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# Supporting Information for:

# Supramolecular polymers for organocatalysis in water

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## Characterisation of compound 1

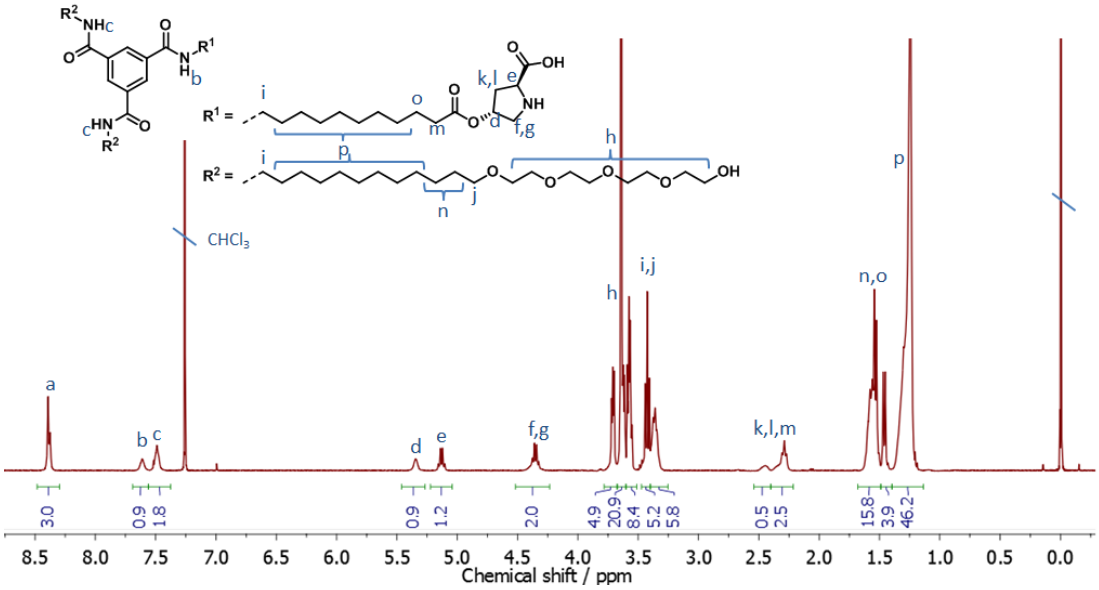



**Figure S1** $^{1}$H NMR spectrum (400 MHz, $CDCl_3$) of **1**.

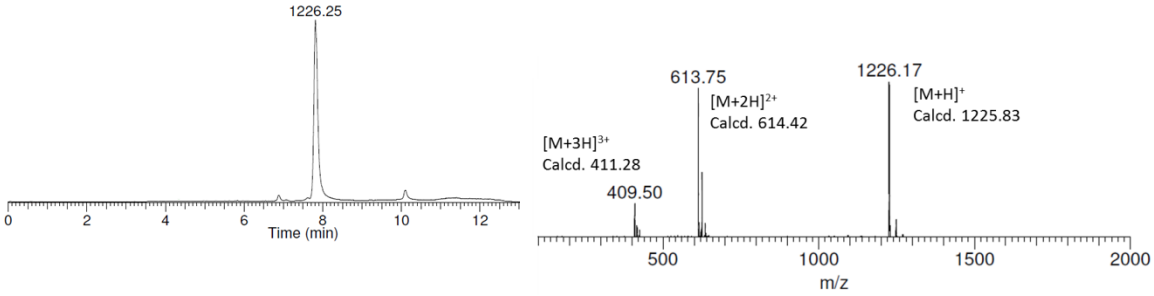



