Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting Information

Mechanism and Optimisation of Homoboroproline Bifunctional Catalytic Asymmetric Aldol Reaction: Lewis Acid Tuning Through *In situ* Esterification

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General Information

All ^{1}H NMR were recorded with either Brucker Avance-400, Varian Inova-500 or Varian VNMRS-700 spectrometers. ^{13}C NMR were recorded on Varian Inova-500 of Varian VNMRSA-700 spectrometers at frequencies of 126,176 MHz. ^{11}B NMR were recorded with the Brucker Avance-400 or Varian Inova-500 at a frequency of 128MHz. Chemical shifts are expressed as parts per million (ppm) downfield from the internal stamdard TMS for ^{1}H and ^{13}C and to external $BF_3{\cdot}Et_2O$ for ^{11}B. Elemental analysis was performed using an Exeter Analytical E-440 Elemental Analyser. IR spectra were recorded with a Perkin-Elmer 1615 FTRIR spectrometer. Melting points were determined using an Electrothermal melting point apparatus. Chiral HPLC analyses were performed on a Gilson HPLC system equipped with a Gilson 321 pump, a Gilson 234 autoinjector, two Gilson valvemates, a Gilson UV-Vis detector 118 using a OJ-H chiralcel column. Glassware was oven dried (130 ^{o}C) as required and cooled under a positive pressure of argon. Dry solvents were prepared using the Innovative Technology Inc. solvent purification system and analysed with Metrohm 831 KF coulometer. All other chemicals and materials were purchased directly from standard chemical suppliers. Compound **1a** was prepared as reported in the literature.[1] Purification by medium pressure column chromatography was performed using silica gel 35-70 μm. TLC was performed on Polygram SIL G/UV_{254} plastic backed silica gel plates with visualization achieved using UV lamp, or by staining with $KMnO_4$. All evaporations were carried out at 20 mmHg on a Büchi rotary evaporator, followed by drying *in vacuo* (<2 mmHg). Molecular sieves were activated by heating at 250 °C.

General procedure for the formation of the calibration curves

Standard solutions with concentrations from 0.1M to 0.02M were prepared by dissolving the appropriate amount of the relevant compound (*p*-nitrobenzaldehyde, aldol condensation product **2** and aldol elimination product **3**) in acetone. From each concentrated standard solution 50 μL were dissolved in 95 μL of a hexane and IPA (9:1) solution, forming diluted solutions with the lowest concentration being 0.001M and the highest 0.005M. In each sample (10 mol%) of naphthalene was added as an internal standard. The absorption of every concentration was measured three times using chiral HPLC.

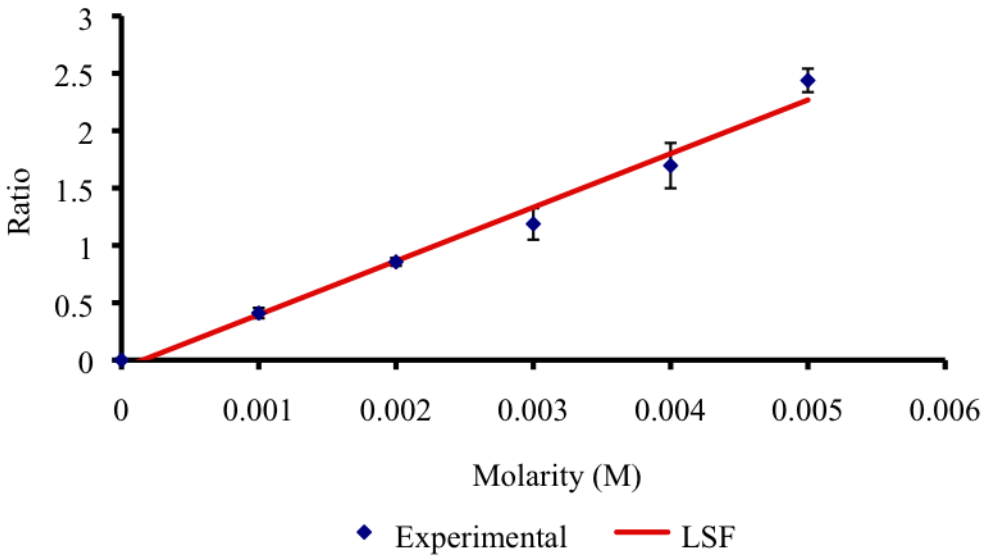

Figure 1: Calibration curve of *p*-nitrobenzaldehyde (y = 467.99 x -007197)

