)

Following the general procedure, **7e** was isolated by FC on silica (hexane/EtOAc 3:1) in 20% yield as a pale-yellow oil (t_1 = 120 min; t_2 = 30 h). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.67 (d, *J* = 4.9 Hz, 1H), 8.09 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.37 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.34 (td, *J* = 7.5, 1.7 Hz, 1H), 7.28 (td, *J* = 7.5, 1.5 Hz, 1H), 4.79 – 4.65 (m, 2H), 3.44 (dd, *J* = 13.4, 5.3 Hz, 1H), 2.43 (m, 1H), 1.34 (d, *J* = 6.2 Hz, 3H), 1.32 (d, *J* = 5.8 Hz, 3H), 1.31 (d, *J* = 5.8 Hz, 3H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 160.6 (d, *J* = 17.2 Hz), 135.4, 133.2 (d, *J* = 3.3 Hz), 131.8, 129.9, 128.8, 127.1, 76.0 (d, *J* = 156.0 Hz), 71.0 (d, *J* = 7.4 Hz), 70.7 (d, *J*= 7.1 Hz), 30.0 (d, *J* = 3.3 Hz), 24.4 (d, *J* = 3.3 Hz), 24.3 (d, *J* = 3.3 Hz), 24.2 (d, *J* = 5.4 Hz), 24.1 (d, *J* = 5.3 Hz), 21.3 (d, *J* = 10.7 Hz), 19.4 (d, *J* = 7.3 Hz).^{31}P NMR (101 MHz, $CDCl_3$) δ 23.0. HRMS calculated for $[C_{17}H_{27}ClNO_3P\text{-}C_7H_3Cl+H]^+$: 238.1567; found: 238.1568. The ee was determined by HPLC using a Chiralpak IC column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 6.1 min, τ_{minor} = 5.0 min (72% ee). $[\alpha]^{20}_D$ = -5.8 (*c* = 0.84, $CHCl_3$).



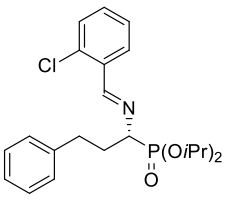
7f (*R*,*E*)-Diisopropyl (1-((2-chlorobenzylidene)amino)-3-methylbutyl)phosphonate (Table 2, entry 5)

Following the general procedure, **7f** was isolated by FC on silica (hexane/EtOAc 3:1) in 62% yield as a pale-yellow oil (t_1 = 180 min; t_2 = 24 h). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.72 (d, *J* = 5.2 Hz, 1H), 8.06 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.37 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.34 (dt, *J* = 7.1, 1.7 Hz, 1H), 7.28 (dt, *J* = 7.5, 0.9 Hz, 1H), 4.72 (m, 2H), 3.78 (ddd, *J* = 14.1, 11.3, 2.7 Hz, 1H), 2.05-2.10 (m, 1H), 1.66-1.71 (m, 1H), 1.57 – 1.49 (m, 1H), 1.36 (d, *J* = 6.2 Hz, 3H), 1.33 (d, *J* = 6.2 Hz, 3H), 1.31 (d, *J* = 6.2 Hz, 3H), 1.24 (d, *J* = 6.2 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H).^{13}C NMR (176 MHz, $CDCl_3$) δ 160.6 (d, *J* = 16.5 Hz), 135.3, 133.2 (d, *J* = 3.3 Hz), 131.8, 129.9, 128.8, 127.1, 71.1 (d, *J* = 7.3 Hz), 71.0 (d, *J* = 6.8 Hz), 67.8 (d, *J* = 156.9 Hz), 38.7 (d, *J* = 4.5 Hz), 24.7 (d, *J* = 14.9 Hz), 24.3 (d, *J* = 4.1 Hz), 24.3 (d, *J* = 4.1 Hz), 24.1 (d, *J* = 5.1 Hz), 24.1 (d, *J* = 5.1 Hz), 23.7 (d, *J* = 11.3 Hz), 20.6 (d, *J* = 8.2 Hz). ^{31}P NMR (101 MHz, $CDCl_3$) δ 23.3. HRMS calculated for $[C_{18}H_{29}ClNO_3P\text{-}C_7H_3Cl+H]^+$: 252.1723; found: 252.1726. The ee was determined by HPLC using a Chiralpak IC column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 5.7 min, τ_{minor} = 4.7 min (91% ee). $[\alpha]^{20}_D$ = -12.1 (*c* = 1.59, $CHCl_3$).



7g (*R*,*E*)-Diisopropyl (1-((2-chlorobenzylidene)amino)pent-4-en-1-yl)phosphonate (Table 2, entry 6)

Following the general procedure, **7g** was isolated by FC on silica (hexane/EtOAc 3:1) in 63% yield as a pale-yellow oil (t_1 = 180 min; t_2 = 24 h). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.70 (d, *J* = 5.0 Hz, 1H), 8.06 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.37 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.34 (td, *J* = 8.0, 1.7 Hz, 1H), 7.28 (td, *J* = 7.5, 1.4 Hz, 1H), 5.84 – 5.63 (m, 1H), 5.03 – 4.97 (m, 2H), 4.85 – 4.64 (m, 2H), 3.70 (ddd, *J* = 13.3, 10.2, 3.1 Hz, 1H), 2.34 – 2.02 (m, 3H), 1.98 – 1.91 (m, 1H), 1.35 (d, *J* = 6.2 Hz, 3H), 1.33 (d, *J* = 6.2 Hz, 3H), 1.31 (d, *J* = 6.2 Hz, 3H), 1.25 (d, *J* = 6.2 Hz, 3H).^{13}C NMR (176 MHz, $CDCl_3$) δ 161.2 (d, *J* = 16.8 Hz), 137.4, 135.4, 133.1 (d, *J* = 3.1 Hz), 131.9, 129.9, 128.7, 127.1, 115.8, 71.1 (d, *J* = 5.8 Hz), 71,0 (d, *J* = 5.6 Hz), 68.9 (d, *J* = 154.9 Hz), 30.7 (d, *J* = 15.6 Hz), 29.2 (d, *J* = 4.0 Hz), 24.3 (d, *J* = 3.3 Hz), 24.2 (d, *J* = 3.7 Hz), 24.1 (d, *J* = 4.1 Hz), 24.1 (d, *J* = 4.2 Hz).^{31}P NMR (101 MHz, $CDCl_3$) δ 22.6. HRMS calculated for $[C_{18}H_{27}ClNO_3P\text{-}C_7H_3Cl+H]^+$: 250.1567; found: 250.1571. The ee was determined by HPLC using a Chiralpak IC column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 6.5 min, τ_{minor} = 5.2 min (95% ee). $[\alpha]^{20}_D$ = -3.0 (*c* = 1.46, $CHCl_3$).