**Figure S2**: LC-MS (ESI) trace of pure compound **1** (left) and mass trace of the peak (right).

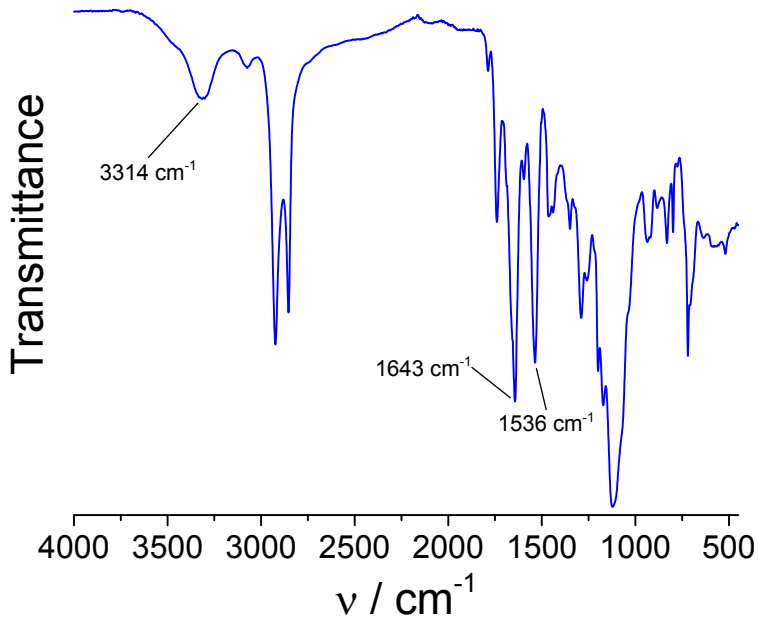
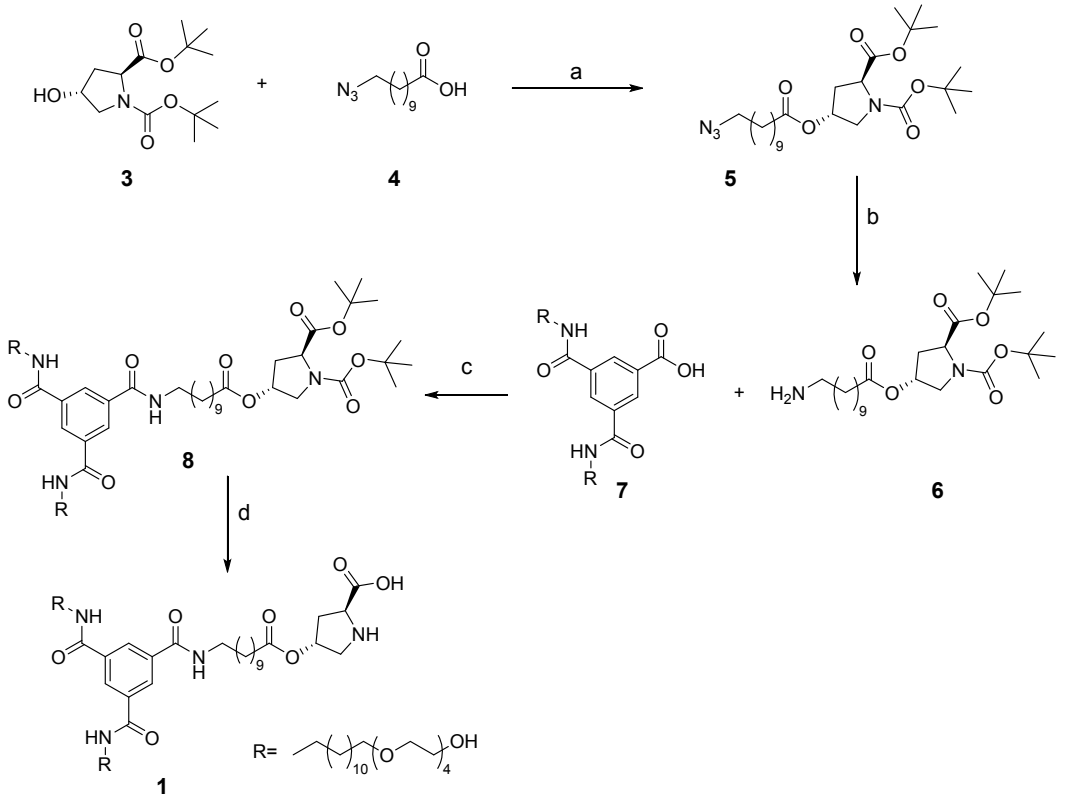



**Figure S3**: IR spectrum of **1** in bulk.

## Details on the synthesis procedure to prepare BTA 1




During the storage of **6,** oligomerisation of **6** yielded amide oligomers **6B** and **6C** (~20% impurity, based on LC-MS), which were not removed at this stage (Figure S1).

