Electronic supplementary information

An easy entry to optically active α-amino phosphonic acid derivatives using phase transfer catalysis (PTC)

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Experimental details:

General methods: 1H, 13C, 31P and 19F NMR were recorded on a Varian AS 400 spectrometer running at 400, 100, 162 and 376 MHz, respectively, in CDCl3 as the solvent, unless otherwise stated. Chemical shifts are reported in the δ scale relative to residual solvent peaks for 1H and 13C NMR (1H NMR: 7.26 ppm for CDCl3 and 4.79 ppm for D2O/NaOH, 13C NMR: 77.0 ppm for CDCl3) or using an external reference for 31P, 19F NMR and 13C in D2O (31P NMR: 0.0 ppm for K3PO4 85%, 19F NMR: -163.0 ppm for CF3I, 13C NMR in D2O/NaOH: 0.0 ppm for sodium 3-(trimethylsilyl)-propionate). 13C NMR, 19F NMR and 31P NMR spectra were recorded on a broad band decoupled mode. Coupling constants (J) are given in Hertz. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES) ionisation techniques. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC, using a UV detector operating at 215 nm. Melting points were measured on a Büchi smp-20 apparatus and are uncorrected. Chromatographic purifications were performed using 70-230 mesh silica.

Materials: All commercially available solvents and reagents were used as received. α-Amido sulfones 1a-l were obtained following literature procedures.1 Racemic samples were obtained at room temperature using tetrabutylammonium bromide as the catalyst.

Preparation of N-(2-fluorobenzyl)-hydroquininium bromide (4f): α-Fluorobenzyl bromide (289 µL, 2.4 mmol) was added to a suspension of hydroquinine (652 mg, 2.0 mmol) in toluene (6 mL). The resulting mixture was heated to 80 °C with stirring. After 4 h the reaction mixture was allowed to cool to room temperature and evaporated in vacuo. The residue was dissolved in the minimal amount of CH2Cl2 (ca. 1 mL), and poured onto Et2O (ca. 20 mL) with stirring. The resulting precipitate was collected by suction filtration, washed several times with Et2O giving 4f as a light pink solid (793 mg, 77% yield). mp >210 °C; [α]D20 -109 (c 0.20 in CHCl3); δH 0.78 (3 H, t, J 7.1), 1.22-1.33 (2 H, m), 1.41-1.50 (1 H, m), 1.67-1.85 (2 H, m), 1.90 (1 H, br s), 2.04 (1 H, br s), 2.30-2.45 (1 H, m), 2.73-2.80 (1 H, m), 3.08-3.18 (1 H, br dt, J 6.4 and 11.5), 3.33 (1 H, br t, J 11.5), 3.66 (1 H, dd, J 7.2 and 11.0), 3.96 (3 H, s), 4.51 (1 H, d, J 12.1), 5.15 (1 H, td, J 3.3 and 11.7), 6.48 (1 H, d, J 11.7), 6.53 (1 H, d, J 7.7), 6.76 (1 H, d, J 6.9), 7.10 (1 H, d, J 2.7), 7.16-7.21 (1 H, m), 7.33 (1 H, dt, J 1.1 and 7.7), 7.39 (1 H, dd, J 2.6 and 9.3), 7.49-7.57 (1 H, m), 7.81 (1 H, d, J 4.9), 8.06 (1 H, d, J 9.0), 8.27 (1 H, dt, J 1.8 and 7.8), 8.79 (1 H, d, J 4.8); δC 11.2, 21.0, 23.8, 25.2, 26.4, 36.1, 50.9, 55.8, 57.3, 63.2, 63.4, 71.3, 100.6, 114.5 (d, J 13), 115.9 (d, J 22), 120.6, 121.4, 125.8 (d, J 26), 126.0, 132.4, 133.4 (d, J 9), 136.2, 142.9, 144.2, 147.8, 158.2, 162.0 (d, J 248); δ3 -114.5; m/z (ESI) 435 [M+]².