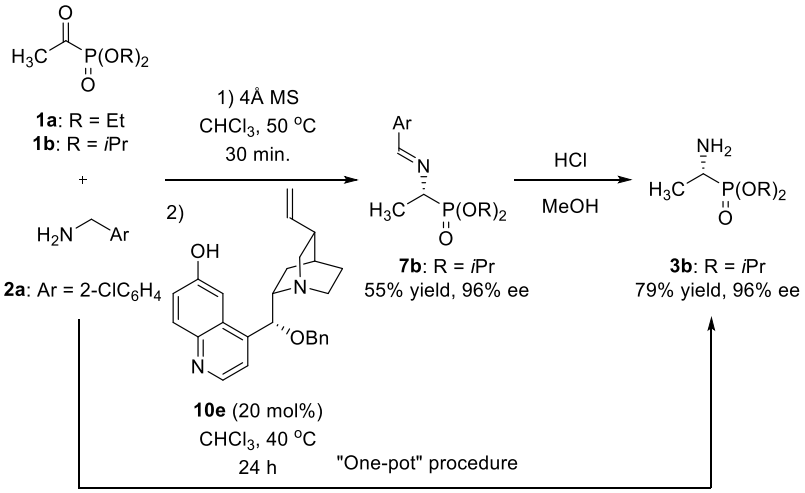


7h (*R*,*E*)-Diisopropyl (1-((2-chlorobenzylidene)amino)-3-phenylpropyl)phosphonate (Table 2, entry 7)

Following the general procedure, **7h** was isolated by FC on silica (hexane/EtOAc 3:1) in 40% yield as a pale-yellow oil (t_1 = 30 min; t_2 = 30 h). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.68 (d, *J* = 5.0 Hz, 1H), 8.09 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.38 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.35 (dt, *J* = 7.6, 1.7 Hz, 1H), 7.30 (dt, *J* = 7.5, 1.4 Hz, 1H), 7.28 – 7.24 (m, 2H), 7.18 – 7.14 (m, 3H), 4.74 – 4.65 (m, 2H), 3.64 (ddd, *J* = 13.5, 10.3, 3.1 Hz, 1H), 2.73 (ddd, *J* = 14.0, 9.1, 4.9 Hz, 1H), 2.49 (dt, *J* = 13.9, 8.4 Hz, 1H), 2.41 – 2.25 (m, 2H), 1.34 (d, *J* = 6.2 Hz, 3H), 1.31 (d, *J* = 6.2 Hz, 3H), 1.29 (d, *J* = 6.2 Hz, 3H), 1.21 (d, *J* = 6.2 Hz, 3H).^{13}C NMR (176 MHz, $CDCl_3$) δ 161.36 (d, *J* = 16.5 Hz), 141.0, 135.5, 133.1 (d, *J* = 3.3 Hz), 132.0, 129.9, 128.8, 128.7 (2C), 128.6 (2C), 127.1, 126.1, 71.1 (d, *J* = 4.0 Hz), 71.0

(d, *J* = 3.6 Hz), 68.8 (d, *J* = 156.9 Hz), 32.8 (d, *J* = 15.7 Hz), 31.6 (d, *J* = 3.9 Hz), 24.3 (d, *J* = 3.5 Hz), 24.2 (d, *J* = 3.8 Hz), 24.2 (d, *J* = 5.1 Hz), 24.1 (d, *J* = 5.1 Hz). ^{31}P NMR (101 MHz, $CDCl_3$) δ 22.4. HRMS calculated for $[C_{22}H_{29}ClNO_3P\text{-}C_7H_3Cl+H]^+$: 300.1723; found: 300.1729. The ee was determined by HPLC using a Chiralpak IC column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 7.4 min, τ_{minor} = 6.0 min (94% ee). $[\alpha]^{20}_D$ = -15.6 (*c* = 1.70, $CHCl_3$).

4. Biomimetic asymmetric synthesis of α-aminophosphonates 3 – general procedure



3a: R = Et
73% yield, 89% ee

3b: R = *i*Pr
74% yield, 96% ee
$[\alpha]_D^{rt}$: -2.5 (c = 1.15, MeOH)
lit. $[\alpha]_D^{rt}$: -1.5 (c = 0.85, MeOH) ref. 4 (ESI)

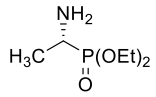
"Step-wise" procedure

An ordinary screw-cap vial was charged with a magnetic stirring bar, aminophosphonate **7b** (0.1 mmol, 1 equiv), MeOH (0.5 mL) and aqueous 1N HCl (0.5 mL). Upon stirring at room temperature for 2 h, the resulting mixture was extracted with hexane (3x5 mL). The combined organic phases were washed with 1N HCl (0.5 mL). The aqueous phases were combined, brought to pH 8.0 with solid $NaHCO_3$, extracted with CH_2Cl_2 (3x5 mL), dired $MgSO_4$, filtered, concentrated and subjected to FC on silica gel to give α-aminophosphonate **3b**.

"One-pot" procedure

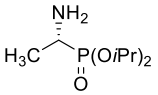
An ordinary screw-cap vial was charged with a magnetic stirring bar, the corresponding acylphosphonate **1a** or **1b** (0.2 mmol, 1 equiv.), $CHCl_3$ (0.4 mL), 2-chlorobenzylamine **2a** (0.2 mmol, 1 equiv.) and powdered molecular sieves 4Å (100 mg). The resulting mixture was heated at 50 °C for 30 min. After cooling the reaction mixture to room temperature, catalyst **10e** (0.02 mmol, 0.2 equiv) was added. Subsequent heating of the reaction at 40 °C for 24 h resulted in a complete consumption of the imine **7**. Subsequently, the reaction mixture was filtered to remove molecular sieves and concentrated. The resulting residue was dissolved in MeOH (1 mL) and aqueous 1N HCl (1 mL) was added. Upon stirring at room temperature for 2 h, the resulting mixture was extracted with hexane (3x5 mL). The combined organic phases were washed with 1N HCl (1 mL). The aqueous phases were combined, brought to pH 8.0 with solid $NaHCO_3$, extracted with CH_2Cl_2 (3x5 mL), dired $MgSO_4$, filtered, concentrated and subjected to FC on silica gel to give α-aminophosphonates **3**.

3a (*R*)-Diethyl (1-aminoethyl)phosphonate (Scheme 5)



Following the general "one-pot" procedure, **3a** was isolated by FC on silica (CH_2Cl_2/MeOH 20:1) in 73% yield as a pale-yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.21 – 4.06 (m, 4H), 3.10 (dq, J = 9.0, 7.2 Hz, 1H), 1.36 – 1.31 (m, 9H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 62.3 (d, J = 4.9 Hz), 62.25 (d, J = 4.5 Hz), 44.4 (d, J = 149.3 Hz), 17.4, 16.7 (d, J = 5.5 Hz, 2C). ^{31}P NMR (101 MHz, $CDCl_3$) δ 30.5. HRMS calculated for $[C_6H_{16}NO_3P+H]^+$: 182.0941; found: 182.0944. The ee was determined by HPLC using a Chiralpak IC column [hexane/*i*PrOH (70:30)]; flow rate 1.0 mL/min; τ_{major} = 13.1 min, τ_{minor} = 11.8 min (89% ee). $[\alpha]^{20}_D$ = -4.3 (*c* = 0.64, $CHCl_3$).

