Electronic Supplementary Information

Chitosan aerogel: a recyclable, heterogeneous organocatalyst for the asymmetric direct aldol reaction in water

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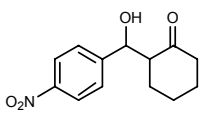
Experimental Details

General Methods. ^{1}H, ^{13}C NMR spectra were recorded on a Varian AS 400 or 600 spectrometer. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD-H, Chiralcel OJ-H), using a UV detector operating at 254 nm.

Materials. Analytical grade solvents and commercially available reagents were used as received. Chromatographic purifications were performed using 70-230 mesh (chromatography) or 230-400 mesh silica gel (flash chromatography). Racemic samples were prepared using *rac*-proline as the catalyst. Chitosan from Aldrich, extracted from the crab shell, was characterized by an acetylation degree of 8% determined by infrared and ^{1}H NMR and a molecular weight of 700000 $g.mol^{-1}$ determined by viscosimetry. The chitosan was purified before use according to the following procedure. It was dissolved at 1% (w/v) during 15 hours, in an aqueous solution containing a stoechiometric amount of acetic acid with respect to the number of amine functions in the chitosan. The solution was filtered over Millipore nitrocellulose filters of 3 μm; 1.2μm; 0.8 μm; 0.45 μm and 0.2 μm. Then, a 50% ammoniac solution is introduced until pH 9. Then, precipitated chitosan was washed with distilled water by centrifugation until the conductivity of the solution was the same as the distilled water (6-9 μSiemens). Chitosan was dried by lyophilisation. Chitosan aerogel microspheres (0.90 ± 0.05 mg, 350 $m^2.g^{-1}$, 5.2 $mmol.g^{-1}$ accessible NH_2 groups) were prepared as described previously.[1]

General procedure for the aldol reaction. In a vial equipped with a magnetic stirring bar were sequentially added chitosan aerogel microspheres (15 beads, 13.5 mg, corresponding to 22 mol % free amino units respect to the acceptor), the aldol acceptor (0.30 mmol), eventually the additive (2,4-dinitrophenol (DNP) or stearic acid, 0.060 mmol, 20 mol %), H_2O (1.5 mL for cyclohexanone or 0.90 mL for hydroxyacetone, tetrahydro-4*H*-pyran-4-one and acetone) and the ketone donor (6.0 mmol). The mixture was gently stirred at r.t. for the stated time. EtOAc/Et_2O were then added, and the phases separated. The aqueous phase, containing the chitosan beads, was then extracted with EtOAc/Et_2O (2 x). The combined organic phases were evaporated, and the crude product analysed by ^{1}H NMR spectroscopy, to determine the diastereomeric ratio. The aldol adducts **1** were finally obtained by chromatographic purification or as outlined below.

2-(Hydroxy(4-nitrophenyl)methyl)cyclohexanone (1a). Following the general procedure and performing the reaction without additives (48 h reaction time), the title compound was obtained in 85 % yield as a white solid and as a mixture of diastereoisomers, after chormatography on silica gel (*n*-hexane/EtOAc from 85:15 to 75:25). The diastereomeric ratio, as determined by ^{1}H NMR analysis of the crude mixture, was found to be 70/30, favouring the *anti* isomer. The



enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralpak ADH column, flow 0.75 mL.min^{-1}, *n*-hexane/*i*-PrOH 90:10: *anti* isomer: t_{maj} 43.9 min, t_{min} 33.1 min, 84 % ee; *syn* isomer: t_{maj} 29.5 min, t_{min} 26.1 min, 60 % ee). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.23-8.17 (m, $2H_{anti}$, $2H_{syn}$), 7.54-7.45(m, $2H_{anti}$, $2H_{syn}$), 5.48 (br t, *J* = 2.6 Hz, $1H_{syn}$), 4.90 (dd, *J* = 8.5, 3.1 Hz, $1H_{anti}$), 4.07 (d, *J* = 3.1 Hz, $1H_{anti}$), 3.18 (d, *J* = 3.1 Hz, $1H_{syn}$), 2.69-2.27 (m, $2H_{anti}$, $2H_{syn}$), 2.19-2.05 (m, $1H_{anti}$, $1H_{syn}$), 1.92-1.23 (m, $6H_{anti}$, $6H_{syn}$). HRMS: calculated for $C_{13}H_{15}NNaO_4$ [M + Na^+]: 272.0899; found: 272.0989. Spectral and analytical data are consistent with literature values.[2]