N-(2-fluorobenzyl)-hydroquinuninidium bromide (4g): Following the procedure used for 4f, the title compound was obtained as a light pink solid (793 mg, 77% yield). mp >210 °C; [α]D20 +125 (c 0.33 in CHCl3); δH 0.89 (3 H, t, J 7.2), 1.03 (1 H, ddd, J 5.1, 9.6 and 13.9), 1.54-1.86 (4 H, m), 1.91 (1 H, br s), 2.07 (1 H, br s), 2.49 (1 H, br t, J 12.4), 2.91 (1 H, br q, J 10.0), 3.44 (1 H, br t, J 3.5), 3.71 (1 H, br t, J 10.3), 3.79 (1 H, br t, J 9.2), 3.93 (3 H, s), 4.39-4.47 (1 H, m), 4.81 (1 H, d, J 12.2), 6.24 (1 H, d, J 11.9), 6.61 (1 H, d, J 6.0), 6.72 (1 H, d, J 6.3), 7.13 (1 H, br t, J 8.9), 7.19 (1 H, d, J 2.6), 7.20-7.24 (2 H, m), 7.45 (1 H, d, J 9.2), 7.60 (2 H, d, J 8.2), 7.68 (1 H, s), 7.82 (1 H, d, J 4.8); δC 17.8, 21.0, 24.0, 25.2, 26.4, 31.1, 36.1, 45.4, 50.9, 55.8, 57.3, 63.0, 63.3, 71.3, 100.6, 114.4, 120.6, 121.4, 125.8 (d, J 26), 126.0, 132.1, 133.4 (d, J 9), 136.2, 142.9, 144.2, 147.8, 158.2, 162.0 (d, J 248); δ3 -114.5; m/z (ESI) 435 [M+]².

7.28 (1 H, dt, J 1.2 and 7.6), 7.32 (1 H, dd, J 2.6 and 9.2), 7.44-7.51 (1 H, m), 7.82 (1H, d, J 4.5), 7.99 (1 H, d, J 9.3), 8.12 (1 H, dt, J 1.7 and 7.6), 8.70 (1 H, d, J 4.5); δ 11.4, 21.0, 24.2, 24.3, 24.6, 36.1, 55.8, 55.9, 56.4, 56.9, 64.6, 69.6, 100.8, 114.7 (d, J 13), 116.0 (d, J 22), 120.5, 121.4, 125.5, 125.6, 132.1, 133.2 (d, J 8), 136.3, 142.8, 144.2, 147.6, 158.1, 161.9 (d, J 249); δ -113.4; m/z (ESI) 435 [M⁺].

General procedure for the catalytic reaction of dimethylphosphate 2e with α-amido sulfones 1: Dimethylphosphate 2b (14 μL, 0.15 mmol for N-Boc α-amido sulfones 1a, c, e, g, i, j, l) was added to a test tube containing a mixture of α-amido sulfone 1 (0.10 mmol) and catalyst 4f (2.6 mg, 0.005 mmol) in toluene (1 mL). After the resulting mixture had been cooled to -78 °C, finely ground KOH (17 mg, 0.30 mmol), weighted in a oven-dried vial, was added in one portion. The reaction mixture was then vigorously stirred at the same temperature without any precaution to exclude moisture or air. After 60 h, sat. NH₄Cl (ca. 2 mL) was added, and the mixture was allowed to warm to room temperature. The toluene layer was separated, and the aqeous phase extracted twice with toluene (ca 1 mL). The combined organic extracts were then charged directly on a silica gel column, and the product was obtained using a n-hexane/EtOAc/acetone 5:3:2 mixture as eluent.

