Asymmetric organocatalytic synthesis of quaternary α-hydroxy phosphonates: En route to α-aryl phosphaisoserines

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1. **General Information.** Spectra were recorded at \(^1\text{H}\) NMR (400 MHz); \(^{13}\text{C}\) NMR (100 MHz); \(^{31}\text{P}\) NMR (162 MHz) with the solvent peak used as the internal reference (7.26 and 77.0 ppm for \(^1\text{H}\) and \(^{13}\text{C}\) respectively). Column chromatography was performed on silica gel (Merck Kieselgel 60). Analytical TLC was performed on aluminum backed plates (1.5 × 5 cm) pre-coated (0.25 mm) with silica gel (Merck, Silica Gel 60 F\(_{254}\)). Compounds were visualized by exposure to UV light or by dipping the plates in solutions of KMnO\(_4\), anisaldehyde or phosphomolibdic acid stains followed by heating. Melting points were recorded in a metal block and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 MC polarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak OJ/AD-H/IA/IB columns). Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. Formaldehyde tert-butyl hydrazone 2,\(^{[1]}\) not commercially available \(\alpha\)-keto phosphonates 3,\(^{[2]}\) and catalysts I-IV\(^{[3]}\) were synthesized according to literature procedures.

Keto phosphonate 3\(_g\) was prepared according to procedures reported in the literature.\(^{[2]}\) \(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.20 (d, \(J = 8.4\) Hz, 1H), 7.51 (s, 1H), 7.40 (d, \(J = 8.4\) Hz, 1H), 3.91 (d, \(J = 10.8\) Hz, 6H). \(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)) \(\delta\) 198.2 (d, \(J = 184.1\) Hz), 139.8, 133.8, 133.0, 131.5, 131.0, 127.2, 126.9, 54.5 (d, \(J = 7.5\) Hz). HRMS: calculated for \([\text{C}_9\text{H}_{10}\text{Cl}_2\text{O}_4\text{P}]^+\) 282.9688; found: 282.9680.


2. General procedure for the thermal reaction of tert-butyl hydrazone 2 with α-keto phosphonate 3.

Formaldehyde tert-butyl hydrazone 2 (94 µL, 0.8 mmol) was added to a solution of α-keto phosphonate 3 (0.4 mmol) in toluene (0.5 mL) at room temperature. The mixture was stirred until consumption of starting material (TLC monitoring).

3. General procedure for the catalytic enantioselective reactions of tert-butyl hydrazone 2 with α-keto phosphonate 3.

Formaldehyde tert-butyl hydrazone 2 (134 µL, 1.2 mmol) was added to a solution of α-keto phosphonate 3 (0.6 mmol) and catalyst I (0.06 mmol, 48 mg) in toluene (0.6 mL) at −78 °C. The mixture was stirred for the time as specified in Table 2 (TLC monitoring).


Following the general procedure for the catalytic enantioselective reactions of hydrazone 2 with α-keto phosphonates 3. After consumption of starting material, MeOH (2 mL) and MMPP (742 mg, 3 equiv.) were subsequently added at −78 °C. The reaction mixture was allowed to warm up to room temperature for completion (2-3 h.). The mixture was then diluted with H2O (5 mL), extracted with CH2Cl2 (3 x 10 mL), dried over Na2SO4 and concentrated in vacuo. The resulting residue was purified by column chromatography (1:3 Hexane-AcOEt) to afford pure products 6. Enantiomeric excess (ee) was determined by HPLC analysis.

5. Characterization of azoxy compounds 6

\[6a\]: white solid (168 mg, 85%); M.p. = 72-74 °C. 1H NMR (300 MHz, CDCl3) δ 7.61 (d, J = 8.0 Hz, 2H), 7.37 (t, J = 8.0 Hz, 2H), 7.30 (t, J = 8.0 Hz, 1H), 4.23 (dd, J = 17.6, 5.9 Hz, 1H), 4.03 (t, J = 17.8 Hz, 1H), 3.85 (d, J = 11.3 Hz, 1H), 3.76 (d, J = 10.4 Hz, 3H), 3.52 (d, J = 10.4 Hz, 3H), 1.47 (s, 9H), 13C NMR (125 MHz, CDCl3) δ 138.2, 128.2 (d, J = 2.6 Hz), 127.8 (d, J = 2.9 Hz), 125.9 (d, J = 4.3 Hz), 77.3, 77.0 (d, J = 162.7 Hz), 58.5 (d, J = 5.8 Hz), 54.3 (d, J = 7.4 Hz), 53.8 (d,

$J = 7.5 \text{ Hz}$), 28.1. $^{31}$P NMR (162 MHz, CDCl$_3$) δ 23.3. HRMS: $m/z$ calculated for [C$_{14}$H$_2$N$_2$O$_3$P]$^+$: 331.1423; found: 331.1422. The enantiomeric excess was determined by HPLC using a Chiralpak OJ column [hexane/i-PrOH (90:10)]; flow rate 1 mL/min; $\tau_{\text{major}} = 22.5 \text{ min}$, $\tau_{\text{minor}} = 12.9 \text{ min (90\% ee)}; [\alpha]_D^{20} = +23.0 \text{ (c 0.5, CHCl}_3$).

