Supporting Information

NMR relaxation time measurements of solvent effects in an organocatalysed asymmetric aldol reaction over silica SBA-15 supported proline

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Materials and methods

Homogeneous and heterogeneous aldol reactions were performed under an argon atmosphere using oven-dried glassware. All solvents (THF : tetrahydrofuran; DCM : dichloromethane; DMF : dimethylformamide; toluene; cyclohexane; Ethanol, DMA : N,N-dimethylacetamide) were dried using standard drying agents and freshly distilled prior to use. Reactions performed at temperature higher than the room temperature were carried out using an oil bath. Reactions were monitored by NMR using durene as internal standard and TLC (Aluminum plate, silica gel coated with fluorescent indicator F254). Flash column chromatography was performed on silica gel 60 (200–400 mesh). ¹H NMR spectra (characterization and conversion) were recorded in CDCl₃ at room temperature employing Bruker AVIII HD 400 MHz spectrometer. The chemical shifts in ¹H spectra were referenced to trimethylsilane (TMS). Elemental analyses were performed using a FLASH 2000 Series CHNS/O analyzer (ThermoFisher Scientific), FT-IR analyses were performed using the Bruker Instrument Vertex 70. Nitrogen adsorption-desorption isotherms were recorded on a Quantachrome Quadrasorb porosimeter. Samples were degassed at 150 °C for 18 h prior to recording N₂ adsorption/desorption isotherms. BET surface areas were calculated over the relative pressure range 0.02-0.2. Mesopore properties were calculated the BJH method applied to the desorption branch of the isotherm. Benzaldehyde, hydroxyacetone, tert-butyl bromide, Boc protected hydroxyproline, benzytriethylammonium chloride, propargyl bromide (80wt. % toluene), (3-chloropropyl)trimethoxysilane, sodium, Pluronic P123, 1,3,5-trimethylbenzene, hydrochloric acid and tetraethylorthosilicate were purchased from Sigma-Aldrich and used as received. T₁ and T₂ relaxation measurements have been performed using a Magritek Benchtop 43 MHz spinsolve.
Preparation of pore expanded SBA-15

SBA-15 was produced using the procedure reported by Zhao et al. Pluronic P123 (10 g) was dissolved in water (74.5 cm$^3$) and hydrochloric acid (2M, 291.5 cm$^3$), stirring at 35 °C. Tetraethoxysilane (23.4 cm$^3$) was added and left for 20 h under agitation. The resulting gel was aged under sealed conditions for 24 h at 80 °C without agitation. The solid was filtered, washed with water (1000 cm$^3$) and dried at room temperature before calcination at 500 °C for 6 h in air (ramp rate 1°C min$^{-1}$). Pore characterization is shown in Figure SI1.

![Figure SI1. Nitrogen porosimetry isotherm (left) and BJH pore size distribution (right).](image)
Preparation of supported catalyst 4

Synthesis of di-tert-butyl (2S,4R)-4-hydroxypyrrolidine-1,2-dicarboxylate

A suspension of Boc protected 4-hydroxyproline (1 eq., 8.34 mmol, 1.927 g), benzyltriethylammonium chloride (1 eq., 8.34 mmol, 1.9 g), potassium carbonate (26 eq., 217 mmol, 30 g) and tert-butyl bromide (40 eq., 334 mmol, 38.8 mL) in DMA (N,N,-dimethylacetamide, 40 mL) was vigorously stirred in a 100ml round bottom flask, at 55 °C for 21 hours. The suspension was then allowed to cool to room temperature and distilled water was added until the suspension turned into a clear transparent solution. This solution was extracted with EtOAc (5x25 mL), the organic layers were collected and concentrated with a rotary evaporator; the crude mixture was then re-dissolved with 30 mL of Et₂O and finally washed with brine (3x20 mL), and with distilled water (2x20mL) to remove any remaining DMA. The organic layer was dried over magnesium sulfate and concentrated. The crude was used in the next step without further purification. Crude yield: 2 g, 6.95 mmol, 83%, spectrum in accordance with reported data¹. ¹H NMR (400 MHz, CDCl₃): δ 4.49 (br, 1H), 4.27 - 4.34 (m, 1H), 3.64 (dd, J = 11.6, 4.5 Hz, 1H), 3.45 - 3.57 (m, 1H), 2.28 - 2.34 (m, 1H), 2.04–2.10 (m, 1H), 1.86 (br, 1H), 1.48 (s, 18H).
$^1$H-NMR spectrum (CDCl$_3$) of di-tert-butyl (2S,4R)-4-hydroxyproline-1,2-dicarboxylate
Synthesis of di-tert-butyl (2S,4R)-4-(prop-2-yn-1-yloxy)pyrrolidine-1,2-dicarboxylate

NaH and pentane (5mL) were added in a 25ml round bottom flask; the suspension was stirred in order to remove the mineral oil for 5 min; pentane was removed and DMF (5 mL) added.