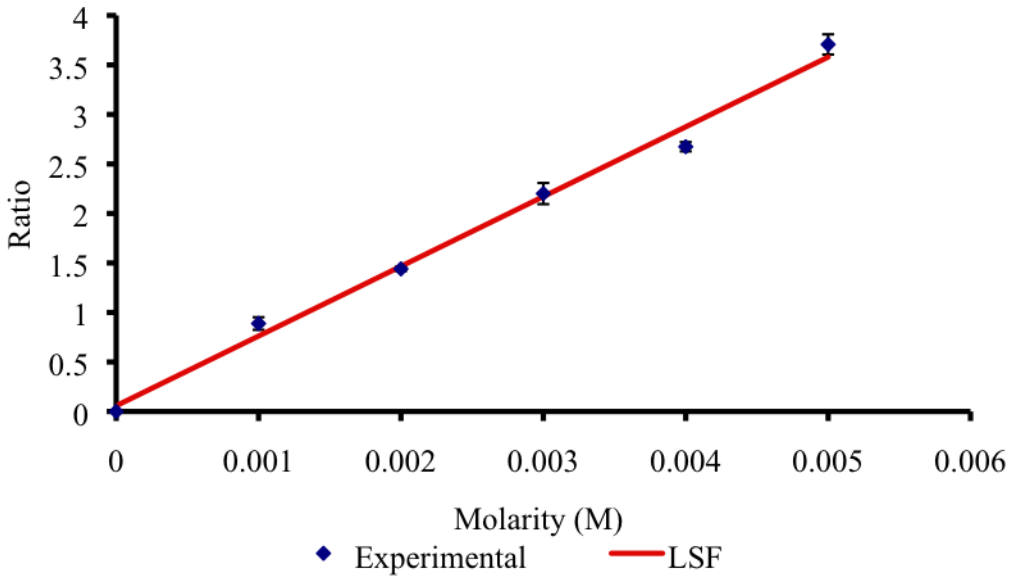

Figure 2: Calibration curve of the aldol product **2** (y = 704.39 + 0.0575)

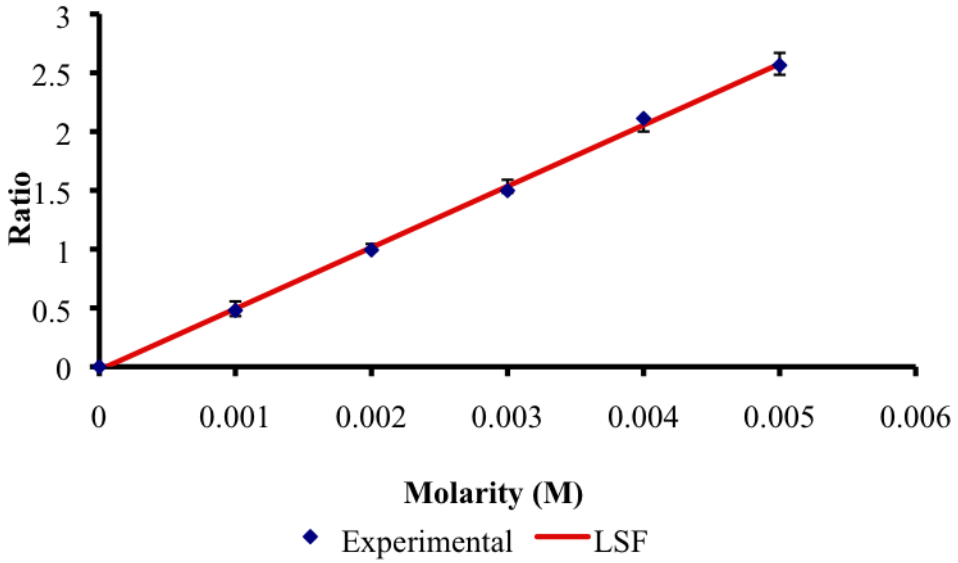

Figure 3: Calibration curve of the aldol condensation product **3** (y = 520.62 x -0.0271)

General procedure for monitoring the aldol reaction over time using HPLC system - See main paper, Figure 4

Compound **1a** (16.5mg, 0.1 mmol) and di*iso*propyl-D-tartrate (21 µL, 0.1 mmol) were stirred at 25 °C in the presence of 200 mg of 3 Å molecular sieves in acetone (5 mL) for 2h before *p*-nitrobenzaldehyde (75.6 mg, 0.5 mmol), triethylamine (13.9 µL, 0.1 mmol) and naphthalene (6.4 mg, 10 mol%) were added. Every 1 h, 100 µL were sampled from the reaction mixture, filtered and extracted with 200 µL with sat. aq. NH_4Cl. Then 50 µL of the organic phase were dissolved in 950 µL of hexane and IPA (9:1) solution. The sample was then analysed by chiral HPLC (Figure 4).