The same reaction, performed using DNP as additive (24 h reaction time), gave the title compound in 85 % yield, 76/24 *anti*/*syn* ratio (determined by ^{1}H NMR on the crude mixture), 92 % ee in the *anti* isomer, and 75 % ee in the *syn* isomer (determined by HPLC).

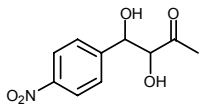
The same reaction, performed using stearic acid as additive (48 h reaction time), gave the title compound in 88 % yield, 69/31 *anti*/*syn* ratio (determined by ^{1}H NMR on the crude mixture), 93 % ee in the *anti* isomer, and 54 % ee in the *syn* isomer (determined by HPLC).

The relative configuration of the two diastereomers was determined by comparison of their ^{1}H NMR spectra with literature data,[2] giving an *anti* relative configuration in the major diastereoisomer.

The absolute configuration of the major *anti* diastereoisomer was assigned as 2S,1'R, by comparison of the HPLC retention times of its two enantiomers with literature values.[3]

For catalyst recycling, at the end of the reaction, both aqueous and organic phase were transferred to a separatory funnel, leaving chitosan beads in the vial, by means of a Pasteur pipette. Chitosan beads were washed twice with H_2O, and these aqueous phases added to the funnel as well for the above described work up and product purification. The washed chitosan beads were then used directly in the next run.

3,4-Dihydroxy-4-(4-nitrophenyl)butan-2-one (1b). Following the general procedure and performing the reaction without additives (48 h reaction time), the title compound was obtained in 90 % yield as a white solid and as a mixture of diastereoisomers, after flash chromatography on silica gel (*n*-hexane/EtOAc 85:15-75:25). The diastereomeric ratio, as determined by ^{1}H NMR analysis of the crude mixture, was found to be 68/32, favouring the *syn* isomer. The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralpak ADH column, flow 0.75 mL.min^{-1}, *n*-hexane/*i*-PrOH 90:10: *anti* isomer: t_{maj} 23.3 min, t_{min} 27.6 min, 90 % ee; *syn* isomer: t_{maj} 44.4 min, t_{min} 32.8 min, 69 % ee). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.26-8.20 (m, $2H_{anti}$, $2H_{syn}$), 7.64-7.57 (m, $2H_{anti}$, $2H_{syn}$), 5.22 (dd, *J* = 7.8, 2.0 Hz, $1H_{syn}$), 5.08 (t, *J* = 4.6 Hz, $1H_{anti}$), 4.48 (t, *J* = 4.8 Hz, $1H_{anti}$), 4.42 (dd, *J* = 4.5, 2.1 Hz, $1H_{syn}$), 3.74 (d, *J* = 4.6 Hz, $1H_{syn}$), 3.68 (d, *J* = 5.0 Hz, $1H_{anti}$), 2.96 (d, *J* = 4.6 Hz, $1H_{anti}$), 2.78 (d, *J* = 7.8 Hz, $1H_{syn}$), 2.36 (s, $3H_{ayn}$), 2.02 (s, $3H_{anti}$). HRMS: calculated for $C_{10}H_{11}NNaO_5$ [M + Na^+]: 248.0535; found: 248.0501. Spectral and analytical data were consistent with literature values.[4]



[1] F. Quignard, R. Valentin and F. Di Renzo, *New J. Chem*., 2008, **32**, 1300.
[2] A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold and S. V. Ley, *Org. Biomol. Chem.*, 2005, **3**, 84.
[3] S. Doherty, J. G. Knight, A. McRae, R. W. Harrington and W. Clegg, *Eur. J. Org. Chem.*, 2008, 1759.
[4] Q. G., X.-F. Wang, L. Wang, X.-Y. Wu and Q.-L. Zhou, *Tetrahedron: Asymmetry*, 2006, **17**, 1537.