The crude intermediate di-tert-butyl (2S,4R)-4-hydroxypyrrolidine-1,2-dicarboxylate, from previous step, was dissolved in DMF (5 mL) and added to the suspension of NaH at -25 °C and allowed to react for 20 min; propargyl bromide was added dropwise. The suspension was allowed to warm to room temperature and stirred overnight. MeOH was added to the suspension (2 mL), followed by brine (15 mL), and the resulting cloudy solution was extracted with DCM (5x10 mL). The organic solvent was partially concentrated until about 15 mL, and washed again with brine (4 x 10 mL) and distilled water (2 x 10 mL), in order to remove the DMF; finally, the organic layers were collected and dried over magnesium sulfate, affording the desired crude product that was used without further purification. Crude yield = 500 mg, 1.54 mmol, 89%. \(^1\)H NMR (400 MHz, CDCl\(_3\), due to BOC hindrance, rotation around N-C bond is limited and in the spectrum rotamers are observed (1:0.4)) δ 4.36 – 4.27 (m, 1H, rotamers) 4.26 – 4.19 (m, 1H), 4.17 – 4.12 (m, 1H, rotamers), 3.67 – 3.56 (m, 1H, rotamers), 3.54 – 3.45 (m, 1H), 2.49 – 2.42 (m, 1H), 2.41 – 2.26 (m, 1H), 2.11 – 2.02 (m, 1H), 1.48 – 1.39 (m, 18H, BOC and t-Bu, rotamers). All spectroscopic data of the product were in agreement with those reported in the literature\(^1\)
$^1$H-NMR spectrum (CDCl$_3$) of di-tert-butyl (2S,4R)-4-(prop-2-yn-1-yloxy)pyrrolidine-1,2-dicarboxylate
Synthesis of (3-azidopropyl)trimethoxysilane

To a flame-dried round bottom flask, under an argon atmosphere, (3-chloropropyl)trimethoxysilane (1.2 mL, 1.31 g, 6.61 mmol, 1 eq), sodium azide (644 mg, 9.915 mmol, 1.5 eq) and anhydrous DMF (4 mL) were added. The reaction was heated and stirred overnight at 100 °C. The reaction was then allowed to cool to RT and diluted with a 15 mL 1:1 mix of water and diethyl ether; the organic layer was washed with water (3x10 mL) and with brine (10 mL). The organic layer was dried over magnesium sulfate and concentrated by rotary evaporator affording the desired product that was used in the next step without further purification. Crude yield = 1.2 g, 89%. $^1$H NMR (400 MHz, CDCl$_3$) δ 3.60 (s, 9H), 3.29 (t, J = 6.9 Hz, 2H), 1.79 - 1.68 (m, 2H), 0.72 (t, J = 7.0 Hz, 2H).
$^1$H-NMR spectrum (CDCl$_3$) of (3-azidopropyl)trimethoxysilane
Synthesis of di-tert-butyl (2S,4R)-4-((1-(3-(trimethoxysilyl)propyl)-1H-1,2,3-triazol-4-yl)methoxy)pyrrolidine-1,2-dicarboxylate

To a solution of (3-azidopropyl)trimethoxysilane (106 mg, 1 eq., 0.55 mmol) and di-tert-butyl (2S,4R)-4-(prop-2-yn-1-yloxy)pyrrolidine-1,2-dicarboxylate (180 mg, 1.05 eq., 0.58 mmol) in 5 mL of THF, TEA (Triethylamine, 150 µL, 1.1 mmol, 2 eq.) and copper iodide (2 mg, 0.011 mmol, 0.02 eq.) were added and the reaction was stirred for 24 hours at RT. After complete consumption of the (3-azidopropyl)trimethoxysilane (checked by NMR, by complete disappearance of the peak at 3.32 ppm (CH$_2$N of the (3-azidopropyl)trimethoxysilane)), the crude was used directly in the next step without further purification and work up, due to the instability of the compound (290 mg). $^1$H NMR (400 MHz, CDCl$_3$, due to BOC hindrance, rotation around N-C bond is limited, and in the spectrum rotamers are observed (1:0.5)). δ 7.54 (s, 1H, triazole), 4.63 – 4.57 (m, 1H), 4.38 – 4.29 (m, 2H), 4.27 – 4.17 (m, 2H), 3.77 – 3.70 (m, 4H), 3.67 – 3.45(m, 9H, CH$_3$O), 2.60 – 2.53 (m, 1H), 2.45 – 2.24 (m, 1H, rotamers), 2.09 – 1.96 (m, 2H, rotamers), 1.89 - 1.78 (m, 4H, rotamers), 1.47 - 1.38 (m, 18H, CH$_3$ (BOC and t-Bu)), 1.05 (t, J = 7.2 Hz, 1H), 0.92 – 0.77 (m, 1H), 0.62 (t, J = 7.4, 2H, CH$_2$Si).
$^1$H-NMR spectrum (CDCl$_3$) of di-tert-butyl (2S,4R)-4-((1-(3-(trimethoxysilyl)propyl)-1H-1,2,3-triazol-4-yl)methoxy)pyrrolidine-1,2-dicarboxylate
Synthesis of anchored SBA-15 proline catalyst 4