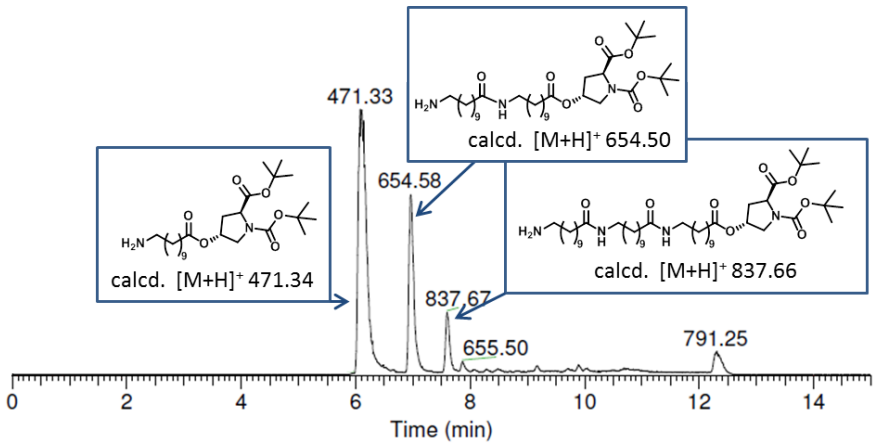
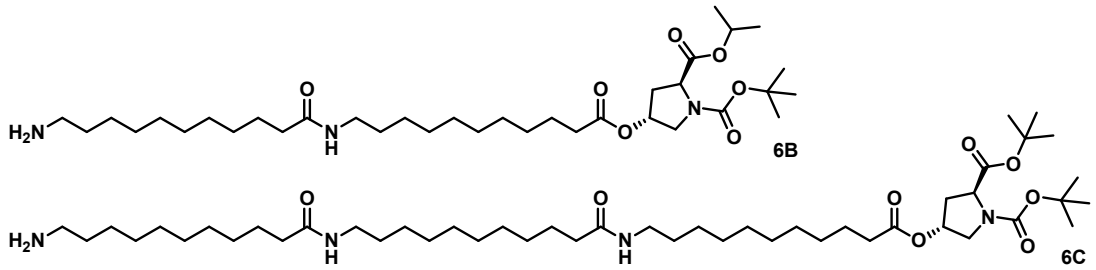



Figure S4: LCMS trace showing desired **6** and the self-condensated oligomers **6B** and **6C**.




MALDI-TOF: calcd. [**6B** + Na]$^+$ 676.49, found 676.47; [**6C** + Na]$^+$ 859.65, found 859.63. ESI: calcd. [**6B** + H]$^+$ 654.50, found 654.50; [**6C** + H]$^+$ 837.66, found 837.67.

Since the impurities present in **6** remained present during the synthesis of **8**, also here an oligomer was observed in th LC trace (ESI: calcd. [**8B** + Na]$^+$ 1587.10, found 1587.17). Finally, the undesired oligomers were removed after the synthesis of **1** by reverse phase column chromatography (water/acetonitrile 50/50 to 30/70 v/v) yielding **1** as a pure, sticky, white solid (182 mg, 70%).

## Catalysis experiments

A 15 mM stock solution of the catalyst **1** or a 1:1 mixture of **1** and **2** was prepared in methanol. The appropriate amount of stock solution was transferred to a 1.5 mL vial and the solvent was removed under a stream of argon at room temperature and subsequently in the vacuum oven at 40°C. Water (Milli-Q grade, 0.5 mL) was added and the mixture was sonicated for 2 minutes using either a Branson 2510 2510E-DTH sonicator or a VWR Ultrasonic cleaner USC 300T. Equilibration overnight at room temperature yielded clear solutions. Then, aldehyde (3.77 mg, 0.025 mmol, 1eq) and ketone (24.50 mg, 0.250 mmol, 10 eq) was added and the mixture was mixed vigorously for 24 hours at room temperature. The aldol products were extracted with diethyl ether (3 x 1 mL) and the organic extracts were dried in air. The crude products were analysed by $^{1}$H-NMR (400 MHz, $CDCl_3$) (for the determination of the conversion and diastereomeric excess) and chiral HPLC (for the determination of the enantiomeric excess) equipped with Chiralpak-IA chiral column in hexane/THF 75:25, 1 mL/min.