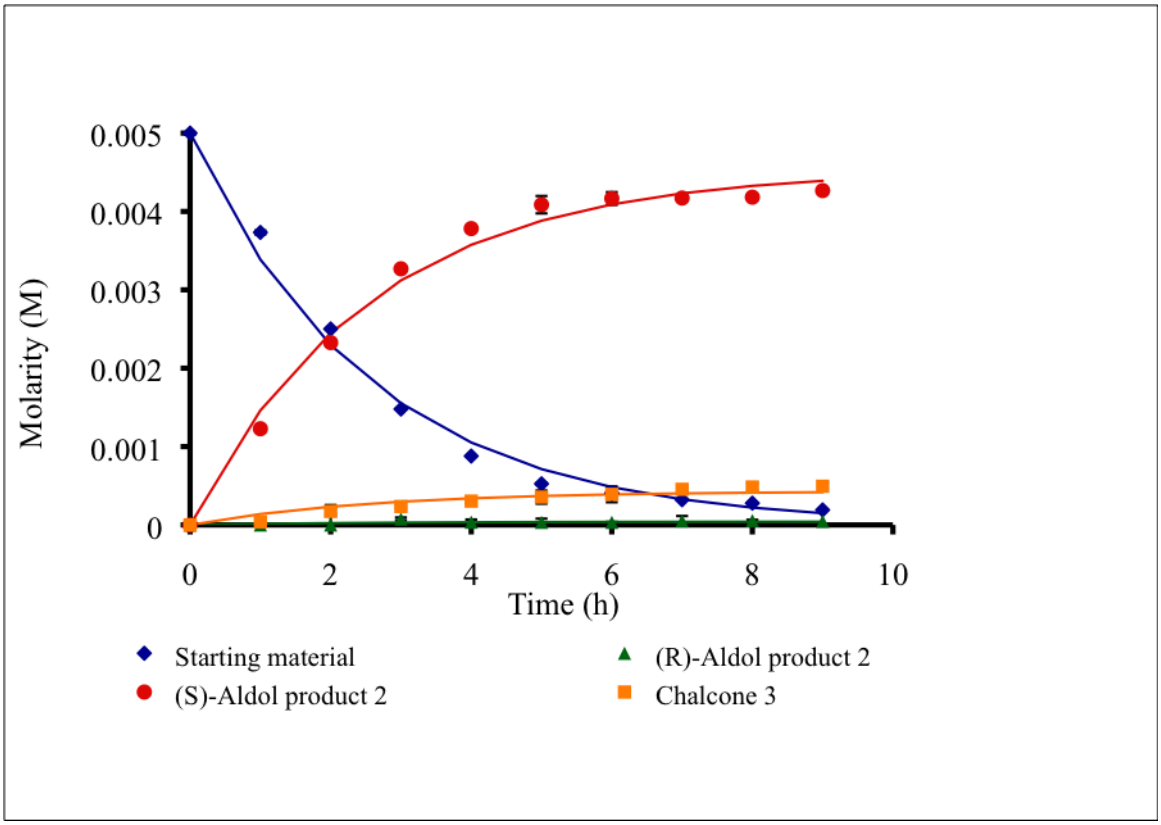

Figure 4: Molarity of the starting material, (*S*)-aldol product **2**, (*R*)-aldol product **2** and chalcone **3** over time when the reaction was carried out in neat acetone using the di*iso*propyl-D-tartrate derived catalyst, *i.e.* **10b**.