3b (*R*)-Diisopropyl (1-aminoethyl)phosphonate (Scheme 5)



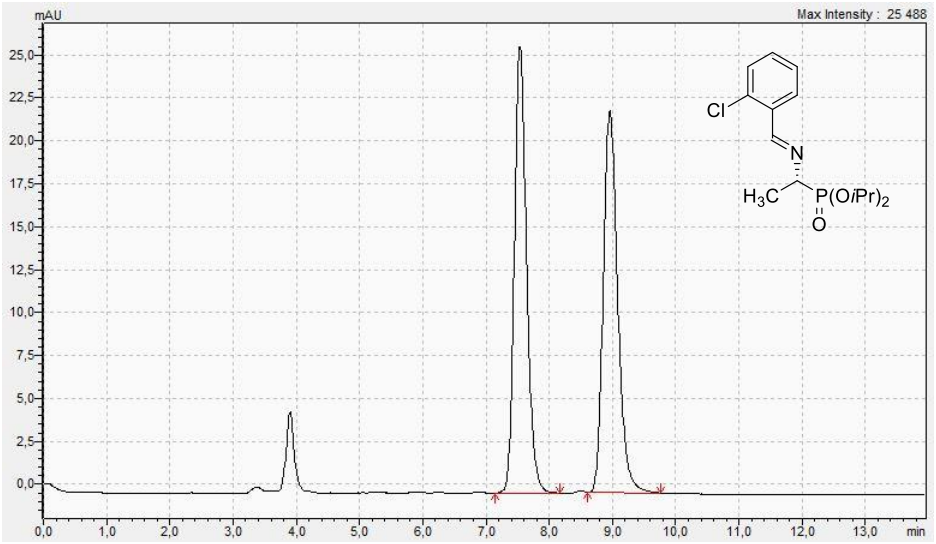
Following either the general "step-wise" or "one-pot" procedure, **3b** was isolated by FC on silica (CH_2Cl_2/MeOH 20:1) in 79% or 74% yield, respectively, as a pale-yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.72 (dtd, *J* = 7.8, 6.2, 1.6 Hz, 2H), 3.02 (dq, *J* = 9.0, 7.2 Hz, 1H), 1.37 (ddd, *J* = 9.8, 6.2, 2.8 Hz, 2H), 1.36 – 1.34 (m, 3H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.32 (d, *J* = 6.5 Hz, 3H), 1.31 (d, *J* = 6.8 Hz, 3H), 1.29 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 70.6 (d, *J* = 7.4 Hz), 70.5 (d, *J* = 7.2 Hz), 44.9 (d, *J* = 149.7 Hz), 24.3 (d, *J* = 2.0 Hz), 24.25 (d, *J* = 1.4 Hz, 2C), 24.2 (d, *J* = 1.4 Hz), 17.33. ^{31}P NMR (101 MHz, $CDCl_3$) δ 28.5. HRMS calculated for $C_8H_{20}NO_3P+H]^+$: 210.1254; found: 210.1255. The ee was determined by HPLC using a Chiralpak IC column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 9.0 min, τ_{minor} = 7.2 min (96% ee). $[\alpha]^{20}_D$ = -2.5 (*c* = 1.15, MeOH).[4]

[4] C. Yuan, C. Xu and Y. Zhang, *Tetrahedron* 2003, **59**, 6095.

5. HPLC traces

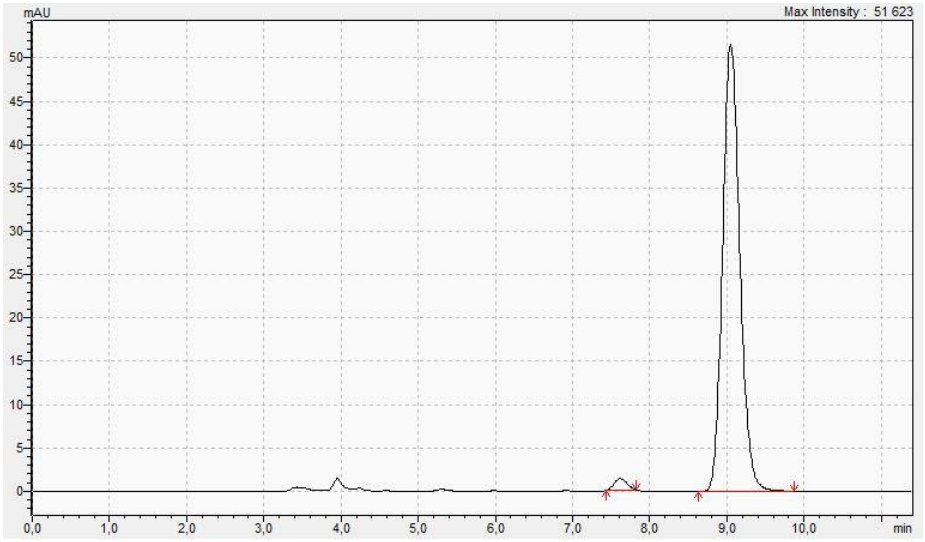
7b (*R*,*E*)-Diisopropyl (1-((2-chlorobenzylidene)amino)ethyl)phosphonate (Table 2, entry 1)

Racemic sample



Peak#	Name	Ret. Time	Area	Area%
1		7,536	347945	49,657
2		8,959	352747	50,343
Total			700692	100,000

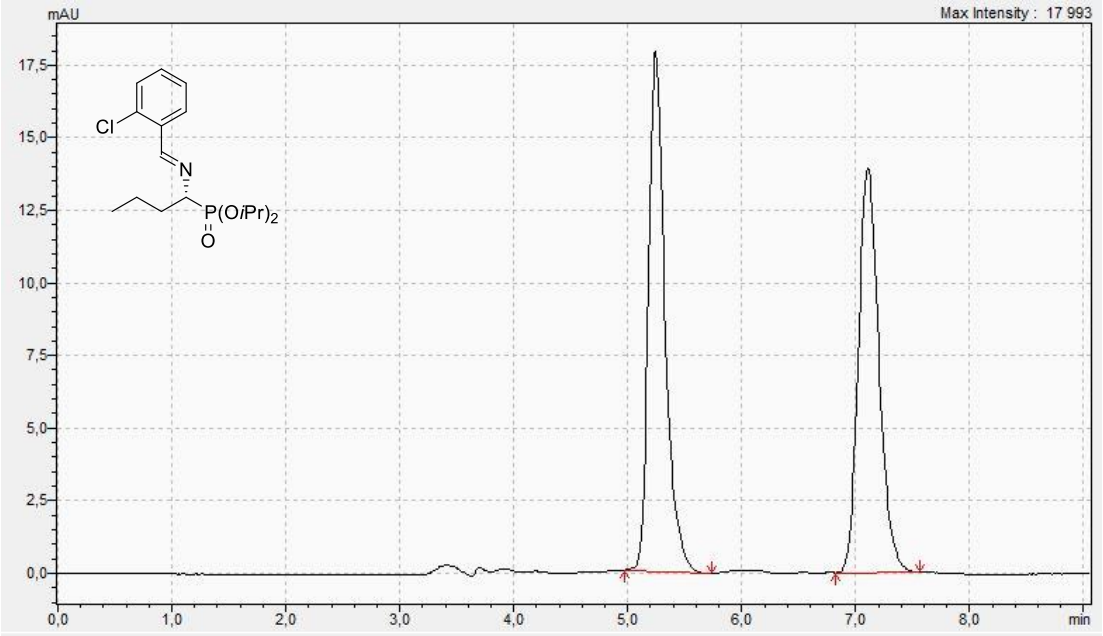
Enantiomerically enriched sample



Peak#	Name	Ret. Time	Area	Area%
1		7,620	15241	1,871
2		9,049	799277	98,129
Total			814519	100,000

