Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

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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† Electronic Supplementary Information

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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*-dimethylacetoamide) 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 flourescent indicator F254). Flash column chromatography was performed on silica gel 60 (200–400 mesh). ^{1}H NMR spectra (characterization and conversion) were recorded in $CDCl_3$ at room temperature employing Bruker AVIII HD 400 MHz spectrometer. The chemical shifts in ^{1}H 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 N_2 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, benzyltriethylammonium 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. T_1 and T_2 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.**

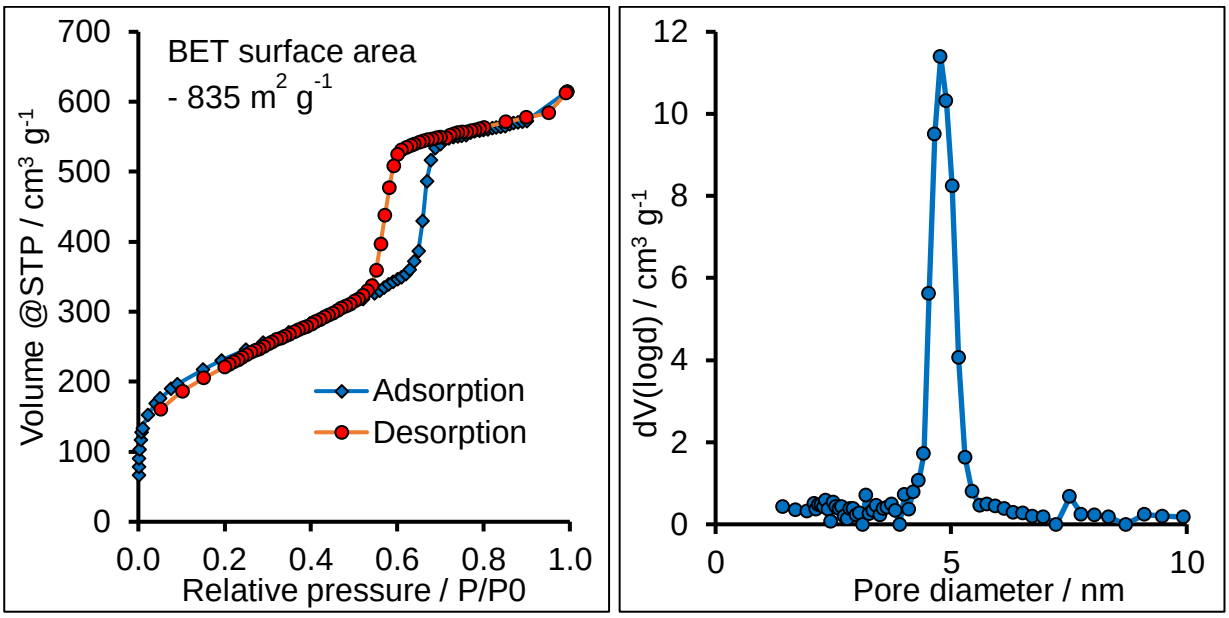
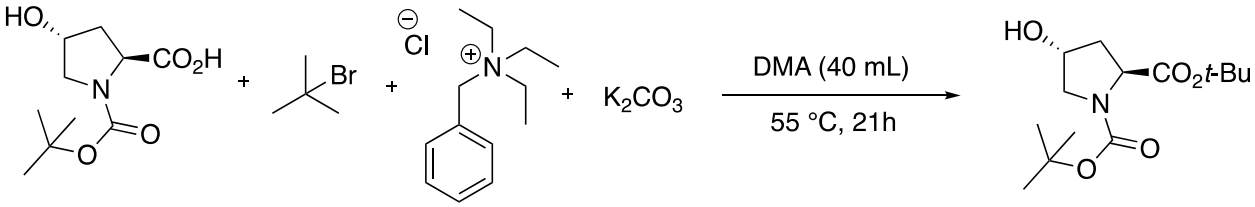


Figure SI1. Nitrogen porosimetry isotherm (left) and BJH pore size distribution (right).