Preliminary catalysis experiments with mixtures of **1** and **2** at a *L*-proline loading of 1 mol% showed excellent diastereomeric excesses of 96%, and enantiomeric excesses of 98% (Table S1, entry 1). In these reactions, the samples were stirred with a magnetic stir bar in small glass vials, a method that we previously found to be highly reproducible.[1] However, the conversions varied between 40 and 83%, indicating a poor reproducibility. In order to gain more control over our system and increase the reproducibility of the activity, different sample preparation methods and reaction conditions were explored that have been described in literature to yield improved catalytic behaviour towards the aldol reaction of *L*-proline based catalysts in water. We first tested the influence of a temperature treatment as described by Huerta et al[4] and the addition of the substrates in toluene as reported by Rodríguez *et al*.[2] Both methods were unsuccessful for our system (Table S1, entries 2-3). Subsequently, a surfactant was added to the system, since this was reported to increase catalyst activity by various groups including Mase and co-workers[3] and Cheng and co-workers.[4] However, for our system, both the activity of the

catalyst and reproducibility of the system became worse upon addition of surfactant (Table S1, entry 4).

**Table S1**: Screening of different reaction conditions to increase the reproducibility.

| Entry | $c_{\text{L-Pro}}$ (mol%) | $x_1$ (%) | $x_2$ (%) | Sample treatment | Conversion† (%) | $de_{\text{anti}}$† (%) | $ee_{\text{anti}}$‡ (%) |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 50 | 50 | Magnetic stirring[a] | 62±18 | 96 | 98 |
| 2 | 1 | 50 | 50 | Temp. treat.[b] | 18±7 | n.d. | n.d. |
| 3 | 1 | 50 | 50 | Toluene layer[c] | 0 | n.a. | n.a. |
| 4 | 1 | 50 | 50 | Surfactant[d] | 25±26 | 74 | 57 |
| 5 | 1 | 50 | 50 | Shaker with beads[e] | >99 | 30 | 1 |

Conditions: reaction volume = 0.5 mL $H_2O$; aldehyde concentration: 50 mM; substrate ratio (*p*-nitrobenzaldehyde:cyclohexanone) = 1:10; $c_{\text{L-Pro}}$ = mole fraction of BTA **1** with respect to the aldehyde; $x_1$ = mole fraction of BTA **1;** $x_2$ = mole fraction of BTA **2**; reaction time = 24 h; reaction was conducted at room temperature; † determined by $^1$H-NMR; ‡ determined by chiral HPLC. [a] Results following the general procedure. [b] The sample was heated to 80 °C, stirred at this temperature for 10 minutes, and slowly cooled down to room temperature (20 °C $h^{-1}$) before equilibration. [c] The reagents were added dissolved in 125 µL of toluene. [d] 0.67 µM (10 mol% compared to the total BTA concentration in the sample) Triton-X 100 was added to the sonicated sample. [e] 10 glass beads were added to the vial and the sample was fixed on a plate shaker and shaken at 400 rpm during the reaction. n.a. = not applicable; n.d. = not determined.

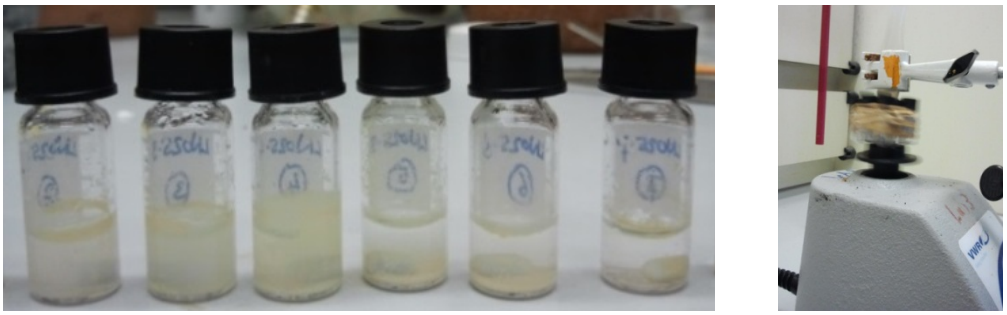


**Figure S5:** (A) Various catalysis samples after 24 h reaction time showing the inhomogeneous nature of the samples; (B) Action shot of the experimental setup for the catalysis experiments using a vortex mixer.