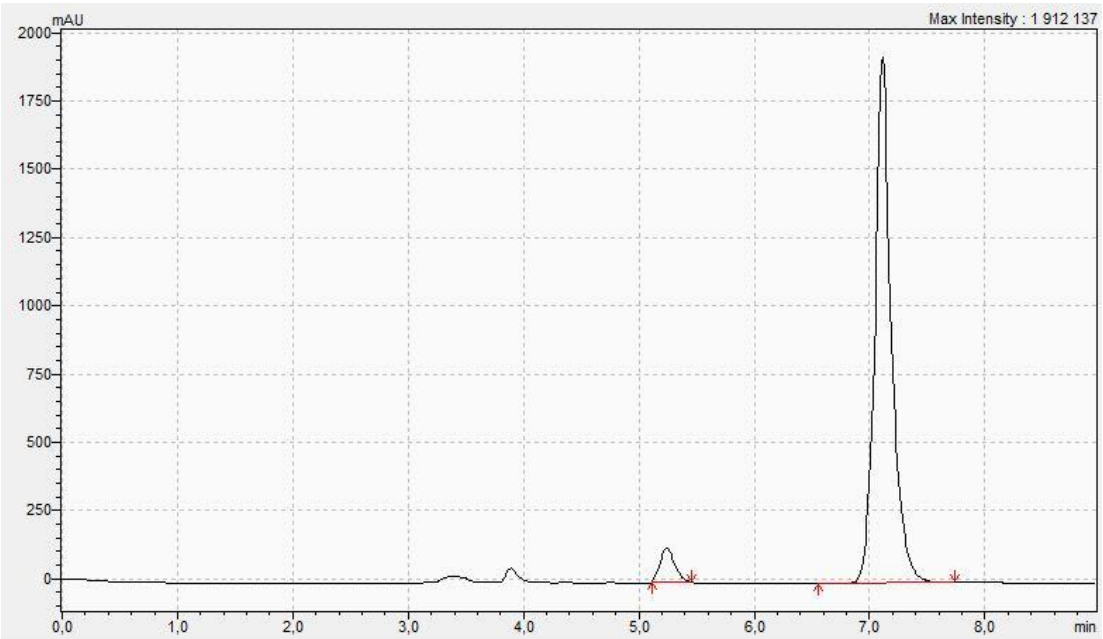
7c (*R*,*E*)-Diisopropyl (1-((2-chlorobenzylidene)amino)butyl)phosphonate (Table 2, entry 2)

Racemic sample



Peak#	Name	Ret. Time	Area	Area%
1		5,245	180036	50,715
2		7,107	174962	49,285
Total			354997	100,000

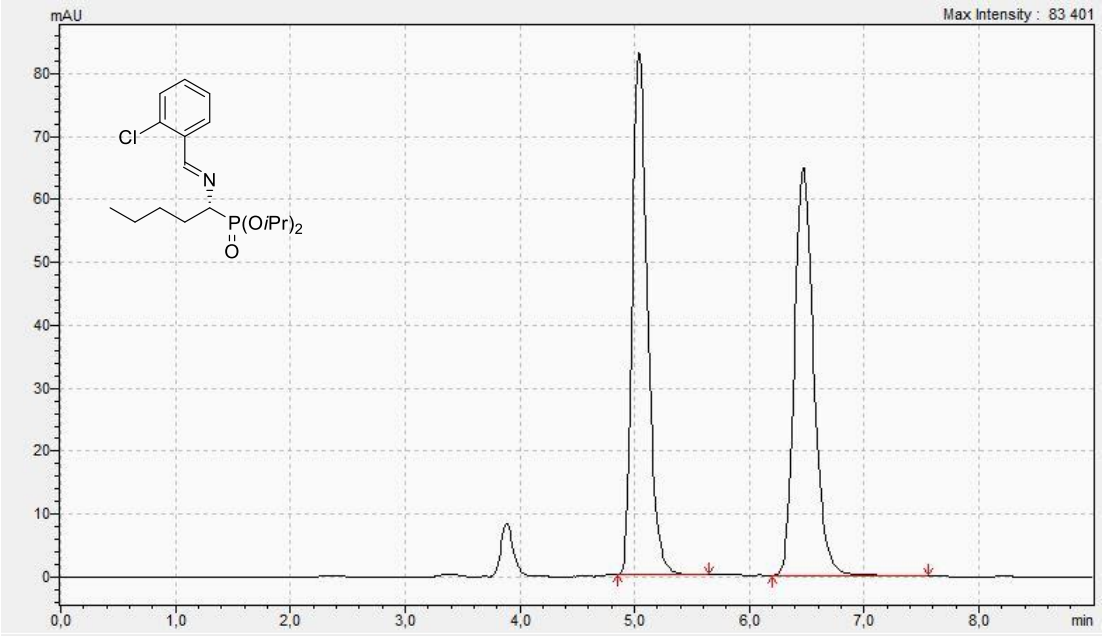
Enantiomerically enriched sample



Peak#	Name	Ret. Time	Area	Area%
1		5,241	1368959	3,960
2		7,141	33200034	96,040
Total			34568993	100,000

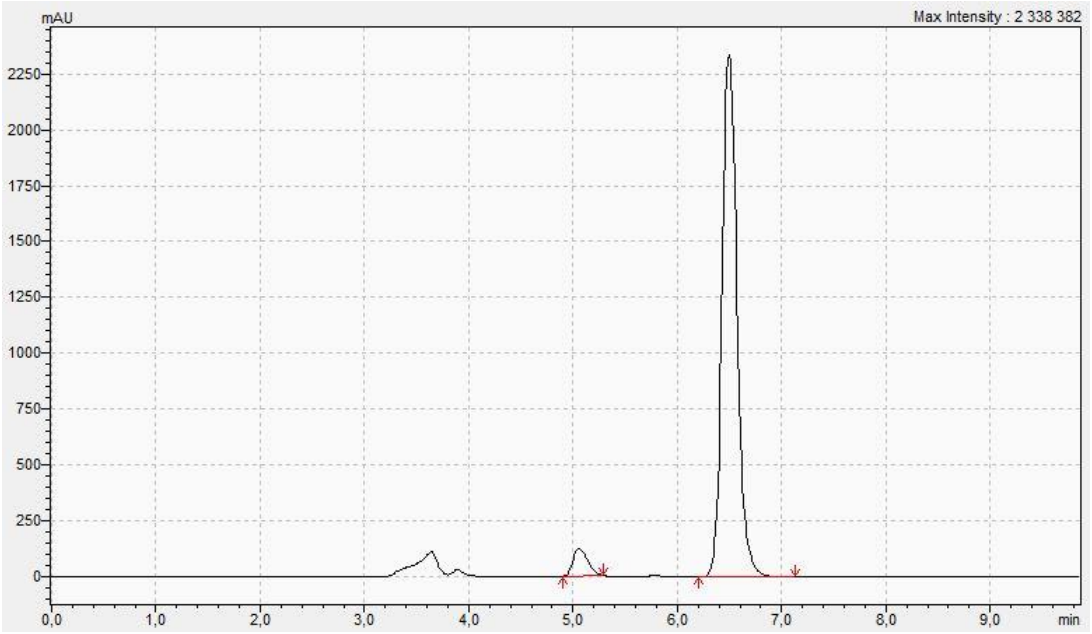
7d (*R*,*E*)-Diisopropyl (1-((2-chlorobenzylidene)amino)pentyl)phosphonate (Table 2, entry 3)

Racemic sample



Peak#	Name	Ret. Time	Area	Area%
1		5,039	767315	50,192
2		6,470	761437	49,808
Total			1528752	100,000