To a solution of tert-butyl (2S,4R)-4-((1-(3-(trimethoxysilyl)propyl)-1H-1,2,3-triazol-4-yl)methoxy)pyrrolidine-1,2-dicarboxylate in dry toluene (15 mL) in a 50 mL round bottom flask, SBA-15 silica was added in one portion. Note: SBA-15 silica was dried in a vacuum oven prior to use (150 °C, under vacuum for 24 h). The flask was equipped with a condenser, sealed and a balloon filled with argon was placed at the top. The reaction was left under reflux for 48 hours. After that the reaction was allowed to cool and the silica was filtered under vacuum. The resulting siliceous powder was washed several times (2 x 10 mL THF, 2 x 10 mL EtOH and 2 x 10 mL hexane). The powder was dried under vacuum at 40 °C for 16 hours, to yield 760 mg of off-white powder. The elemental analysis (NCH, Table SI1) shows complete anchoring of the proline derivative and the resulting loading was calculated (protected proline loading: 0.55 mmol g⁻¹) and FT-IR analysis shown the presence of the functional group of the protected proline (Figure S12).

Figure S12. FT-IR spectrum of the protected proline anchored onto SBA-15.
Table SI1. Elemental Analysis of protected proline anchored onto SBA-15

<table>
<thead>
<tr>
<th>Element</th>
<th>%</th>
<th>Protected proline loading</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>13.09</td>
<td>0.545</td>
</tr>
<tr>
<td>H</td>
<td>2.07</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>3.1</td>
<td>0.553</td>
</tr>
</tbody>
</table>

The $^1$H-NMR spectrum (Figure SI3) of the supernatant shows that only a small amount of non-siliceous functionalized proline remains (this is the unreacted proline derivative of the previous step. Note: the previous reaction was performed with a slight excess of this reagent).

Figure SI3. Comparing of 1H NMR spectrum of supernatant solution after reaction of anchoring with trimetoxyisilicon functionalized protecting proline and propargyl functionalized protected proline.

BOC and t-Butyl protecting groups were removed by treating the resulting powder with a TFA/DCM solution. The resulting functionalized SBA-15 protected proline (750 mg) was suspended in 5 mL of
DCM at 0 °C, and 10 mL of TFA were slowly added. The suspension was then stirred at room temperature for 32 h under nitrogen. After that the suspension was filtered under vacuum and the powder was washed several times (2 x 10 mL THF, 2 x 10 mL 5 % Triethylamine solution in THF, 2 x 10 mL EtOH, 2 x 10 mL THF and 2 x 10 mL hexane). Thus, the resulting catalyst 4 (610 mg) was dried in a vacuum oven at 40 °C for 24 h and Elemental Analysis (Table SI2) and FT-IR (Figure SI4) were performed to evaluate the removal of protecting groups.²

![Figure SI4. FT-IR spectrum of the proline anchored onto SBA-15 (4).](image)

**Table SI2. Elemental Analysis of deprotected proline anchored onto SBA-15 (4)**

<table>
<thead>
<tr>
<th>Element</th>
<th>%</th>
<th>Protected proline loading</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>9.29</td>
<td>0.596</td>
</tr>
<tr>
<td>H</td>
<td>1.84</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>3.36</td>
<td>0.600</td>
</tr>
</tbody>
</table>

Complete deprotection of both groups (BOC and tert-Butyl) is confirmed by EA (loading calculated for C₁₂H₂₂N₄O₈Si) which is in line for carbon and nitrogen. Furthermore, comparing the two FT-IR spectra (Figure SI5) corroborates the complete deprotection by observing the peak shift experienced only for the peaks in the carboxylate groups area (1700/1600 cm⁻¹). Whereas the pore characterization (Figure SI6) of 4 shows none significant variations in pore size and distribution.
Furthermore, the anchoring step has been proved to be highly reproducible. We were able to prepare a new batch with similar catalyst loading (0.53 mmol g\(^{-1}\)) employing the reported procedure.