(R)-tert-Butyl 1-(dimethoxyphosphoryl)-3-phenylpropylcarbamate (3b). Following the general procedure and performing the reaction on a 1 mmol scale, the title compound was obtained as a colourless thick oil in 94% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/PrOH 80:20, flow rate 0.75 mL/min, tₘₐₗ 10.7 min; tₘᵢₐₖ 8.4 min; 88% ee). [α]D²⁰⁻¹₉ (c 0.64 in CHCl₃); δ₁ [some protons show multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 1.47 (9 H, s), 1.78-1.96 (1 H, m), 2.08-2.21 (1 H, m), 2.62-2.73 (1 H, m), 2.76-2.86 (1 H, m), 3.74 (3 H, d, J 10.7), 3.77 (3 H, d, J 10.7), 3.91 (0.1 H, br s), 4.04-4.16 (0.9 H, m), 4.48 (0.1 H, br s), 4.75 (1 H, d, J 9.9), 7.16-7.22 (3 H, m), 7.25-7.31 (2 H, m); δ₂ 28.2, 31.7, 32.0 (d, J 14), 46.1 (d, J 158), 52.9 (d, J 6), 53.1 (d, J 7), 80.1, 126.1, 128.4, 140.8, 155.3; δ₃ 28.3; m/z (ESI) 366 [M⁺ + Na⁺].

To verify the possibility of performing a Boc-deprotection CbzCl derivatisation sequence without affecting the enantiomeric excess of the products, necessary for the determination of the ee of products, racemisation did not occur to a considerable extent.

(S)-tert-Butyl 1-(dimethoxyphosphoryl)-3-phenylpropylcarbamate (ent-3b). Following the general procedure using catalyst 4g derived from hydroquinidine (0.01 mmol, 10 mol%) and using 3 equiv. of dimethyl phosphate 2b, the title compound was obtained as a colourless thick oil in 88% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/PrOH 80:20, flow rate 0.75 mL/min, tₘₐₗ 8.4 min; tₘᵢₐₖ 10.7 min; 34% ee). [α]D²⁰⁺⁶ (c 0.58 in CHCl₃). Spectral data were identical to compound 3b.

(R)-Benzyl 1-(dimethoxyphosphoryl)-3-phenylpropylcarbamate (3d). Following the general procedure the title compound was obtained as a white solid in 95% yield. The ee of the product was determined by HPLC, after conversion into its Cbz derivative 3f through Boc deprotection followed by CbzCl derivatisation (vide supra), using a Daicel Chiralpak AD-H column (hexane/PrOH 80:20, flow rate 0.75 mL/min, tₘₐₗ 10.8 min; tₘᵢₐₖ 13.7 min; 82% ee). mp 59-60 °C; [α]D²⁰⁻¹₁ (c 0.47 in CHCl₃); δ₁ [some protons show multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 0.99-1.33 (6

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H, m), 1.45 (9 H, s), 1.60-1.91 (5 H, m), 3.76 (6 H, d, J 10.4), 3.99 (1 H, ddd, J 4.5, 10.7 and 18.4), 4.52 (0.1 H, br d, J 12.1), 4.78 (0.9 H, d, J 11.4); δ: 25.8 (d, J 12), 26.0, 27.9, 28.0, 28.2, 30.4 (d, J 12), 38.5 (d, J 5), 51.2 (d, J 152), 52.3 (d, J 7), 52.8 (d, J 7), 80.0, 155.5 (d, J 5); δ: 28.1; m/z (ESI) 344 [M+ + Na].

**(R)-Benzy1 cyclohexyl(dimethoxyphosphoryl)methylcarbamate (3f).** Following the general procedure the title compound was obtained as a white solid in 93% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/iprOH 80:20, flow rate 0.75 mL/min, t\textsubscript{maj} 13.7 min; 89% ee). mp 86-88 °C; [\(\alpha\)]\textsubscript{D} -1.3 (c 0.54 in CHCl\textsubscript{3}); δ: 0.97-1.31 (5H, m), 1.58-1.92 (6H, m), 3.69 (3H, d, J 9.3), 3.74 (3H, d, J 10.4), 3.87-3.97 (0.1 H, m), 4.03 (0.9H, ddd, J 4.3, 10.7 and 18.9), 4.80 (0.1 H, br d, J 11.3), 5.06 (0.9H, br d, J 10.6), 5.09 (1H, d, J 12.3), 5.15 (1H, d, J 12.3), 7.30-7.37 (5H, m); δ: 25.9 (d, J 12), 26.0, 27.9, 28.0, 30.4 (d, J 11), 38.5 (d, J 4), 52.0 (d, J 150), 52.8 (d, J 6), 52.9 (d, J 6), 67.2, 128.0, 128.2, 128.5, 136.2, 156.2; δ: 27.5; m/z (ESI) 378 [M+ + Na].