(6b): White solid (173 mg, 81\%), M.P. = 75-77 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.60 (d, $J = 7.4 \text{ Hz}$, 2H), 7.37-7.27 (m, 3H), 4.23 (dd, $J = 17.7, 5.9 \text{ Hz}$, 1H), 4.19-4.04 (m, 3H), 4.02-3.86 (m, 2H), 3.84-3.70 (m, 1H), 1.46 (s, 9H), 1.27 (t, $J = 7.1 \text{ Hz}$, 3H), 1.14 (t, $J = 7.1 \text{ Hz}$, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 138.6, 128.1 (d, $J = 2.0 \text{ Hz}$), 127.3 (d, $J = 3.0 \text{ Hz}$), 126.1 (d, $J = 4.0 \text{ Hz}$), 77.3, 75.5 (d, $J = 162.0 \text{ Hz}$), 63.8 (d, $J = 7.0 \text{ Hz}$), 63.3 (d, $J = 7.0 \text{ Hz}$), 58.7 (d, $J = 6.0 \text{ Hz}$), 28.2, 16.5 (d, $J = 6.0 \text{ Hz}$), 16.4 (d, $J = 6.0 \text{ Hz}$). $^{31}$P NMR (162 MHz, CDCl$_3$) δ 21.3. HRMS: $m/z$ calculated for [C$_{16}$H$_{28}$N$_3$O$_3$P]$^+$: 359.1736; found: 359.1732. The enantiomeric excess was determined by HPLC using a Chiralpak OJ column [hexane/i-PrOH (98:2)]; flow rate 1 mL/min; $\tau_{\text{major}} = 28.2 \text{ min}$, $\tau_{\text{minor}} = 18.2 \text{ min (86\% ee)}; [\alpha]_D^{20} = +17.6 \text{ (c 0.5, CHCl}_3$).

(6c): White solid (196 mg, 95\%); M.p. = 92-94 °C. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.48 (dd, $J = 8.2, 1.9 \text{ Hz}$, 2H), 7.17 (d, $J = 8.0 \text{ Hz}$, 2H), 4.22 (dd, $J = 17.6, 6.0 \text{ Hz}$, 1H), 3.99 (t, $J = 17.9 \text{ Hz}$, 1H), 3.82 (d, $J = 11.0 \text{ Hz}$, 1H), 3.75 (d, $J = 10.4 \text{ Hz}$, 3H), 3.52 (d, $J = 10.3 \text{ Hz}$, 3H), 2.34 (s, 3H), 1.48 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 137.5 (d, $J = 2.5 \text{ Hz}$), 135.3, 128.9 (d, $J = 1.7 \text{ Hz}$), 125.8 (d, $J = 4.2 \text{ Hz}$), 77.2, 75.6 (d, $J = 163.1 \text{ Hz}$), 58.6 (d, $J = 5.9 \text{ Hz}$), 54.3 (d, $J = 7.2 \text{ Hz}$), 53.7 (d, $J = 7.4 \text{ Hz}$), 28.2, 21.1. $^{31}$P NMR (162 MHz, CDCl$_3$) δ 23.5. HRMS: $m/z$ calculated for [C$_{15}$H$_{23}$N$_3$O$_3$P]$^+$: 345.1579; found: 345.1582. The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (90:10)]; flow rate 1 mL/min; $\tau_{\text{major}} = 19.5 \text{ min}$, $\tau_{\text{minor}} = 14.2 \text{ min (97\% ee)}; [\alpha]_D^{20} = +27.1 \text{ (c 0.5, CHCl}_3$).

(6d): Yellow solid (130 mg, 60\%); M.p. = 70-72 °C. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.48 (d, $J = 6.8 \text{ Hz}$, 2H), 6.85 (d, $J = 8.6 \text{ Hz}$, 2H), 4.14 (dd, $J = 17.6, 6.3 \text{ Hz}$, 1H), 3.98 (t, $J = 17.3 \text{ Hz}$, 1H), 3.76 (s, 3H), 3.71 (d, $J = 10.4 \text{ Hz}$, 3H), 3.51 (d, $J = 10.3 \text{ Hz}$, 3H), 1.44 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 159.0 (d, $J = 2.5 \text{ Hz}$), 130.1, 127.2 (d, $J = 4.4 \text{ Hz}$), 113.4 (d, $J = 2.0 \text{ Hz}$), 77.1, 75.3 (d, $J = 163.9 \text{ Hz}$), 58.3 (d, $J = 6.9 \text{ Hz}$), 55.1, 54.2 (d, $J = 7.4 \text{ Hz}$), 53.7 (d, $J = 7.4 \text{ Hz}$), 28.0. $^{31}$P NMR (162 MHz, CDCl$_3$) δ 23.6. HRMS: $m/z$ calculated for [C$_{13}$H$_{25}$N$_3$O$_6$P]$^+$:
361.1529; found: 361.1523. The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (90:10)]; flow rate 1 mL/min; $\tau_{\text{major}}$ = 30.3 min, $\tau_{\text{minor}}$ = 20.2 min (84% ee); $[\alpha]_D^{20} = +17.7$ (c 0.5, CHCl$_3$).