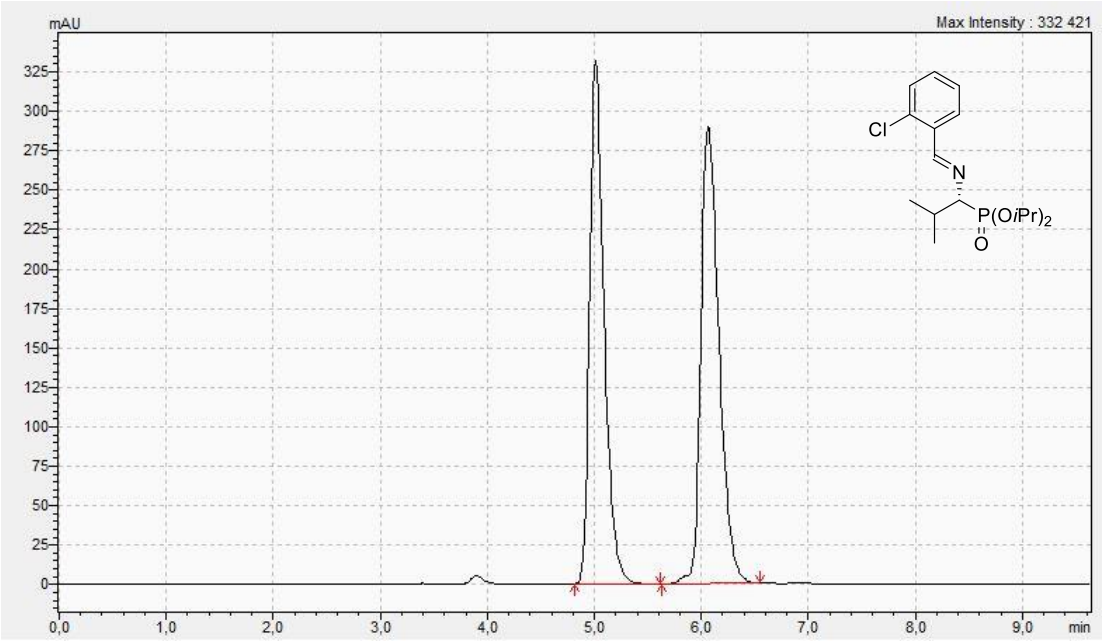
Enantiomerically enriched sample



Peak#	Name	Ret. Time	Area	Area%
1		5,060	1205203	4,913
2		6,495	23325313	95,087
Total			24530516	100,000

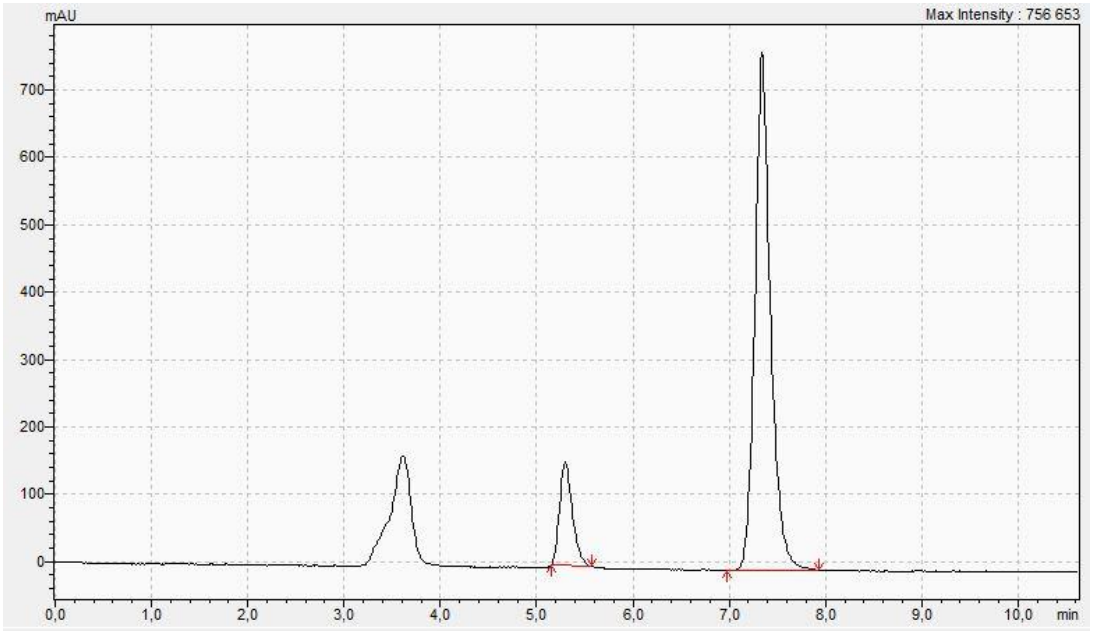
7e (*R*,*E*)-Diisopropyl (1-((2-chlorobenzylidene)amino)-2-methylpropyl)phosphonate (Table 2, entry 4)

Racemic sample



Peak#	Name	Ret. Time	Area	Area%
1		5,013	3118754	47,727
2		6,063	3415848	52,273
Total			6534602	100,000

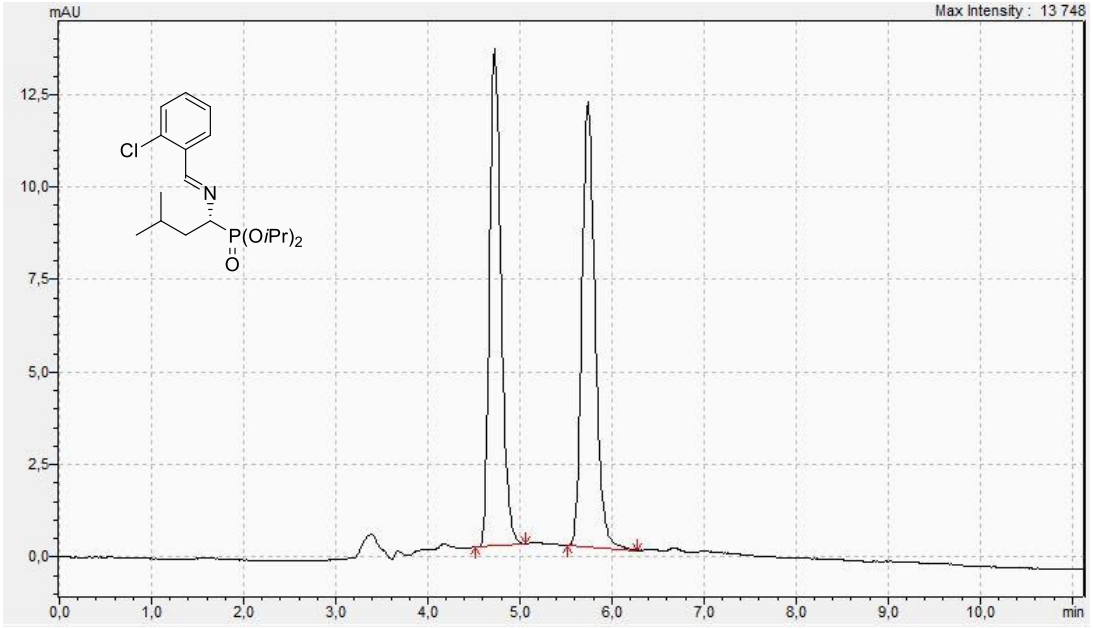
Enantiomerically enriched sample



Peak#	Name	Ret. Time	Area	Area%
1		5,295	1431671	14,117
2		7,341	8709599	85,883
Total			10141270	100,000