**(S)-Benzy1 cyclohexyl(dimethoxyphosphoryl)methylcarbamate (ent-3f).** Following the general procedure using catalyst 4g derived from butyrolactone (0.010 mmol, 10 mol%), the title compound was obtained as a white solid in 99% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/iprOH 80:20, flow rate 0.75 mL/min, t\textsubscript{maj} 13.7 min; 78% ee). [\(\alpha\)]\textsubscript{D} +5 (c 0.68 in CHCl\textsubscript{3}). Spectral data were identical to compound 3f.

**(R)-tert-Butyl 1-(dimethoxyphosphoryl)-3-methylbutylcarbamate (3g).** Following the general procedure the title compound was obtained as a colourless oil in 93% yield. The ee of the product was determined by HPLC, after conversion into its Cbz derivative 3h through Boc deprotection followed by CbzCl derivatisation (vide supra), using a Daicel Chiralpak AD-H column (hexane/iprOH 80:20, flow rate 0.75 mL/min, t\textsubscript{maj} 8.2 min; 83% ee). [\(\alpha\)]\textsubscript{D} -1.3 (c 0.60 in CHCl\textsubscript{3}); δ: [some protons show multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 0.91 (3 H, d, J 6.8), 0.93 (3 H, d, J 6.8), 1.43 (9 H, s), 1.49-1.59 (2 H, m), 1.67-1.78 (1 H, m), 3.75 (3 H, d, J 10.7), 3.76 (3 H, d, J 10.5), 3.95-4.05 (0.1 H, m), 4.13 (0.9 H, ddd, J 5.5, 10.4 and 20.7), 4.31 (0.1 H, d, J 9.9), 4.57 (0.9 H, d, J 10.4); δ: 21.1, 23.2, 24.4 (d, J 13), 28.2, 38.4, 44.7 (d, J 156), 52.9 (d, J 6), 53.1 (d, J 6), 80.0, 155.2; δ: 29.2; m/z (ESI) 318 [M+ + Na].

**(R)-Benzy1 1-(dimethoxyphosphoryl)-3-methylbutylcarbamate (3h).** Following the general procedure the title compound was obtained as a colourless oil in 66% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/iprOH 80:20, flow rate 0.75 mL/min, t\textsubscript{maj} 8.2 min; 83% ee). [\(\alpha\)]\textsubscript{D} -1.3 (c 0.63 in CHCl\textsubscript{3}); δ: [some protons show multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 0.93 (3 H, d, J 6.8), 0.93 (3 H, d, J 6.8), 1.43 (9 H, s), 1.49-1.59 (2 H, m), 1.67-1.78 (1 H, m), 3.75 (3 H, d, J 10.7), 3.76 (3 H, d, J 10.5), 3.95-4.05 (0.1 H, m), 4.13 (0.9 H, ddd, J 5.5, 10.4 and 20.7), 4.31 (0.1 H, d, J 9.9), 4.57 (0.9 H, d, J 10.4); δ: 21.1, 23.2, 24.4 (d, J 13), 28.2, 38.4, 44.7 (d, J 156), 52.9 (d, J 6), 53.1 (d, J 6), 80.0, 155.2; δ: 29.2; m/z (ESI) 352 [M+ + Na].

**Absolute configuration of compound 3h was determined to be R by comparison of its optical rotation with a literature value:**

Measured optical rotation (86% ee): [\(\alpha\)]\textsubscript{D} -33 (c 0.63 in CHCl\textsubscript{3})

Lit.\(^{2}\) [\(\alpha\)]\textsubscript{D} -54.6 (c 1 in CHCl\textsubscript{3}) for the (R)-isomer.