General procedure for monitoring the aldol reaction over time using HPLC system - See main paper, Figure 5

Compound **1a** (16.5mg, 0.1 mmol) and (*R*,*R*)-hydrobenzoin (21.4 mg, 0.1 mmol) were stirred at 25 °C in the presence of 200 mg of 3 Å molecular sieves in DMF (5 mL) for 2h before *p*-nitrobenzaldehyde (75.6 mg, 0.5 mmol), acetone (0.37 mL, 5 mmol), triethylamine (13.9 µL, 0.1 mmol) and naphthalene (6.4 mg, 10 mol%) were added. Every 1 h, 100 µL were sampled from the reaction mixture, filtered and extracted with 200 µL with sat. aq. NH_4Cl. Then 50 µL of the organic phase were dissolved in 950 µL of hexane and IPA (9:1) solution. The sample was then analysed by chiral HPLC (Figure 5).

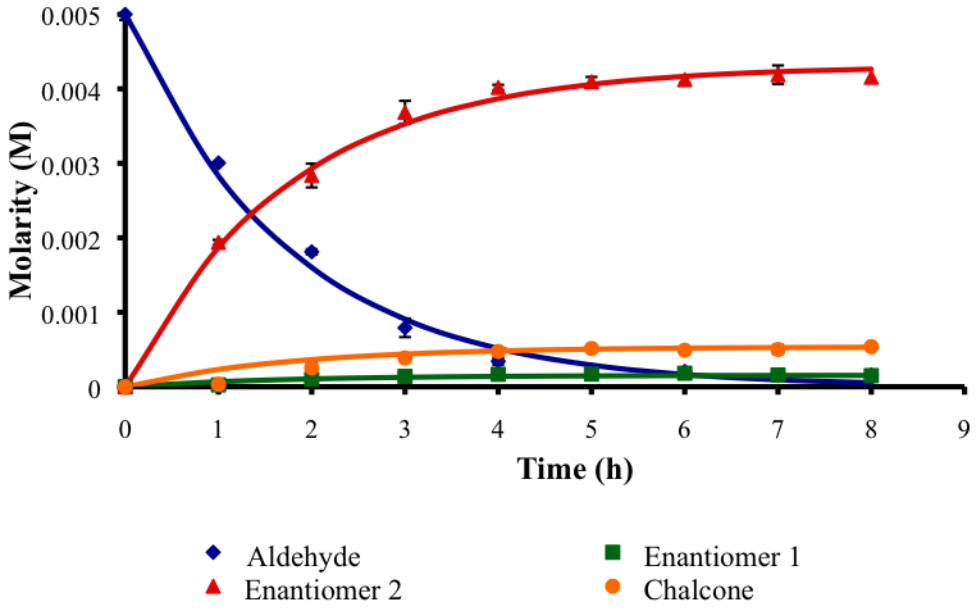

Figure 5: Molarity of the starting material, (*S*)-aldol product **2**, (*R*)-aldol product **2** and chalcone **3** over time when the reaction was carried out in DMF using the (*R*,*R*)-hydrobenzoin derived catalyst, *i.e.* **11**.

Procedure for monitoring the aldol reaction in the presence of compound 12 **over time using HPLC system**

Compound **1a** (16.5mg, 0.1 mmol) and (*meso*)-hydrobenzoin (21.4 mg, 0.1 mmol) were stirred at 25 ^{o}C in the presence of 200 mg of 3 Å molecular sieves in DMF (5 mL) for 2h before *p*-nitrobenzaldehyde (75.6 mg, 0.5 mmol), acetone (0.37 mL, 5 mmol), triethylamine (13.9 µL, 0.1 mmol) and naphthalene (6.4 mg, 10 mol%) were added. Every 1 h, 100 µL were sampled from the reaction mixture, filtered and extracted with 200 µL with sat. aq. NH_4Cl. Then 50 µL of the organic phase were dissolved in 950 µL of hexane and IPA (9:1) solution. The sample was then analysed by chiral HPLC (Figure 6).