(6e): White solid (181 mg, 83%); M.p. = 86-88 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.55 (d, $J$ = 6.7 Hz, 2H), 7.33 (d, $J$ = 8.1 Hz, 2H), 4.18 (dd, $J$ = 17.5, 6.3 Hz, 1H), 4.02 (d, $J$ = 8.6 Hz, 1H), 4.01 (t, $J$ = 16.8 Hz, 1H), 3.76 (d, $J$ = 10.4 Hz, 3H), 3.59 (d, $J$ = 12.0 Hz, 3H), 1.46 (s, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 137.0, 133.6 (d, $J$ = 3.4 Hz), 128.2 (d, $J$ = 2.2 Hz), 127.5 (d, $J$ = 4.2 Hz), 77.2, 75.4 (d, $J$ = 163.7 Hz), 58.2 (d, $J$ = 6.0 Hz), 54.2 (d, $J$ = 7.4 Hz), 53.9 (d, $J$ = 7.4 Hz), 28.0. $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ 22.8. HRMS: $m/z$ calculated for [C$_{14}$H$_{22}$ClN$_2$O$_3$P]$^+$: 365.1033; found: 365.1028. The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (90:10)]; flow rate 1 mL/min; $\tau_{\text{major}}$ = 37.1 min, $\tau_{\text{minor}}$ = 13.9 min (98% ee); $[\alpha]_D^{20} = +28.2$ (c 0.5, CHCl$_3$).

(6f): White solid (175 mg, 80%); M.p. = 122-124 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.94 (td, $J$ = 7.9, 2.1 Hz, 1H), 7.40-7.25 (m, 3H), 4.60-4.32 (m, 3H), 3.78 (d, $J$ = 10.2 Hz, 3H), 3.76 (d, $J$ = 10.2 Hz, 3H), 1.49 (s, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 136.0, 131.8 (d, $J$ = 4.6 Hz), 131.3 (d, $J$ = 2.0 Hz), 129.9 (d, $J$ = 4.2 Hz), 129.2 (d, $J$ = 2.7 Hz), 126.7 (d, $J$ = 2.3 Hz), 77.2, 76.7 (d, $J$ = 163.0 Hz), 57.6 (d, $J$ = 5.6 Hz), 54.3 (d, $J$ = 7.5 Hz), 54.2 (d, $J$ = 7.4 Hz), 28.1. $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ 23.1. HRMS: $m/z$ calculated for [C$_{14}$H$_{22}$ClN$_2$O$_3$P]$^+$: 365.1033; found: 365.1027. The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (90:10)]; flow rate 1 mL/min; $\tau_{\text{major}}$ = 12.1 min, $\tau_{\text{minor}}$ = 14.0 min (92% ee); $[\alpha]_D^{20} = +21.5$ (c 0.5, CHCl$_3$).

(6g): White solid (192 mg, 80%); M.p. = 108-110 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.85 (dd, $J$ = 8.7, 2.1 Hz, 1H), 7.36 (s, 1H), 7.34-7.28 (m, 1H), 4.49 (dd, $J$ = 17.7, 15.3 Hz, 1H), 4.32 (dd, $J$ = 17.9, 4.4 Hz, 1H), 3.78 (d, $J$ = 10.0 Hz, 3H), 3.76 (d, $J$ = 10.1 Hz, 3H), 1.44 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 134.9, 134.4 (d, $J$ = 3.4 Hz), 132.5 (d, $J$ = 4.5 Hz), 131.0 (d, $J$ = 4.2 Hz), 130.9 (d, $J$ = 2.4 Hz), 126.9 (d, $J$ = 2.0 Hz), 77.2, 76.6 (d, $J$ = 163.9 Hz), 57.4 (d, $J$ = 5.9 Hz), 54.4 (d, $J$ = 6.9 Hz), 54.3 (d, $J$ = 6.7 Hz), 28.1. $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ 22.5. HRMS: $m/z$ calculated for [C$_{14}$H$_{22}$Cl$_2$N$_2$O$_3$P]$^+$: 399.0643; found: 399.0639. The enantiomeric
excess was determined by HPLC using a Chiralpak IB column [hexane/i-PrOH (90:10)]; flow rate 1 mL/min; \( \tau_{\text{major}} = 10.3 \min \), \( \tau_{\text{minor}} = 9.6 \min \) (97% \( ee \)); \([\alpha]_D^{20} = +25.1 \) (c 0.5, CHCl3).

(6h): White solid (202 mg, 82%); M.p. = 97-99 °C. \(^1\)H NMR (300 MHz, CDCl3) \( \delta \): 7.79 (s, \( J = 4.1 \), 2.0 Hz, 1H), 7.57-7.51 (m, 1H), 7.46-7.41 (m, 1H), 7.24-7.20 (m, 1H), 4.22 (dd, \( J = 17.5 \), 6.2 Hz, 1H), 4.20 (dd, \( J = 17.4 \), 6.2 Hz, 1H), 4.06 (t, \( J = 16.6 \) Hz, 1H), 3.89 (d, \( J = 11.4 \) Hz, 1H), 3.78 (d, \( J = 10.4 \) Hz, 3H) 3.60 (d, \( J = 10.4 \) Hz, 3H), 1.52 (s, 9H). \(^{13}\)C NMR (75 MHz, CDCl3) \( \delta \): 140.8, 130.8 (d, \( J = 2.8 \) Hz), 129.6 (d, \( J = 2.6 \) Hz), 129.1 (d, \( J = 4.5 \) Hz), 124.8 (d, \( J = 4.0 \) Hz), 122.4 (d, \( J = 2.9 \) Hz), 77.2, 75.4 (d, \( J = 163.7 \) Hz), 58.3 (d, \( J = 5.7 \) Hz), 54.3 (d, \( J = 7.5 \) Hz), 54.0 (d, \( J = 7.4 \) Hz), 28.1. \(^{31}\)P NMR (162 MHz, CDCl3) \( \delta \): 22.6. HRMS: \( m/z \) calculated for \([\text{C}_{14}\text{H}_{22}\text{BrN}_2\text{O}_3\text{P}]^+\) : 409.0528; found: 409.0519. The enantiomeric excess was determined by HPLC using a Chiralpak OJ column [hexane/i-PrOH (98:2)]; flow rate 1 mL/min; \( \tau_{\text{major}} = 31.1 \min \), \( \tau_{\text{minor}} = 23.6 \min \) (96% \( ee \)); \([\alpha]_D^{20} = +11.7 \) (c 0.5, CHCl3).