Figure S15. FT-IR spectra of protected proline (blue) and proline (purple) both anchored onto SBA-15 (4).

Figure S16. Nitrogen porosimetry isotherm (left) and BJH pore size distribution (right).
General procedure for the aldol reaction between hydroxyacetone and benzaldehyde

1) Homogeneous
To a mixture of L-proline (35 mg, 30 mol%) and solvent (see table in the manuscript for details on the solvents screened) (800 μL) in a 5 mL vial, hydroxyacetone (200 μL, 2.86 mmol, 29 eq) and benzaldehyde (0.1 mmol, 1 eq) were added. The reaction mixture was stirred at room temperature for 24 h. The reaction was quenched with NH₄Cl 0.5 M (5 mL). Then the aqueous mixture was extracted with DCM (4 x 5 mL) and the combined organic layers washed with brine and dried over MgSO₄ and concentrated in vacuo after filtration.

2) Heterogenous
To a suspension of solid catalyst 4 (68 mg, 41 mol%), hydroxyacetone (200 μL, 2.86 mmol, 29 eq) and solvent (800 μL), benzaldehyde (0.1 mmol, 1 eq) was added. The reaction mixture was stirred at room temperature for up to 5 days. The reaction was quenched with NH₄Cl 0.5 M (5 mL). Then the aqueous mixture was extracted with DCM (4 x 5 mL) and the combined organic layers was washed with brine and dried over MgSO₄ and concentrated in vacuo after filtration.

For each reaction: 1 mL of internal standard (durene) in CDCl₃ was added to the reaction mixture to evaluate the conversion. Conversion and dr were determined by ¹H-NMR of the crude reaction mixture.

¹H NMR (500 MHz, CDCl₃, mixture of diastereoisomers) δ 7.41 – 7.24 (m, 5H), 5.03 – 4.83 (m, 1H, diastereoisomers), 4.40 (t, J = 4.4 Hz, 1H), 4.31 (s, 1H), 3.60 (d, J = 5.0 Hz, 1H), 3.57 (d, J = 5.0 Hz, 1H), 2.78 (d, J = 4.4 Hz, 1H), 2.69 (d, J = 6.9 Hz, 1H), 2.16 (s, 3H, CH₃), 1.90 (s, 3H, CH₃).

the ee value was determined by HPLC on a chiral stationary phase (OD-H Chiralcel ®, n-hexane:IPA 94:6, 1 mL/min, t_minor: 19.3 min, t_major: 22.9 min)
Preparation of the samples for NMR measurements and $T_1$ and $T_2$ plots

Samples were prepared by soaking the powder (4 or SBA-15) in the liquid (solvents or reagents). After 24 hours the powder was dried on a pre-soaked filter paper, in order to remove any excess liquid on the external surface, and transferred into 5 mm diameter NMR tubes, which were then sealed.

A standard inversion recovery sequence was used to measure $T_1$ (Figure SI7).

General parameters: repetition time 12000 ms; min delay: 10 – 250 ms; Max delay: 1000 - 12000 ms; Dwell time: 50 - 20 µs

![Figure SI7. Rappresentation of inversion recovery sequence employed to measure the $T_1$.](image)

Whereas, the CPMG sequence was used to evaluate the $T_2$ (Figure SI8).

General parameters: Echo time: 500 µs; number of Echo per step 5-50; number of steps:16; number of scan 32-64; repetition time 5000 ms; Dwell time: 50 - 20 µs

![Figure SI8. Rappresentation of CPMG sequence employed to measure the $T_2$.](image)
The resulting FIDs were integrated and the normalized signal intensity vs time were plotted to obtain the relaxation time constants using the two equations shown below [1] (Figure S19) and (Figure S110) [2] to estimate $T_1$ and $T_2$, respectively.

**Figure S19.** FIDs (IR) of cyclohexane in the catalyst, after phasing and baseline correction, plotted vs time to obtain the $T_1$ value.

$$M_z = M_0 (1 - 2e^{-t/T_1})$$  (1)
Figure SI10. FIDs (CPMG) of cyclohexane in the catalyst, after phasing and baseline correction, plotted vs time to obtain the $T_2$ value.

\[ M_{xy} = M_0 e^{-\frac{t}{T_2}} \]  

(2)
References