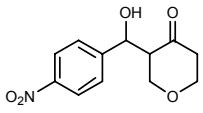
The same reaction, performed using DNP as additive (24 h reaction time), gave the title compound in 90 % yield, 36/64 *anti*/*syn* ratio (determined by ^{1}H NMR on the crude mixture), 90 % ee in the *anti* isomer, and 68 % ee in the *syn* isomer (determined by HPLC).

The same reaction, performed using stearic acid as additive (48 h reaction time), gave the title compound in 83 % yield, 33/67 *anti*/*syn* ratio (determined by ^{1}H NMR on the crude mixture), 83 % ee in the *anti* isomer, and 65 % ee in the *syn* isomer (determined by HPLC).

The relative configuration of the two diastereomers was determined by comparison of their ^{1}H NMR spectra with literature data,[4] giving a *syn* relative configuration in the major diastereoisomer.

The absolute configuration of the major *syn* diastereoisomer was assigned as 3R,4S, by comparison of the HPLC retention times of its two enantiomers with literature values.[5]

3-(Hydroxy(4-nitrophenyl)methyl)dihydro-2*H*-pyran-4(3*H*)-one (1c). Following the general procedure and performing the reaction without additives (48 h reaction time), the title compound was obtained in 76 % yield as a white solid and as a mixture of diastereoisomers, after flash chormatography on silica gel (*n*-hexane/EtOAc 80:20-70:30). The diastereomeric ratio, as determined by ^{1}H NMR analysis of the crude mixture, was found to be 66/34, favouring the *anti* isomer. The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralpak ADH column, flow 0.75 mL.min^{-1}, *n*-hexane/*i*-PrOH 90:10: *anti* isomer: t_{maj} 30.6 min, t_{min} 26.3 min, 70 % ee; *syn* isomer: t_{maj} 21.4 min, t_{min} 17.8 min, 30 % ee). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.26-8.20 (m, $2H_{anti}$, $2H_{syn}$), 7.54-7.48 (m, $2H_{anti}$, $2H_{syn}$), 5.54 (br s, $1H_{syn}$), 4.98 (d, J = 8.5 Hz, $1H_{anti}$), 4.28-4.18 (m, $1H_{anti}$, $1H_{syn}$), 3.88-3.67 (m, $3H_{anti}$, $4H_{syn}$), 3.46 (dd, J = 11.4, 10.1 Hz, $1H_{anti}$), 2.99-2.83 (m, $1H_{anti}$, $1H_{syn}$), 2.78-2.62 (m, $1H_{anti}$, $1H_{syn}$); 2.58-2.42 (m, $1H_{anti}$, $1H_{syn}$). HRMS: calculated for $C_{12}H_{13}NNaO_5$ [M + Na^+]: 274.0691; found: 274.0685. Spectral and analytical data were consistent with literature values.[6]

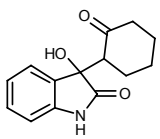


The same reaction, performed using DNP as additive (24 h reaction time), gave the title compound in 78 % yield, 70/30 *anti*/*syn* ratio (determined by ^{1}H NMR on the crude mixture), 72 % ee in the *anti* isomer, and 24 % ee in the *syn* isomer (determined by HPLC).

The relative configuration of the two diastereomers was determined by comparison of their ^{1}H NMR spectra with literature data,[6] giving an *anti* relative configuration in the major diastereoisomer.

The absolute configuration of the major *anti* diastereoisomer was assigned as S at the cyclohexanone chiral center, and R at the hydroxy substituted center, by analogy with the reaction performed using cyclohexanone.