(6i): Oil (175 mg, 84%); \(^1\)H NMR (300 MHz, CDCl3) \( \delta \): 7.60-7.53 (m, 2H), 7.03 (t, \( J = 8.6 \) Hz, 2H), 4.17 (dd, \( J = 17.5 \), 6.2 Hz, 1H), 4.01 (t, \( J = 17.0 \) Hz, 1H), 3.93 (d, \( J = 11.3 \) Hz, 1H), 3.75 (d, \( J = 10.4 \) Hz, 3H), 3.56 (d, \( J = 10.3 \) Hz, 3H), 1.45 (s, 9H). \(^{13}\)C NMR (125 MHz, CDCl3) \( \delta \): 162.3 (dd, \( J = 246.7 \), 3.2 Hz), 134.1 (d, \( J = 3.0 \) Hz), 127.8 (m), 115.0 (d, \( J = 21.4 \) Hz), 77.3, 75.4 (d, \( J = 164.1 \) Hz), 58.3 (d, \( J = 6.5 \) Hz), 54.3 (d, \( J = 7.5 \) Hz), 53.8 (d, \( J = 7.4 \) Hz), 28.1. \(^{31}\)P NMR (162 MHz, CDCl3) \( \delta \): 23.1. (d, \( J = 3.5 \) Hz). \(^{19}\)F NMR (376.5 MHz, CDCl3) \( \delta \): –114.7. HRMS: \( m/z \) calculated for \([\text{C}_{14}\text{H}_{22}\text{FN}_2\text{O}_3\text{P}]^+\) : 349.1329; found: 349.1320. The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (90:10)]; flow rate 1 mL/min; \( \tau_{\text{major}} = 23.7 \min \), \( \tau_{\text{minor}} = 11.4 \min \) (95% \( ee \)); \([\alpha]_D^{20} = +13.4 \) (c 0.8, CHCl3).

(6j): White solid (167 mg, 80%); M.p. = 108-110 °C. \(^1\)H NMR (300 MHz, CDCl3) \( \delta \): 7.75 (t, \( J = 7.9 \) Hz, 1H), 7.33-7.27 (m, 1H), 7.18 (t, \( J = 7.6 \) Hz, 1H), 7.02 (dd, \( J = 12.0 \), 8.2 Hz, 1H), 4.35-4.21 (m, 3H), 3.72 (d, \( J = 10.5 \) Hz, 6H), 1.44 (s, 9H). \(^{13}\)C NMR (100 MHz, CDCl3) \( \delta \): 159.4 (dd, \( J = 248.4 \), 4.3 Hz), 129.9 (dd, \( J = 8.6 \), 3.0 Hz), 129.0 (t, \( J = 4.0 \) Hz), 125.5 (d, \( J = 12.1 \) Hz), 124.1 (m), 115.9 (dd, \( J = 23.8 \), 2.6 Hz), 77.1, 75.0 (dd, \( J = 165.5 \), 4.2 Hz), 57.3 (dd, \( J = 7.5 \), 5.9 Hz), 54.1 (dd, \( J = 7.3 \), 4.9 Hz), 28.1. \(^{31}\)P NMR (162 MHz, CDCl3) \( \delta \): 22.6. (d, \( J = 5.5 \) Hz).
19F NMR (376.5 MHz, CDCl₃) δ −109.8. (d, J = 5.4 Hz). HRMS: m/z calculated for [C₁₄H₂₃FN₂O₅P]⁺: 349.1329; found: 349.1335. The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (90:10)]; flow rate 1 mL/min; τ_major = 15.5 min, τ_minor = 11.3 min (97% ee); [α]D²⁰ = +3.3 (c 0.5, CHCl₃).

(6k): Oil (131 mg, 68%); 1H NMR (400 MHz, CDCl₃) δ 7.43 (s, 1H), 6.43 (t, J = 3.2 Hz, 1H), 6.38 (s, 1H), 4.18-4.02 (m, 2H), 3.77 (d, J = 10.4 Hz, 3H), 3.75 (d, J = 10.4 Hz, 3H), 1.50 (s, 9H). 13C NMR (100 MHz, CDCl₃) δ 151.5 (d, J = 1.6 Hz), 142.8 (d, J = 2.8 Hz), 110.7 (d, J = 2.6 Hz), 108.6 (d, J = 6.3 Hz), 77.2, 73.2 (d, J = 170.0 Hz), 56.2 (d, J = 5.4 Hz), 54.2 (d, J = 7.1 Hz), 54.0 (d, J = 7.2 Hz), 28.2. 31P NMR (162 MHz, CDCl₃) δ 34.5. HRMS: m/z calculated for [C₁₂H₂₂N₂O₅P]⁺: 321.1216; found: 321.1205. The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (90:10)]; flow rate 1 mL/min; τ_major = 20.5 min, τ_minor = 13.3 min (96% ee); [α]D²⁰ = +13.1 (c 0.5, CHCl₃).