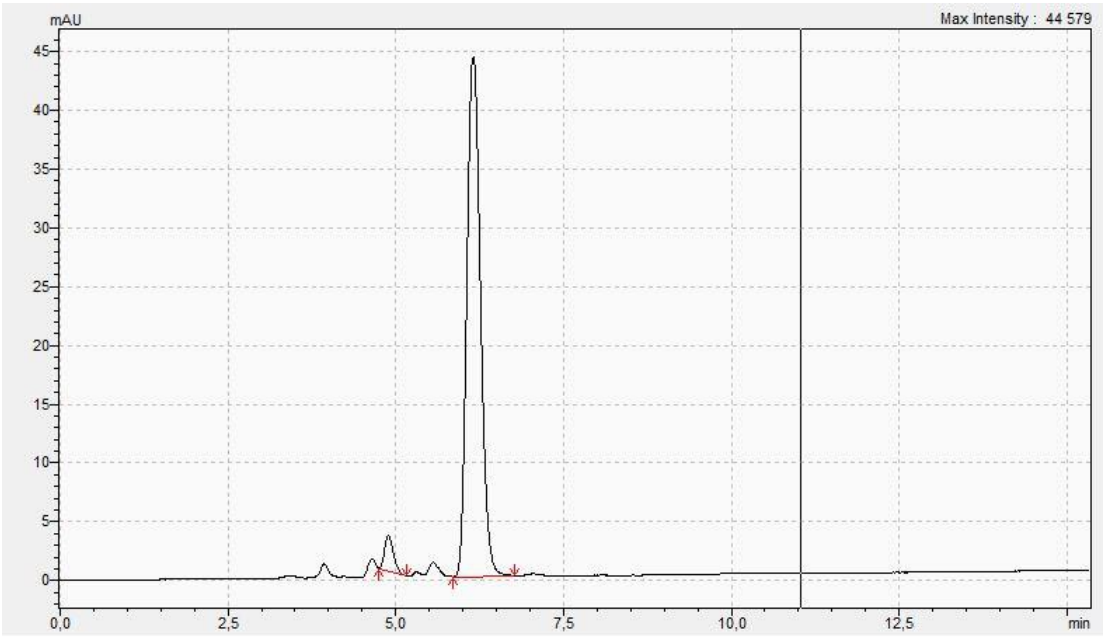
7f (*R*,*E*)-Diisopropyl (1-((2-chlorobenzylidene)amino)-3-methylbutyl)phosphonate (Table 2, entry 5)

Racemic sample



Peak#	Name	Ret. Time	Area	Area%
1		4,727	117472	49,625
2		5,740	119249	50,375
Total			236721	100,000

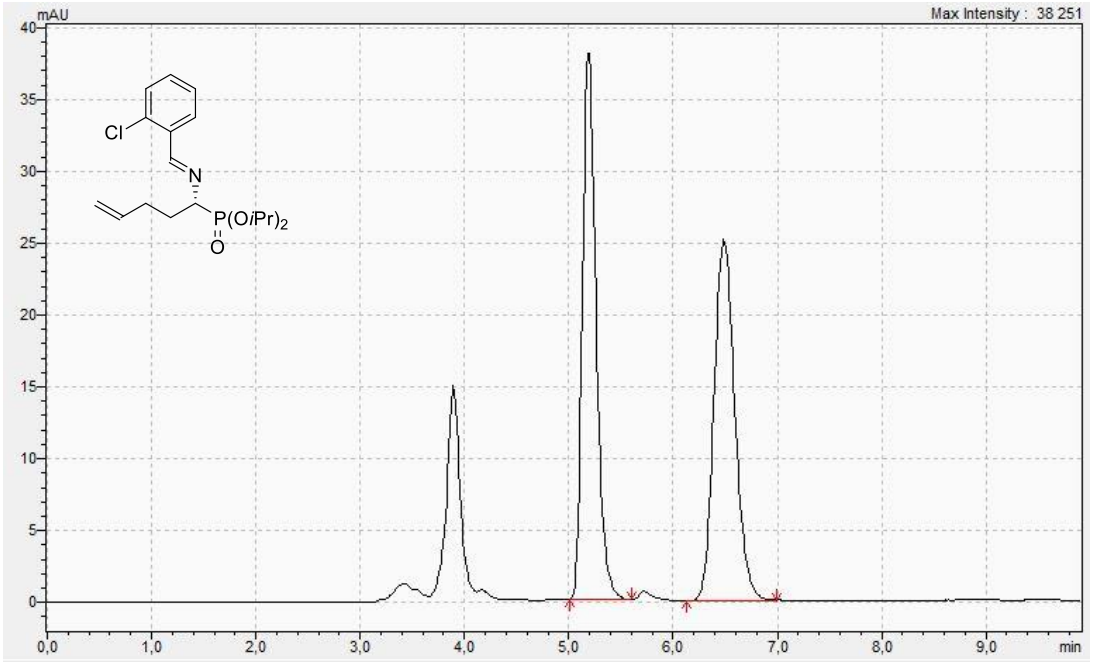
Enantiomerically enriched sample



Peak#	Name	Ret. Time	Area	Area%
1		4,890	28772	4,521
2		6,155	607569	95,479
Total			636340	100,000

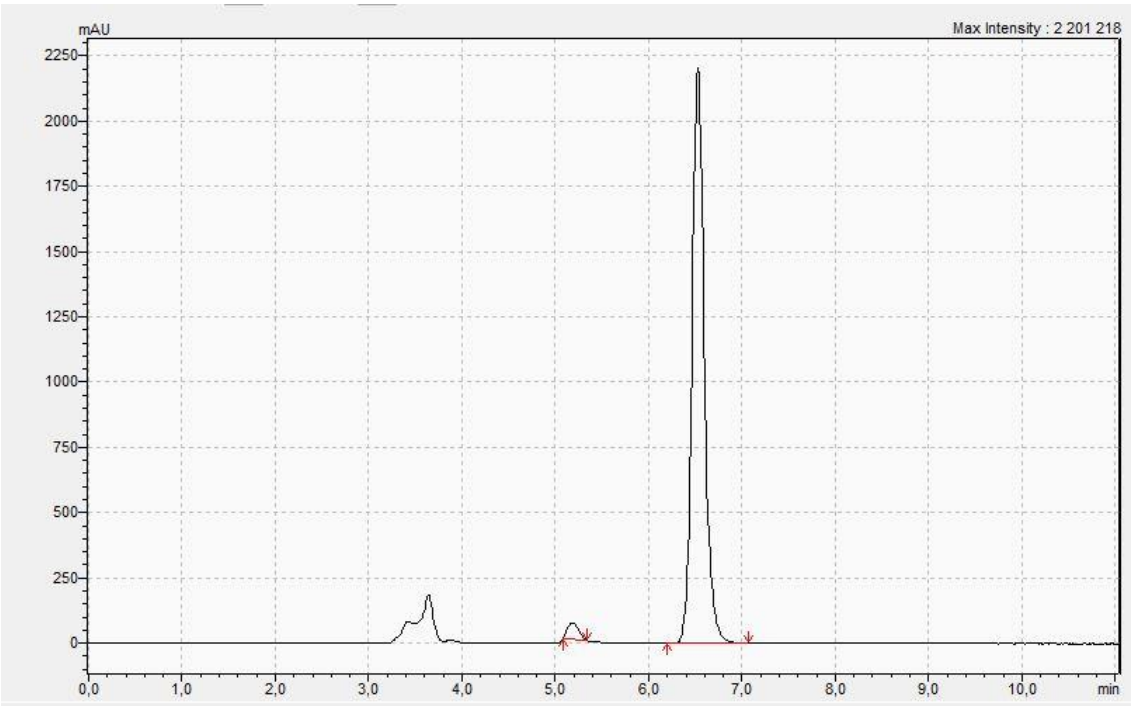
7g (*R*,*E*)-Diisopropyl (1-((2-chlorobenzylidene)amino)pent-4-en-1-yl)phosphonate (Table 2, entry 6)

Racemic sample



Peak#	Name	Ret. Time	Area	Area%
1		5,189	346879	49,898
2		6,487	348295	50,102
Total			695173	100,000