**(R)-tert-Butyl 1-(dimethoxyphosphoryl)heptylcarbamate (3i).** Following the general procedure the title compound was obtained as a colourless oil in 84% yield. The ee of the product was determined by HPLC, after conversion into its Cbz derivative through Boc deprotection followed by CbzCl derivatisation (vide supra), using a Daicel Chiralpak AD-H column (hexane/iprOH 80:20, flow rate 0.75 mL/min, t\textsubscript{maj} 7.4 min; 87% ee). [\(\alpha\)]\textsubscript{D} -25 (c 0.53 in CHCl\textsubscript{3}); δ: [some protons show multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 0.86 (3 H, t, J 6.4), 1.21-1.38 (8 H, m), 1.43 (9 H, s), 1.74-1.85 (2 H, m), 3.76 (3 H, d, J 10.6), 3.77 (3 H, d, J 10.6), 3.85-3.95 (0.1 H, m), 4.05 (0.9 H, tdd, J 3.6, 10.9 and 19.4), 4.32 (0.1 H, br s), 4.62 (0.9 H, d, J 9.8); δ: 14.0, 22.5, 25.6 (d, J 14), 28.2, 28.7, 29.8, 31.5, 46.6 (d, J 155), 52.8 (d, J 6), 53.0 (d, J 7), 80.0, 155.3; δ: 28.8; m/z (ESI) 346 [M+ + Na].

**(R)-Benzy1 1-(dimethoxyphosphoryl)hexylcarbamate (3j).** Following the general procedure the title compound was obtained as a colourless oil in 97% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/iprOH 80:20, flow rate 0.75 mL/min, t\textsubscript{maj} 7.9 min; 95% ee). [\(\alpha\)]\textsubscript{D} -25 (c 0.62 in CHCl\textsubscript{3}); δ: [some protons show multiple resonances for the
presence of different rotamers due to restricted rotation around the C-N bonds] 0.86 (3 H, t, J 6.7), 1.19-1.52 (6 H, m), 1.76-1.93 (2 H, m), 3.71 (3 H, d, J 10.4), 3.74 (3 H, d, J 10.8), 3.91-4.02 (0.1 H, m), 4.08 (0.9 H, dtd, J 3.8, 10.6 and 20.8), 4.73 (0.1 H, d, J 9.2), 4.98 (0.9 H, d, J 10.4), 5.09 (1 H, d, J 12.2), 5.13 (1 H, d, J 12.2), 7.27-7.37 (5 H, m); δC: 13.9, 22.3, 25.3 (d, J 13), 29.7, 31.2, 47.2 (d, J 156), 52.9 (d, J 7), 53.1 (d, J 7), 67.1, 128.0, 128.2, 128.5, 136.3, 156.0; δα: 28.2; m/z (ESI) 366 [M+ + Na].

(S)-Benzyl 1-(dimethoxyphosphoryl)hexylcarbamate (ent-3j). Following the general procedure using catalyst 4g derived from hydroquinidine (10 mol%) the title compound was obtained as a colourless oil in 94% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/iPrOH 80:20, flow rate 0.75 mL/min, tR 9.8 min; tR 7.9 min; 84% ee). [α]D +22 (c 0.60 in CHCl3). Spectral data were identical to compound 3j.

(R)-tert-Butyl 1-(dimethoxyphosphoryl)propylcarbamate (3k). Following the general procedure the title compound was obtained as a colourless oil in 78% yield. The ee of the product was determined by HPLC, after conversion into its Cbz derivative through Boc deprotection followed by CbzCl derivatisation (vide supra), using a Daicel Chiralpak AD-H column (hexane/iPrOH 80:20, flow rate 0.75 mL/min, tR 8.4 min; 10.4 min 10% yield; 80% ee). [α]D +27 (c 0.40 in CHCl3); δC [some protons show multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 1.01 (3 H, t, J 7.6), 1.44 (9 H, s), 1.50-1.64 (1 H, m), 1.82-1.96 (1 H, m), 3.76 (3 H, d, J 10.7), 3.77 (3 H, d, J 10.5), 4.01 (1 H, dtd, J 4.0, 10.3 and 20.5), 4.33 (0.1 H, br s), 4.65 (0.9 H, d, J 10.5); δα: 10.4 (d, J 13), 23.3, 28.2, 47.9 (d, J 156), 52.9 (d, J 7), 53.1 (d, J 7), 80.0, 155.5; δα: 28.6; m/z (ESI) 290 [M+ + Na].