(6l): Yellow solid (141 mg, 70%); M.p. = 114-116 °C. 1H NMR (300 MHz, CDCl₃) δ 7.29 (dt, J = 5.1, 1.4 Hz, 1H), 7.14 (td, J = 3.4, 1.1 Hz, 1H), 7.01 (dd, J = 5.0, 3.7 Hz, 1H), 4.25 (d, J = 7.5 Hz, 1H), 4.18-3.90 (m, 2H), 3.77 (d, J = 10.4 Hz, 3H), 3.65 (d, J = 10.4 Hz, 3H), 1.48 (s, 9H). 13C NMR (75 MHz, CDCl₃) δ 142.8, 127.0 (d, J = 3.0 Hz), 125.4 (d, J = 3.0 Hz), 125.1 (d, J = 5.7 Hz), 77.2, 74.9 (d, J = 169.6 Hz), 58.8 (d, J = 6.3 Hz), 54.3 (d, J = 7.6 Hz), 54.1 (d, J = 7.4 Hz), 28.0. 31P NMR (162 MHz, CDCl₃) δ 34.9. HRMS: m/z calculated for [C₁₂H₂₁N₂O₅PS]⁺: 337.0987; found: 337.0995. The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (90:10)]; flow rate 1 mL/min; τ_major = 17.3 min, τ_minor = 14.2 min (95% ee); [α]D²⁰ = +8.8 (c 0.5, CHCl₃).

(6m): Following the general procedure at −15 °C for 48 hours (first step), the product was isolated as a yellow oil (45 mg, 25%); 1H NMR (400 MHz, CDCl₃) 3.84 (dd, J = 17.3, 7.7 Hz, 1H), 3.80 (d, J = 8.0 Hz, 3H), 3.77 (d, J = 8.0 Hz, 3H), 3.57 (dd, J = 22.7, 18.3 Hz, 1H), 2.36-2.25 (m, 1H), 1.55 (s, 9H), 1.05 (d, 6H, J = 8.0 Hz). 13C NMR (100 MHz, CDCl₃) δ 76.8 (d, J = 158.0 Hz), 53.9 (d, J = 6.2 Hz), 53.6 (d, J = 10.0 Hz), 53.0 (d, J = 8.7 Hz), 33.1 (d, J = 5.0 Hz), 28.1, 17.4, 16.7 (d, J = 10.0 Hz). 31P NMR (162 MHz, CDCl₃) δ 28.0. HRMS: m/z calculated for [C₁₁H₂₅N₂O₅PNa]⁺: 319.1393; found: 319.1389. The enantiomeric excess was determined by HPLC using a
Chirapal IA column [hexane/i-PrOH (90:10)]; flow rate 1 mL/min; $\tau_{\text{major}} = 11.7 \text{ min}$, $\tau_{\text{minor}} = 13.1 \text{ min}$ (47% ee); $\left[\alpha\right]_D^{25} = +53.4$ (c 2.8, CHCl₃).

6. General procedure for the one-pot synthesis of $\beta$-amino-$\alpha$-hydroxyphosphonates 5.

Following the general procedure for the catalytic enantioselective reactions of hydrazones with $\alpha$-keto phosphonates, after consumption of starting material, Et₂O (5.4 mL) and HCl aq. (2.4 mL, 6M) were subsequently added at $-78 \, ^\circ\text{C}$. The mixture was allowed to warm up to 0 °C for completion (3-8 h.). The organic phase was separated and the water phase was extracted with Et₂O (2 x 10 mL) and CH₂Cl₂ (3 x 10 mL). The organic solvents were removed under reduced pressure affording crude aldehydes 8. 4-Methoxyaniline (103 mg, 0.8 mmol) and NaCNBH₃ (75 mg, 1.2 mmol) were immediately added to a solution of crude aldehydes 8 in dichloromethane (3 mL) at room temperature. The mixture was stirred until consumption of starting material (TLC monitoring, 2-3 h.). The organic solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (1:3 Toluene-AcOEt) to afford pure products 5. Enantiomeric excess (ee) was determined by HPLC analysis.

7. Characterization of $\beta$-amino-$\alpha$-hydroxyphosphonates 5

(5a): Yellow oil (84 mg, 40%); $^1$H NMR (400 MHz, CDCl₃) δ 7.65 (d, $J = 7.7$ Hz, 2H), 7.41 (t, $J = 7.6$ Hz, 2H), 7.33 (t, $J = 6.4$ Hz, 1H), 6.76 (d, $J = 8.9$ Hz, 2H), 6.67 (d, $J = 8.9$ Hz, 2H), 3.96 (dd, $J = 12.6, 6.4$ Hz, 1H), 3.82 (d, $J = 10.3$ Hz, 3H), 3.73 (s, 3H), 3.60-3.50 (m, 1H), 3.57 (d, $J = 10.3$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl₃) δ 153.2, 141.6, 138.3, 128.4, 127.9, 125.8, 116.0, 114.7, 75.0 (d, $J = 162.0$ Hz), 55.7, 54.4 (d, $J = 7.2$ Hz), 53.9 (d, $J = 7.6$ Hz), 52.8 (d, $J = 5.5$ Hz). $^{31}$P NMR (162 MHz, CDCl₃) δ 23.9. HRMS: m/z calculated for [C₁₇H₂₃NO₅P]⁺: 352.1308; found: 352.1298. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [Hexano:i-PrOH (90:10), flow rate 1 mL/min; $\tau_{\text{major}} = 42.8$ min, $\tau_{\text{minor}} = 41.0$ min (95% ee); $\left[\alpha\right]_D^{20} = +9.7$ (c 0.5, CHCl₃).