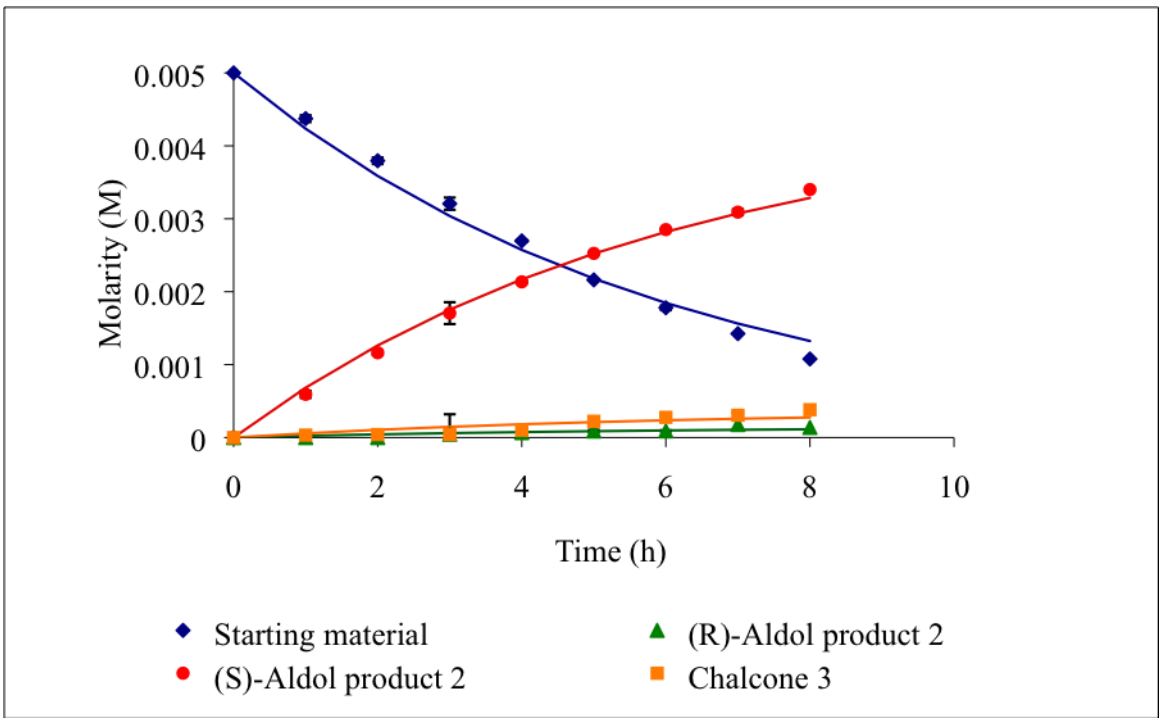

Figure 6: Molarity of the starting material, (*S*)-aldol product **2**, (*R*)-aldol product **2** and chalcone **3** over time when the reaction was carried out in DMF using the (*meso*)-hydrobenzoin derived catalyst, *i.e.* **12**.

Procedure for investigating possible kinetic resolution of racemic aldol product 2 in the absence of acetone - See main paper Figure 6 and 7

Compound **1a** (16.5mg, 0.1 mmol) and (*R*,*R*)-hydrobenzoin (21.4 mg, 0.1 mmol) were stirred at 25 ^{o}C in the presence of 200 mg of 3 Å molecular sieves in DMF (5 mL) for 2h before racemic aldol condensation product **2** (104.6 mg, 0.5 mmol), triethylamine (13.9 µL, 0.1 mmol) and naphthalene (6.4 mg, 10 mol%) were added. Every 1 h, 100 µL were sampled from the reaction mixture, filtered and extracted with 200 µL with sat. aq. NH_4Cl. Then 50 µL of the organic phase were dissolved in 950 µL of hexane and IPA (9:1) solution. The sample was then analysed by chiral HPLC.

Procedure for investigating possible kinetic resolution of racemic aldol product 2 in the presence of acetone

Compound **1a** (16.5mg, 0.1 mmol) and (*R*,*R*)-hydrobenzoin (21.4 mg, 0.1 mmol) were stirred at 25 ^{o}C in the presence of 200 mg of 3 Å molecular sieves in DMF (5 mL) for 2h before racemic aldol condensation product **2** (104.6 mg, 0.5 mmol), acetone (0.37 mL, 5 mmol), triethylamine (13.9 µL, 0.1 mmol) and naphthalene (6.4 mg, 10 mol%) were added. Every 1 h, 100 µL were sampled from the reaction mixture, filtered and extracted with 200 µL with sat. aq. NH_4Cl. Then 50 µL of the organic phase were dissolved in 950 µL of hexane and IPA (9:1) solution. The sample was then analysed by chiral HPLC (Figures 7and 8).