(R)-tert-Butyl 1-(dimethoxyphosphoryl)ethylcarbamate (3l). Following the general procedure the title compound was obtained as a colourless oil in 84% yield. The ee of the product was determined by HPLC through Boc deprotection followed by CbzCl derivatisation (vide supra), using a Daicel Chiralpak AD-H column (hexane/iPrOH 90:10, flow rate 0.75 mL/min, tR 13.8 min; tR 17.1 min; 79% ee). [α]D +17 (c 0.30 in CHCl3); δC [some protons show multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 1.39 (3 H, d, J 10.8), 4.11-4.26 (1 H, m), 4.85 (0.1 H, br s), 5.09 (0.9 H, d, J 11.0), 5.11 (2 H, s), 7.28-7.37 (5 H, m); δα: 15.9, 28.2, 42.2 (d, J 158), 52.9 (d, J 7), 53.2 (d, J 7), 80.1, 155.0; δα: 29.2; m/z (ESI) 276 [M+ + Na].

(R)-Benzy1 1-(dimethoxyphosphoryl)ethylcarbamate (3m). Following the general procedure the title compound was obtained as a colourless oil in 76% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/iPrOH 90:10, flow rate 0.75 mL/min, tR 13.8 min; tR 17.1 min; 80% ee). [α]D +15 (c 1.0 in CHCl3); δC [some protons show multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 1.39 (3 H, d, J 7.4 and 16.6), 3.73 (3 H, d, J 10.8), 3.75 (3 H, d, J 10.8), 4.11-4.26 (1 H, m), 4.85 (0.1 H, br s), 5.09 (0.9 H, d, J 11.0), 5.11 (2 H, s), 7.28-7.37 (5 H, m); δα: 15.9, 24.2 (d, J 158), 53.0 (d, J 6), 53.2 (d, J 6), 67.1, 128.1, 128.2, 128.5, 136.1, 155.6; δα: 28.6; m/z (ESI) 310 [M+ + Na].

The absolute configuration of compound 3m was determined to be R by comparison of its optical rotation with a literature value:

Measured optical rotation (80% ee): [α]D +15 (c 1.0 in CHCl3)

Lit. [α]D +17.5 (c 1 in CHCl3) for the (R)-isomer.

(R)-tert-Butyl 1-(dimethoxyphosphoryl)-2-phenylethylcarbamate (3n). Following the general procedure the title compound was obtained as a colourless oil in 83% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/iPrOH 80:20, flow rate 0.75 mL/min, tR 10.7 min; tR 8.3 min; 84% ee). [α]D +22 (c 0.73 in CHCl3); δC [some protons show multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 1.20 (2 H, s), 1.38 (7 H, s), 2.61-2.75 (0.2 H, m), 2.83 (0.8 H, td, J 10.2 and 14.5), 3.20 (1 H, ddd, J 5.1, 8.9 and 13.7), 3.76 (6 H, d, J 10.9), 4.12-4.20 (0.2 H, m), 4.41 (0.8 H, dtd, J 4.9, 10.6 and 21.2), 4.49 (0.2 H, br s), 4.68 (0.8 H, br s), 7.19-7.31 (5 H, m); δα: 28.1, 36.0, 47.4 (d, J 157), 52.9 (d, J 7), 53.2 (d, J 7), 80.0, 126.7, 128.4, 129.2, 136.5 (d, J 12), 155.0; δα: 27.8; m/z (ESI) 352 [M+ + Na].