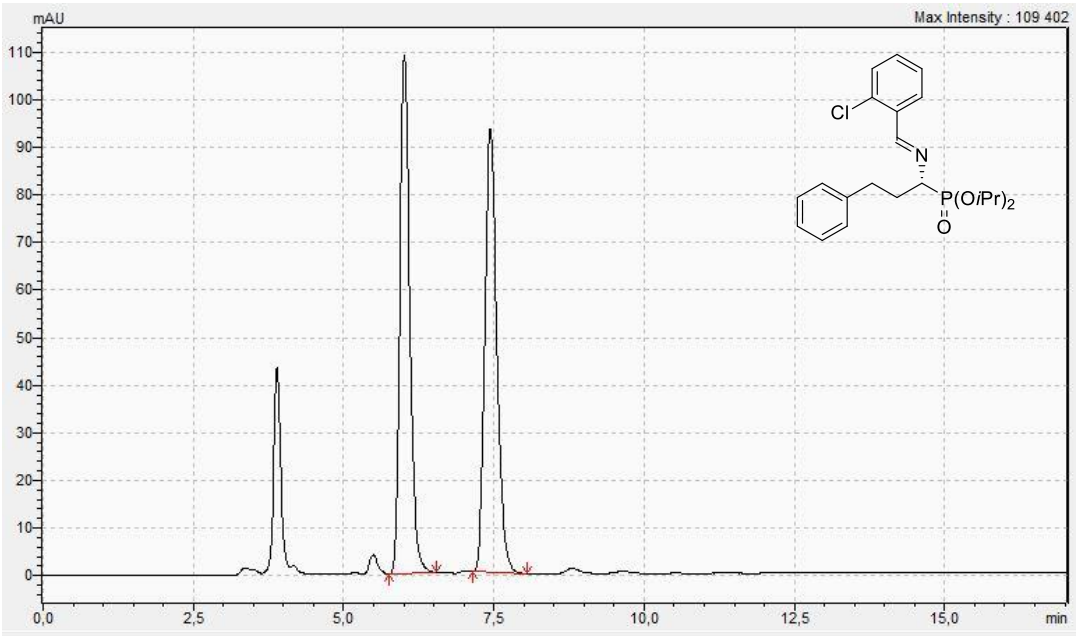
Enantiomerically enriched sample



Peak#	Name	Ret. Time	Area	Area%
1		5,185	542384	2,635
2		6,529	20039164	97,365
Total			20581548	100,000

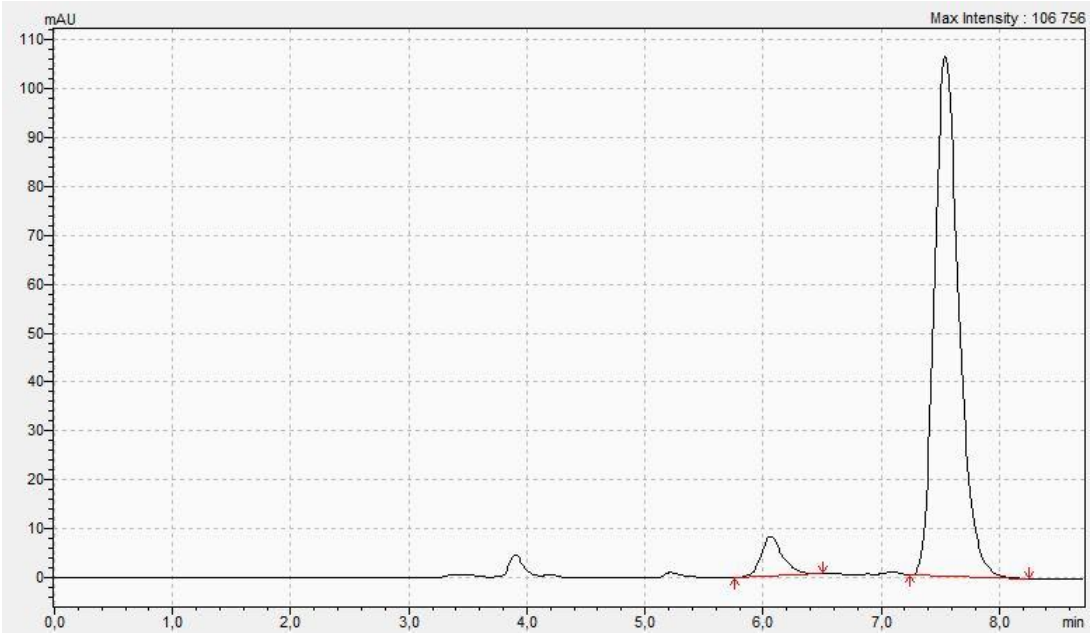
7h (*R*,*E*)-Diisopropyl (1-((2-chlorobenzylidene)amino)-3-phenylpropyl)phosphonate (Table 2, entry 7)

Racemic sample



Peak#	Name	Ret. Time	Area	Area%
1		6,010	1247535	49,085
2		7,442	1294070	50,915
Total			2541604	100,000

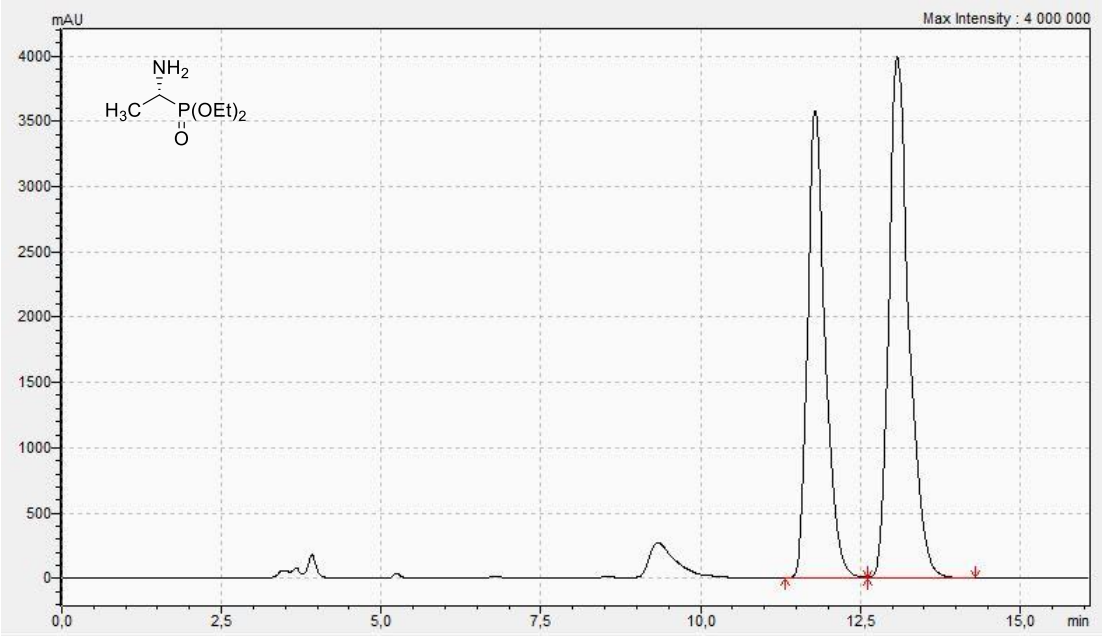
Enantiomerically enriched sample



Peak#	Name	Ret. Time	Area	Area%
1		6,068	1102020	3,198
2		7,589	33359328	96,802
Total			34461348	100,000