(5c): Brown solid (96 mg, 44%); M.p. = 99-101 °C. $^1$H NMR (400 MHz, CDCl₃) δ 7.53 (d, $J = 6.4$ Hz, 2H), 7.21 (d, $J = 8.0$ Hz, 2H), 6.74 (d, $J = 8.8$ Hz, 2H), 6.64 (d, $J = 8.9$ Hz, 2H), 4.37 (bs, 1H), 3.92 (dd, $J = 12.6$, 6.4
Chir: 376.5 MHz, CDCl₃) δ 153.0, 141.7, 137.6, 135.2, 129.0, 125.7, 115.7, 114.6, 75.0 (d, J = 162.2 Hz), 55.6, 54.3 (d, J = 7.3 Hz), 53.8 (d, J = 7.6 Hz), 52.5 (d, J = 6.2 Hz), 21.0. ³¹P NMR (162 MHz, CDCl₃) δ 24.1. HRMS: m/z calculated for [C₁₈H₂₅NO₅P]⁺: 366.1465; found: 366.1456. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane/i-PrOH (80:20)]; flow rate 1 mL/min; τ_major = 23.5 min, τ_minor = 21.2 min (90% ee); [α]D²⁰ = +7.5 (c 0.5, CHCl₃).

(5h): Brown solid (129 mg, 50%); M.p. = 132-134 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.86 (s, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 6.78 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 8.9 Hz, 2H), 4.43 (bs, 1H), 3.94 (dd, J = 12.8, 6.6 Hz, 1H), 3.85 (d, J = 10.3 Hz, 3H), 3.76 (s, 3H), 3.66 (d, J = 10.4 Hz, 3H), 3.54 (dd, J = 20.4, 12.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 153.1, 141.4, 140.9, 131.0, 129.8, 129.0, 124.5, 122.6, 115.9, 114.7, 74.8 (d, J = 164.3 Hz), 55.8, 54.6 (d, J = 7.3 Hz), 53.9 (d, J = 7.8 Hz), 52.7 (d, J = 5.6 Hz). ³¹P NMR (162 MHz, CDCl₃) δ 23.3. HRMS: m/z calculated for [C₁₁H₂₂BrNO₅P]⁺: 430.0413; found: 430.0400. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane/i-PrOH (85:15)]; flow rate 1 mL/min; τ_major = 20.9 min, τ_minor = 19.8 min (90% ee); [α]D²⁰ = +8.3 (c 0.5, CHCl₃).

(5i): Yellow oil (122 mg, 55%); ¹H NMR (400 MHz, CDCl₃) δ 7.83-7.44 (m, 2H), 7.07 (t, J = 8.6 Hz, 2H), 6.74 (d, J = 8.8 Hz, 2H), 6.64 (d, J = 8.8 Hz, 2H), 4.51 (bs, 1H), 3.92 (dd, J = 12.7, 6.4 Hz, 1H), 3.79 (d, J = 10.3 Hz, 3H), 3.72 (s, 3H), 3.59 (d, J = 10.4 Hz, 3H), 3.52 (dd, J = 20.2, 12.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 162.3 (dd, J = 246.9, 2.6 Hz), 153.1, 141.6, 134.1, 127.7 (m), 115.8, 115.2 (d, J = 21.3 Hz), 114.7, 74.8 (d, J = 162.7 Hz), 55.6, 54.4 (d, J = 7.3 Hz), 53.9 (d, J = 7.6 Hz), 52.6 (d, J = 6.2 Hz). ³¹P NMR (162 MHz, CDCl₃) δ 23.7 (d, J = 4.5 Hz). ¹⁹F NMR (376.5 MHz, CDCl₃) δ −114.4 (d, J = 4.4 Hz). HRMS: m/z calculated for [C₁₁H₂₂FNO₅P]⁺: 370.1214; found: 370.1203. The enantiomeric excess was determined by HPLC using a Chiralpak IB column [hexane/i-PrOH (90:10)]; flow rate 1 mL/min; τ_major = 19.0 min, τ_minor = 20.5 min (90% ee); [α]D²⁰ = +3.6 (c 0.5, CHCl₃).
(5j): White solid (102 mg, 46%); M.p. = 111-113 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.79 (t, \(J = 7.8\) Hz, 1H), 7.37-7.27 (m, 1H), 7.21 (t, \(J = 7.6\) Hz, 1H), 7.06 (dd, \(J = 12.1, 8.2\) Hz, 1H), 6.77 (d, \(J = 9.0\) Hz, 2H), 6.72 (d, \(J = 9.1\) Hz, 2H), 4.74 (bs, 1H), 4.32-4.06 (m, 1H), 3.82 (d, \(J = 10.2\) Hz, 3H), 3.74 (s, 3H), 3.72-3.60 (m, 1H), 3.71 (d, \(J = 10.5\) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 159.6 (d, \(J = 248.4\) Hz), 153.4, 141.6, 129.9 (m), 129.2, 125.7 (d, \(J = 12.5\) Hz), 124.3, 116.5, 116.1 (d, \(J = 23.8\) Hz), 114.7, 74.2 (dd, \(J = 164.2, 4.8\) Hz), 55.9, 54.7 (d, \(J = 7.1\) Hz), 53.8 (d, \(J = 7.7\) Hz), 51.5 (dd, \(J = 9.4, 4.0\) Hz). \(^{31}\)P NMR (162 MHz, CDCl\(_3\)) \(\delta\) 23.5 (d, \(J = 5.7\) Hz). \(^{19}\)F NMR (376.5 MHz, CDCl\(_3\)) \(\delta\) -109.7 (d, \(J = 5.7\) Hz). HRMS: m/z calculated for [C\(_{17}\)H\(_{22}\)FNO\(_5\)P]\(^+\): 370.1214; found: 370.1205. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane/i-PrOH (85:15)]; flow rate 1 mL/min; \(\tau_{\text{major}} = 26.2\) min, \(\tau_{\text{minor}} = 34.3\) min (97% ee); [\(\alpha\)]\(_D\)\(^{20}\) = +3.2 (c 0.5, CHCl\(_3\)).
8. NMR spectra:

$^1$H NMR (CDCl$_3$, 300 MHz) of 6a:

$^{13}$C NMR (CDCl$_3$, 125 MHz) of 6a:
$^{31}$P NMR (CDCl$_3$, 162 MHz) of 6a:
$^1$H NMR (CDCl$_3$, 400 MHz) of 6b:

![NMR spectrum of 6b](image)

$^{13}$C NMR (CDCl$_3$, 100 MHz) of 6b:

![NMR spectrum of 6b](image)
$^{31}$P NMR (CDCl$_3$, 162 MHz) of 6b:
$^1$H NMR (CDCl$_3$, 300 MHz) of 6c:

$^{13}$C NMR (CDCl$_3$, 75 MHz) of 6c:
$^{31}$P NMR (CDCl$_3$, 162 MHz) of 6c:
$^1$H NMR (CDCl$_3$, 300 MHz) of 6d:

![NMR Spectrum](image)

$^{13}$C NMR (CDCl$_3$, 75 MHz) of 6d:

![NMR Spectrum](image)
$^{31}$P NMR (CDCl$_3$, 162 MHz) of 6d:
$^1$H NMR (CDCl$_3$, 300 MHz) of 6e:

$^{13}$C NMR (CDCl$_3$, 125 MHz) of 6e:
$^{31}\text{P NMR (CDCl}_3, 162\text{ MHz)}$ of $6e$: 
$^1$H NMR (CDCl$_3$, 300 MHz) of 6f:

$^{13}$C NMR (CDCl$_3$, 125 MHz) of 6f:
$^{31}$P NMR (CDCl$_3$, 162 MHz) of 6f:
$^1$H NMR (CDCl$_3$, 300 MHz) of 6g:

$^{13}$C NMR (CDCl$_3$, 100 MHz) of 6g:
$^{31}$P NMR (CDCl$_3$, 162 MHz) of 6g:
$^1$H NMR (CDCl$_3$, 300 MHz) of 6h:

$^{13}$C NMR (CDCl$_3$, 75 MHz) of 6h:
$^{31}$P NMR (CDCl$_3$, 400 MHz) of 6h:
$^1$H NMR (CDCl$_3$, 300 MHz) of 6i:

$^{13}$C NMR (CDCl$_3$, 125 MHz) of 6i:
$^{31}$P NMR (CDCl$_3$, 162 MHz) of 6i:

![31P NMR spectrum of 6i]

$^{19}$F NMR (CDCl$_3$, 376.5 MHz) of 6i:

![19F NMR spectrum of 6i]
$^1$H NMR (CDCl$_3$, 300 MHz) of $6j$:

$^{13}$C NMR (CDCl$_3$, 100 MHz) of $6j$:
$^{31}\text{P NMR (CDCl}_3, 400\text{ MHz)}$ of 6j:

$^{19}\text{F NMR (CDCl}_3, 400\text{ MHz)}$ of 6j:
$^1$H NMR (CDCl$_3$, 400 MHz) of 6k:

$^{13}$C NMR (CDCl$_3$, 100 MHz) of 6k:
$^{31}$P NMR (CDCl$_3$, 400 MHz) of 6k:
$^1$H NMR (CDCl$_3$, 300 MHz) of 6l:

![1H NMR spectrum of 6l](image1)

$^{13}$C NMR (CDCl$_3$, 75 MHz) of 6l:

![13C NMR spectrum of 6l](image2)
$^{31}$P NMR (CDCl$_3$, 162 MHz) of 6l:
$^1$H NMR (CDCl$_3$, 400 MHz) of 6m:

$^{13}$C NMR (CDCl$_3$, 100 MHz) of 6m:
$^{31}$P NMR (CDCl$_3$, 162 MHz) of 6m:
$^1$H NMR (CDCl$_3$, 400 MHz) of crude 8i:
$^1$H NMR (CDCl$_3$, 400 MHz) of 5a:

$^{13}$C NMR (CDCl$_3$, 100 MHz) of 5a:
$^{31}$P NMR (CDCl$_3$, 162 MHz) of 5a:
$^1$H NMR (CDCl$_3$, 400 MHz) of 5c:

$^{13}$C NMR (CDCl$_3$, 100 MHz) of 5c:
\(^{31}\)P NMR (CDCl\(_3\), 162 MHz) of 5c:
$^1$H NMR (CDCl$_3$, 400 MHz) of 5h:

$^{13}$C NMR (CDCl$_3$, 100 MHz) of 5h:
$^{31}$P NMR (CDCl$_3$, 162 MHz) of 5h:
$^1$H NMR (CDCl$_3$, 400 MHz) of 5i:

![NMR spectrum](image1)

$^{13}$C NMR (CDCl$_3$, 100 MHz) of 5i:

![NMR spectrum](image2)
$^{31}$P NMR (CDCl$_3$, 162 MHz) of 5i:

$^{19}$F NMR (CDCl$_3$, 376.5 MHz) of 5i:
$^1$H NMR (CDCl$_3$, 400 MHz) of 5j:

$^{13}$C NMR (CDCl$_3$, 100 MHz) of 5j:
$^{31}$P NMR (CDCl$_3$, 162 MHz) of 5j:

$^{19}$F NMR (CDCl$_3$, 376.5 MHz) of 5j:
9. HPLC chromatograms

HPLC conditions for 6a: Chiralpak OJ column [hexane/i-PrOH (90:10) 1 mL/min]

Racemic:

Enantioenriched:

<table>
<thead>
<tr>
<th>Processed Channel</th>
<th>Retention Time (min)</th>
<th>Area</th>
<th>% Area</th>
<th>Height</th>
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HPLC conditions for $6b$: Chiralpak OJ column [hexane/i-PrOH (98:2)] 1 mL/min

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Enantioenriched:

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HPLC conditions for 6c: Chiralpak IA column [hexane/i-PrOH (90:10) 1 mL/min]

Racemic:

![Racemic Peak Diagram]

Enantioenriched:

![Enantioenriched Peak Diagram]

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HPLC conditions for 6d: Chiralpak IA column [hexane/i-PrOH (90:10) 1 mL/min]

Racemic:

![Racemic chromatogram](image)

Enantioenriched:

![Enantioenriched chromatogram](image)

<table>
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HPLC conditions for 6e: Chiralpak IA column [hexane/i-PrOH (90:10) 1 mL/min]

Racemic:

Enantioenriched:
HPLC conditions for 6f: Chiralpak IA column [hexane/i-PrOH (90:10) 1 mL/min]

Racemic:

Enantioenriched:

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HPLC conditions for 6g: Chiralpak IB column [hexane/i-PrOH (90:10) 1 mL/min]

Racemic:

Enantioenriched:

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HPLC conditions for 6h: Chiralpak OJ column [hexane/i-PrOH (98:2) 1 mL/min]

Racemic:

Enantioenriched:

Processed Channel: PDA 220.2 nm

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HPLC conditions for 6i: Chiralpak IA column [hexane/i-PrOH (90:10) 1 mL/min]

Racemic:

Enantioenriched:
HPLC conditions for 6j: Chiralpak IA column [hexane/i-PrOH (90:10) 1 mL/min]

Racemic:

Enantioenriched:

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HPLC conditions for 6k: Chiralpak IA column [hexane/i-PrOH (90:10) 1 mL/min]

Racemic:

Enantioenriched:

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HPLC conditions for 61: Chiralpak IA column [hexane/i-PrOH (90:10) 1 mL/min]

Racemic:

Enantioenriched:

Processed Channel: PDA 221.5 nm

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HPLC conditions for 6m: Chiralpak IA column [hexane/i-PrOH (90:10) 1 mL/min]

Racemic:

Enantioenriched:

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HPLC conditions for 5a: Chiralpak AD-H column [hexane/i-PrOH (90:10) 1 mL/min]

Racemic:

![Racemic HPLC graph]

Enantioenriched:

![Enantioenriched HPLC graph]

**Processed Channel: PDA 221.5 nm**

<table>
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HPLC conditions for 5c: Chiralpak AD-H column [hexane/i-PrOH (80:20) 1 mL/min]

Racemic:

Enantioenriched:

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HPLC conditions for 5h: Chiralpak AD-H column [hexane/i-PrOH (85:15) 1 mL/min]

Racemic:

Enantioenriched:

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HPLC conditions for 5i: Chiralpak IB column [hexane/i-PrOH (90:10) 1 mL/min]

Racemic:

Enantioenriched:

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<thead>
<tr>
<th>Processed Channel</th>
<th>Retention Time (min)</th>
<th>Area</th>
<th>% Area</th>
<th>Height</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDA 221.5 nm</td>
<td>18.953</td>
<td>11797844</td>
<td>94.67</td>
<td>389381</td>
</tr>
<tr>
<td>PDA 221.5 nm</td>
<td>20.520</td>
<td>663867</td>
<td>5.33</td>
<td>19819</td>
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</tbody>
</table>
HPLC conditions for 5j: Chiralpak AD-H column [hexane/i-PrOH (85:15) 1 mL/min]

Racemic:

Enantioenriched:

Processed Channel: PDA 219.1 nm

<table>
<thead>
<tr>
<th>Processed Channel</th>
<th>Retention Time (min)</th>
<th>Area</th>
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<tbody>
<tr>
<td>1 PDA 219.1 nm</td>
<td>26.171</td>
<td>5112824</td>
<td>98.60</td>
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<tr>
<td>2 PDA 219.1 nm</td>
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<td>72389</td>
<td>1.40</td>
<td>1955</td>
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