Preparation of (R)-1-amino-3-phenylpropylphosphonic acid hydrochloride (5). In a test tube equipped with magnetic stirrer bar was placed phosphate 3b (0.1 mmol) in HCl 10 M (1.8 mL). The solution was refluxed for 18 h, which was followed by removal of the solvent under reduced pressure. The title compound was obtained as a white solid in 84% yield. The ee of the product was determined by

HPLC, after conversion into its N-Cbz dimethyl derivative 3d according to literature procedure, using a Daicel Chiralpak AD-H column (hexane/iPrOH 80:20, flow rate 0.75 mL/min, \( t_{\text{maj}} \) 12.4 min; \( t_{\text{min}} \) 14.7 min; 85% ee). mp > 300 °C (dec.); \([\alpha]_D^{20} -17 (c 0.48 \text{ in } 1 \text{ N NaOH aq.})
. \Delta_{
}\text{H} (D_2O/NaOH) 1.64 (1 H, br s), 2.07 (1 H, br s), 2.47-2.76 (2 H, m), 2.82-3.00 (1 H, m), 7.27 (1 H, br s), 7.37 (4 H, br s); \Delta_{
}\text{C} (D_2O/NaOH) 35.9 (d, \( J \) 13.5), 37.0, 52.7 (d, \( J \) 138), 128.8, 131.6, 146.2; \Delta_{\text{P}} (D_2O/NaOH) 22.0

\text{m/z} (ESI) 216 [M^+ + H].

Preparation of (R)-benzyl 1-(monomethoxyphosphoryl)ethylcarbamate (6). In a test tube equipped with magnetic stirrer bar was placed phosphonate 3m (0.076 mmol) in NaOH 2 M (0.1 ml). The mixture was stirred at 20 °C overnight. After dilution with H_2O (5 mL), the solution was washed twice with CHCl_3, acidified with 0.7 mL of concentrated HCl, and extracted 4 times with CHCl_3. The combined CHCl_3 extracts were dried (MgSO_4), filtered and the solvent was evaporated to give the title compound was obtained as a pale yellow waxy solid in 88% yield. The ee of the product was determined by HPLC, after conversion into its dimethyl derivative 3m according to literature procedure, using a Daicel Chiralpak AD-H column (hexane/iPrOH 90:10, flow rate 0.75 mL/min, \( t_{\text{maj}} \) 13.8 min; \( t_{\text{min}} \) 17.1 min; 80% ee). \Delta_{\text{H}} [some protons show multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 1.35 (3 H, dd, \( J \) 7.4 and 17.4), 3.72 (3 H, d, \( J \) 11.2), 3.92-4.31 (1 H, m), 5.11 (1 H, s), 5.28 (0.85 H, br s), 5.67 (0.15 H, br s), 7.34 (5 H, br s) 8.30 (1 H, br s); \Delta_{\text{C}} 15.6, 43.0 (d, \( J \) 161), 52.6 (d, \( J \) 6), 67.2, 128.1, 128.2, 128.5, 136.1, 155.8; \Delta_{\text{P}} [^{31}\text{P} spectrum shows multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 28.3 (0.15 P), 28.9 (0.85 P).

Copies of the $^1$H, $^{13}$C, $^{19}$F and $^{31}$P NMR spectra for compounds 4f, 4g, 3b, 3d-n, 5 and 6.

$^1$H NMR

$^{13}$C NMR

$^{19}$F NMR
$^1$H NMR

$^{13}$C NMR

$^{19}$F NMR
$^1$H NMR

$^{13}$C NMR

$^{31}$P NMR
$^1$H NMR

$^{13}$C NMR

$^{31}$P NMR
$^1$H NMR

$^{13}$C NMR

$^{31}$P NMR
$^1$H NMR

$^{13}$C NMR

$^{31}$P NMR
$^1$H NMR

$^{13}$C NMR

$^{31}$P NMR
$^1$H NMR

$^{13}$C NMR

$^{31}$P NMR
$^1$H NMR

$^{13}$C NMR

$^{31}$P NMR
$^1$H NMR

$^{13}$C NMR

$^{31}$P NMR