The reaction mixtures during the aldol reaction appear quite inhomogeneous (Figure S5A), which is attributed to the poor solubility of *p*-nitrobenzaldehyde and aldol products in water. We suspected that the poor reproducibility of the conversion could be attributed to a lack of proper stirring. Therefore, we designed an alternative setup to keep the substrate better dispersed. In this method, the sample was not stirred with a magnetic stir bar, but several glass beads are added to the vial. Subsequently the vials were fixed to a plate shaker and are shaken at 400 rpm during catalysis. This method yielded full conversion (Table S1, entry 5), but a significantly worse selectivity. In further experiments, samples containing only glass beads and no catalyst showed full conversion and poor selectivity as well. Apparently, the glass beads catalyse the reaction in an unspecific way, something that, to our knowledge, has not been reported before.

Finally we decided to use vortex mixing to increase the reproducibility of the conversion. A standard catalysis procedure was developed (Figure S5B). First, organocatalyst **1** (or a mixture of **1** and **2**) was dissolved in MeOH and the appropriate amount was squirted in a sample vial. Then, MeOH was removed in vacuo. Water (Milli-Q) was added and the sample was sonicated for 2 min. After equilibration overnight, a clear but slightly viscous catalyst mixture was obtained. To this mixture was added a 10:1 mixture of cyclohexanone and *p*-nitrobenzaldehyde yielding a final aldehyde concentration of 50 mM in water. The samples were mixed vigorously during 24 hours in order to keep the water-insoluble substrates finely dispersed. Subsequently, the products were removed from the solutions by extraction using diethyl ether. After removal of the ether under a stream of nitrogen, both conversion and diastereomeric excess ($de_{anti}$) were determined by $^1$H NMR analysis. In all cases, no transfer of BTAs to the organic layer was observed, since no BTA peaks can be observed in the $^1$H NMR spectrum. The conversion was determined by comparison of the integral at 10.16 ppm corresponding to the unreacted aldehyde with the integrals at 8.21 ppm and 7.51 ppm corresponding to the aldol product (Figure). The $de_{anti}$ can be determined from the ratio of the product signals at 5.48 ppm (*syn*) and 4.90 ppm (*anti*), respectively.