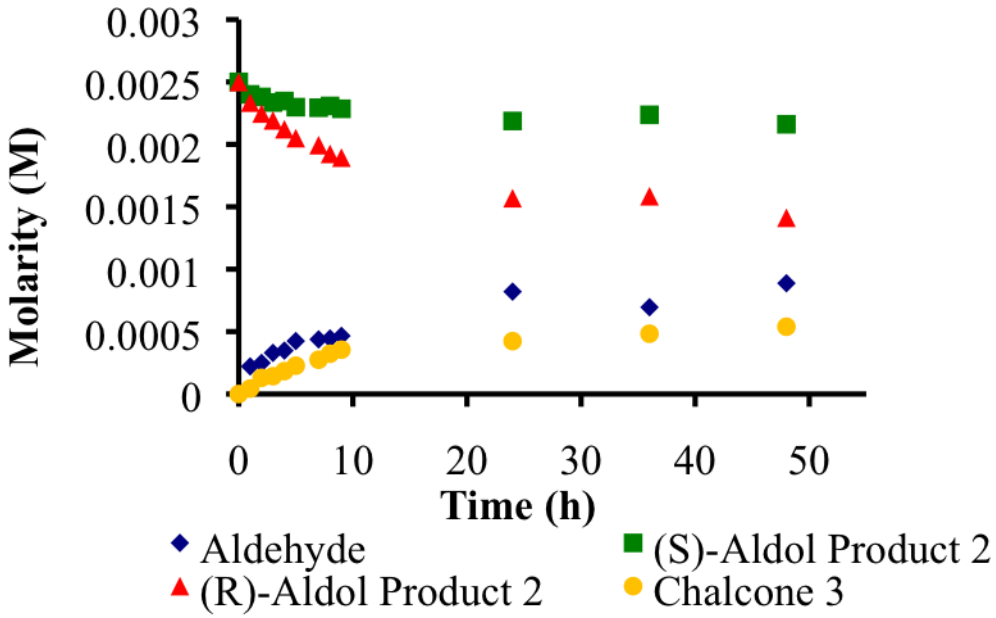

Figure 7: Molarity of the (*S*)-aldol product **2**, (*R*)-aldol product **2** and chalcone **3** over time when the kinetic resolution of racemic aldol **2** was carried out in the presence of acetone.

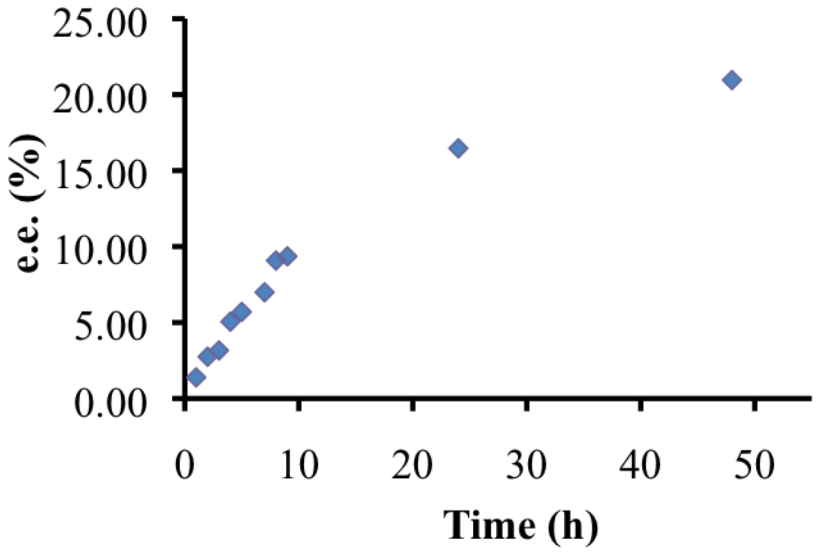

Figure 8: Enantiomeric excess of aldol product **2** over time when the kinetic resolution of racemic aldol **2** was carried out in the presence of acetone.

HPLC conditions used

During the formation of the calibration curves and the procedure of monitoring the aldol reactions the same HPLC conditions were used. The stationary phase was an OJ-H chiral column and the mobile phase a hexane and IPA (9:1) solution. The separation was achieved at 15 °C, with an injection

volume of 8 μL, a wavelength of 200 nm and flow rate 1 mL/min. Retention times: 7.0 min [naphthalene], 25.0 min [*p*-NO_2PhCHO], 37.2 min [(R)-aldol condencation product **2**], 42.3 min [(S)-aldol condensation product **2**], 48.1 min [aldol elimination product **3**].

References

1. K. Arnold, A. S. Batsanov, B. Davies, C. Grosjean, T. Schütz, A. Whiting, K. Zawatzky, *Chem. Commun.* **2008**, 3879-3881.