3-Hydroxy-3-(2-oxocyclohexyl)indolin-2-one (1d). Following the general procedure and performing the reaction without additives (48 h reaction time), the title compound was obtained in 86 % yield as a pale yellow solid and as a mixture of diastereoisomers, purifying the crude solid mixture

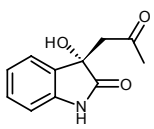


[5] S. S. V. Ramasastry, H. Zhang, F. Tanaka and C. F. Barbas III, *J. Am. Chem. Soc.*, 2007, **129**, 288.
[6] G. Guillena, M. Hita, C. Nájera and S. F. Viózquez, *J. Org. Chem.*, 2008, **73**, 5933.

with *n*-hexane/CH_2Cl_2 washings. The diastereomeric ratio was found to be 98/2 (determined by HPLC analysis). The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralcel OJH column, flow 0.75 mL.min^{-1}, *n*-hexane/*i*-PrOH 80:20: major diastereoisomer: t_{maj} 14.8 min, t_{min} 18.3 min, 80 % ee; minor diastereoisomer: t_{maj} 12.0 min, t_{min} 13.5 min, 27 % ee). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 10.16 (s, 1H), 7.24-7.10 (m, 2H), 6.87-6.71 (m, 2H), 5.79 (s, 1H), 3.06 (dd, J = 13.0, 5.0 Hz, 1H), 2.61-2.53 (m, 1H), 2.36-2.53 (m, 1H), 2.36-2.21 (m, 1H), 2.08-1.58 (m, 5H), 1.53-1.34 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 209.8, 179.4, 144.1, 131.5, 129.3, 125.5, 121.5, 110.1, 74.6, 58.1, 42.1, 27.4, 27.3, 25.1; HRMS: calculated for $C_{14}H_{15}NNaO_3$ [M + Na^+]: 268.0950; found: 268.0925.

The same reaction, performed using DNP as additive (24 h reaction time), gave the title compound in 89 % yield, 97/3 diastereomeric ratio, 77 % ee in the major diastereoisomer, and 30 % ee in the minor diastereoisomer (determined by HPLC).

(*S*)-3-Hydroxy-3-(2-oxopropyl)indolin-2-one (1e). Following the general procedure, but using 12.0 mmol of acetone donor and performing the reaction without additives (48 h reaction time), the title compound was obtained in 95 % yield as a pale yellow solid, purifying the crude solid mixture with *n*-hexane/CH_2Cl_2 washings. The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralcel OJH column, flow 0.75 mL.min^{-1}, *n*-hexane/*i*-PrOH 80:20: t_{maj} 22.2 min, t_{min} 19.1 min, 25 % ee). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 10.18 (br s, 1H), 7.22 (br d, J = 7.2 Hz, 1H), 7.15 (dt, J_t = 7.6 Hz, J_d = 1.3 Hz, 1H), 6.88 (dt, J_t = 7.6 Hz, J_d = 1.0 Hz, 1H), 6.75 (br d, J = 7.6 Hz, 1H), 5.94 (s, 1H), 3.24 (d, J = 16.8 Hz, 1H), 2.97 (d, J = 16.8 Hz, 1H), 1.98 (s, 3H); HRMS: calculated for $C_{11}H_{11}NNaO_3$ [M + Na^+]: 228.0637; found: 228.0660. Spectral and analytical data were consistent with literature values.[7]



The same reaction, performed using DNP as additive (48 h reaction time), gave the title compound in 97 % yield and 5 % ee (determined by HPLC).

The same reaction, performed using DNP as additive (48 h reaction time), gave the title compound in 97 % conversion (determined by ^{1}H NMR) and 5 % ee (determined by HPLC).

The same reaction, performed using stearic acid as additive (48 h reaction time), gave the title compound in 97 % conversion (determined by ^{1}H NMR) and 25 % ee (determined by HPLC).

The absolute configuration of the title compound was assigned as S, by comparison of the HPLC retention times of its two enantiomers with literature values.[7]

[7] A. V. Malkov, M. A. Kabeshov, M. Bella, O. Kysilka, D. A. Malyshev, K. Pluháčková and P. Kočovský, *Org. Lett.*, 2007, **9**, 5473.