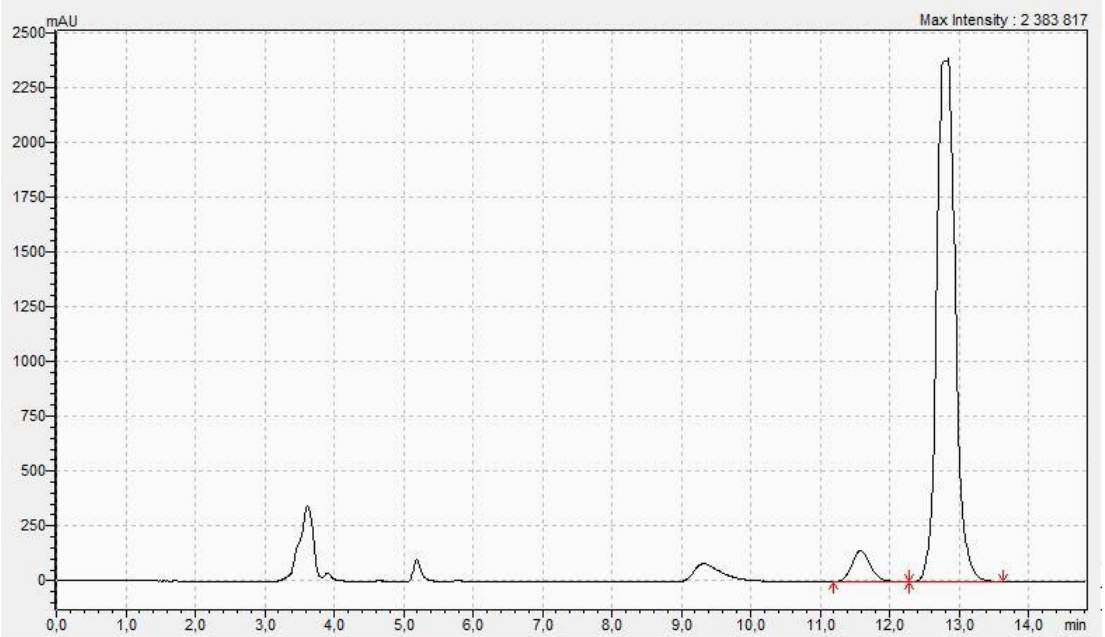
3a (*R*)-Diethyl (1-aminoethyl)phosphonate (Scheme 5)

Racemic sample



Peak#	Name	Ret. Time	Area	Area%
1		11,792	68454166	43,991
2		13,072	87156425	56,009
Total			155610590	100,000

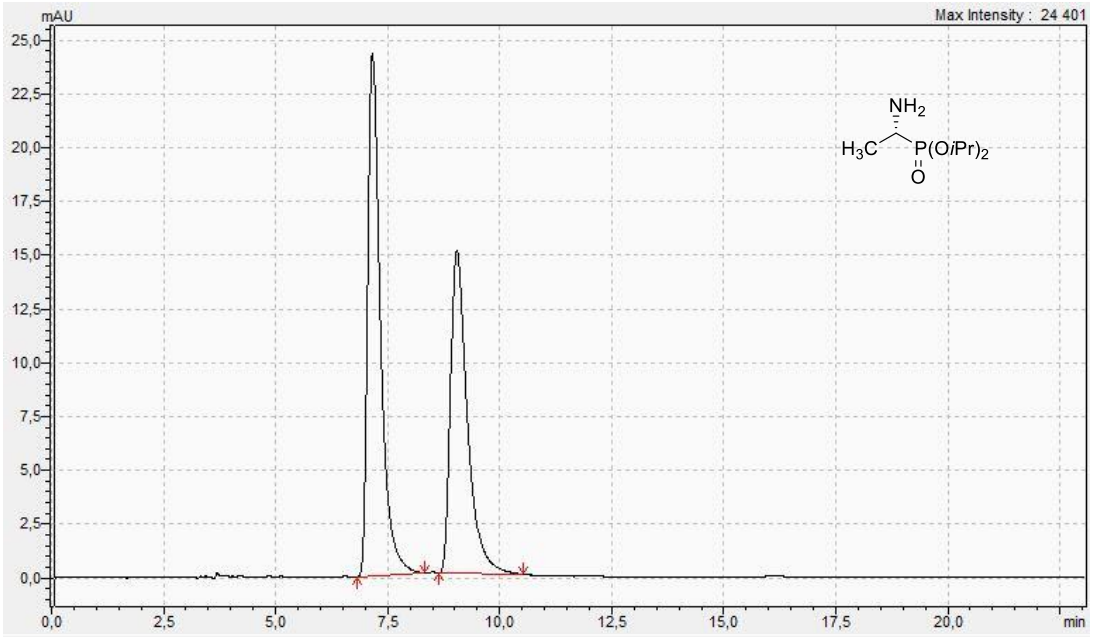
Enantiomerically enriched sample



Peak#	Name	Ret. Time	Area	Area%
1		11,581	2652702	5,672
2		12,850	44114000	94,328
Total			46766702	100,000

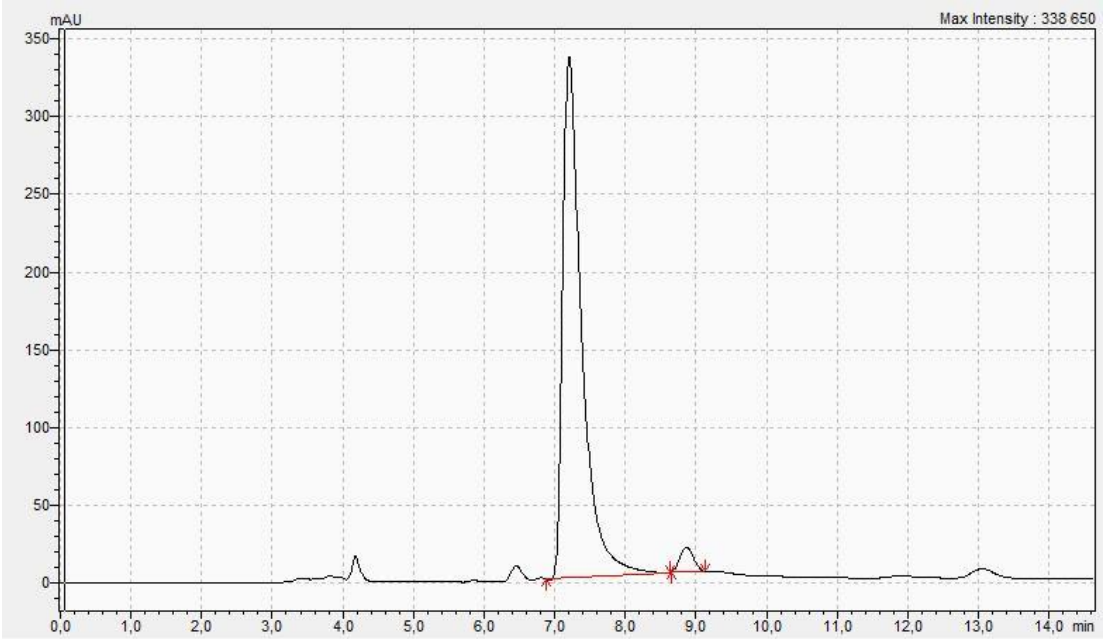
3b (*R*)-Diisopropyl (1-aminoethyl)phosphonate (Scheme 5)

Racemic sample



Peak#	Name	Ret. Time	Area	Area%
1		7,163	478577	54,898
2		9,043	393185	45,102
Total			871762	100,000

Enantiomerically enriched sample



Peak#	Name	Ret. Time	Area	Area%
1		7,204	6315872	97,747
2		8,867	145590	2,253
Total			6461463	100,000