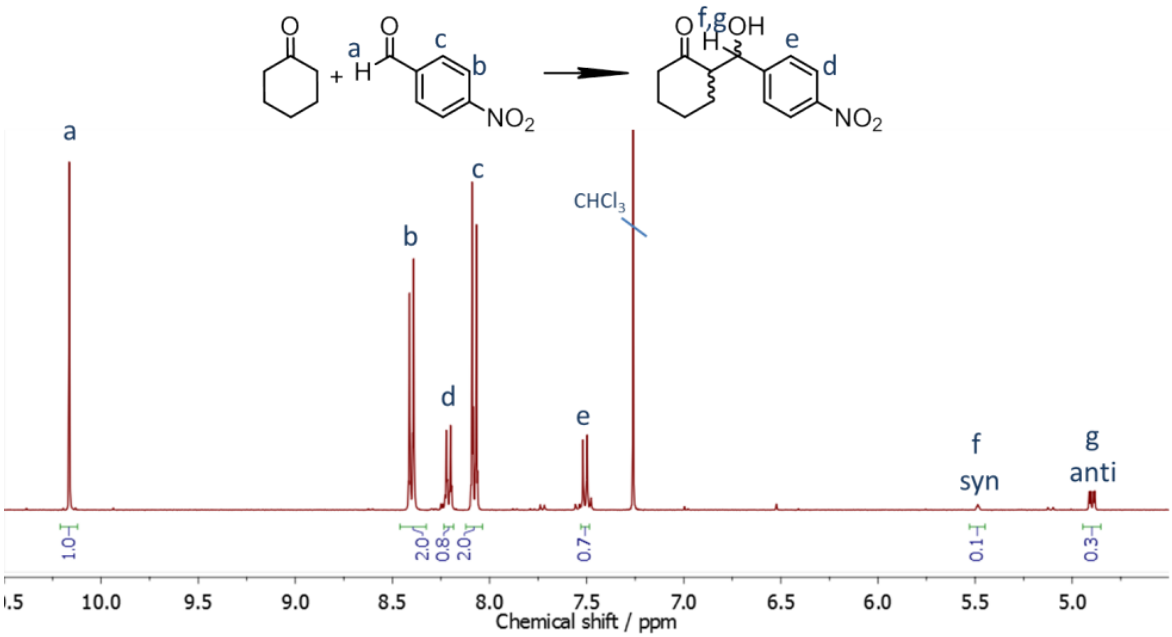



**Figure S6:** $^{1}$H-NMR spectrum (400 MHz, $CDCl_3$) of the crude aldol product obtained after catalysis, showing the signals used for the determination of the conversion (27%) and *de* (65%). The aliphatic region is omitted for clarity.

The enantiomeric excess was determined by HPLC analysis using a chiral column. The value for the $ee_{anti}$ is determined *via* integration of the peak areas corresponding to the two different *anti*-products in the HPLC profile as indicated in Figure  monitored at λ = 268 nm.

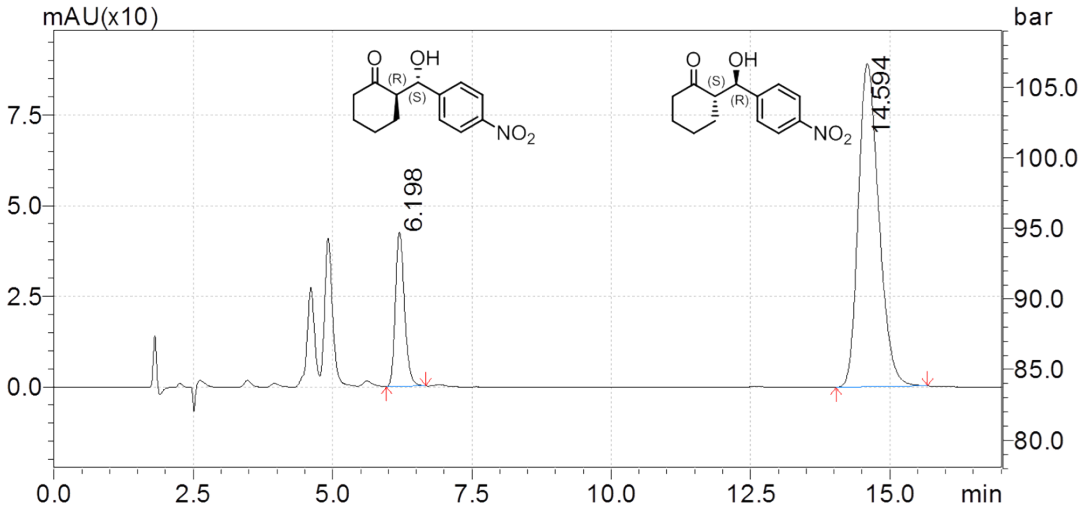



**Figure S7** HPLC profile (λ = 268 nm) for aldol products. The peak with a retention time of 14 min belongs to the anti-enantiomer that is formed predominantly during *L*-proline catalysis whereas the peak at 6.1 min represents the minor anti-enantiomer.

## References


[1] Huerta, E.; van Genabeek, B.; Lamers, B. A. G.; Koenigs. M. M. E.; Meijer, E. W.; Palmans, A. R. A. Chemistry, accepted

[2] Rodríguez-Llansola, F.; Miravet, J. F.; Escuder, B. *Chem. Commun.* **2009**, 7303–7305

[3] Mase, N.; Noshiro, N.; Mokuya, A.; Takabe, K. *Adv. Synth. Catal.* **2009**, *351*, 2791–2796

[4] Peng, Y.-Y.; Ding, Q.-P.; Li, Z.; Wang, P. G.; Cheng, J.-P. *Tetrahedron Lett.* **2003**, *44*, 3871–3875