Preparation of supported catalyst 4

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



MW 231.25
1 eq
8.34 mmol
1.927 g

MW 137,02
40 eq
334 mmol
d = 1.22 g/mL
45.7 gr
38.8 mL

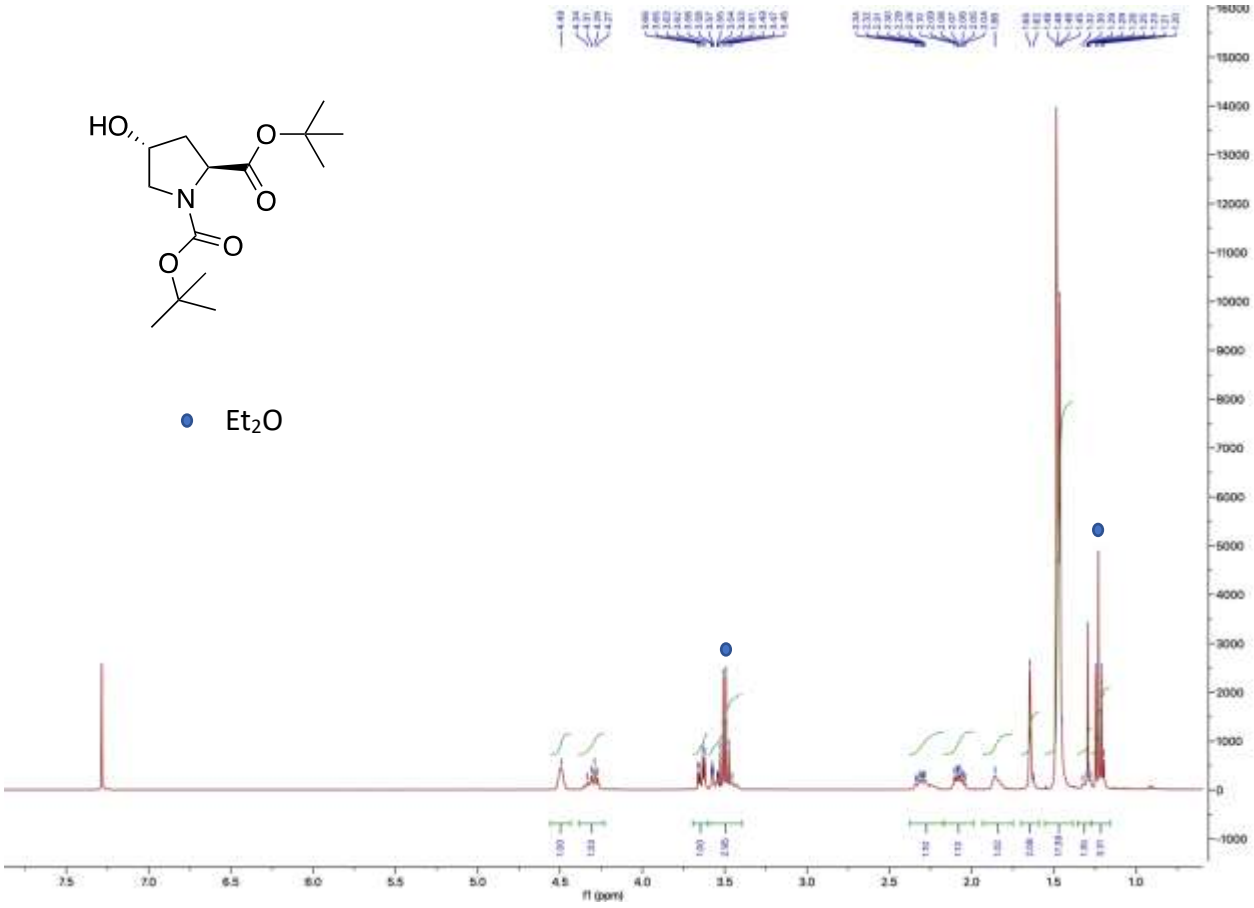
MW 227.77
1 eq
8.34 mmol
1.9 g

MW 138.21
26 eq
217 mmol
30 g

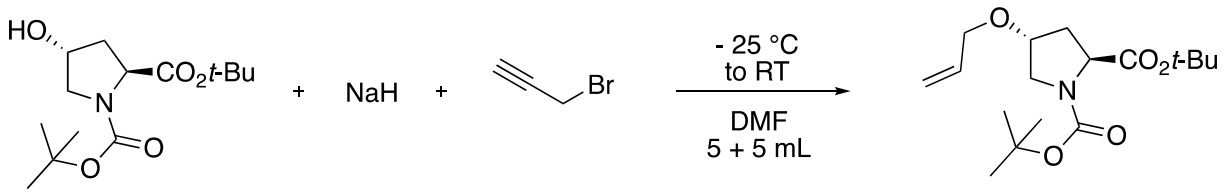
MW 287.17
Y = 2 g
6.95 mmol
83 %

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 Et_2O 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 data[1]. ^{1}H NMR (400 MHz, $CDCl_3$): 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 (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate



Synthesis of di-*tert*-butyl (2*S*,4*R*)-4-(prop-2-yn-1-yloxy)pyrrolidine-1,2-dicarboxylate

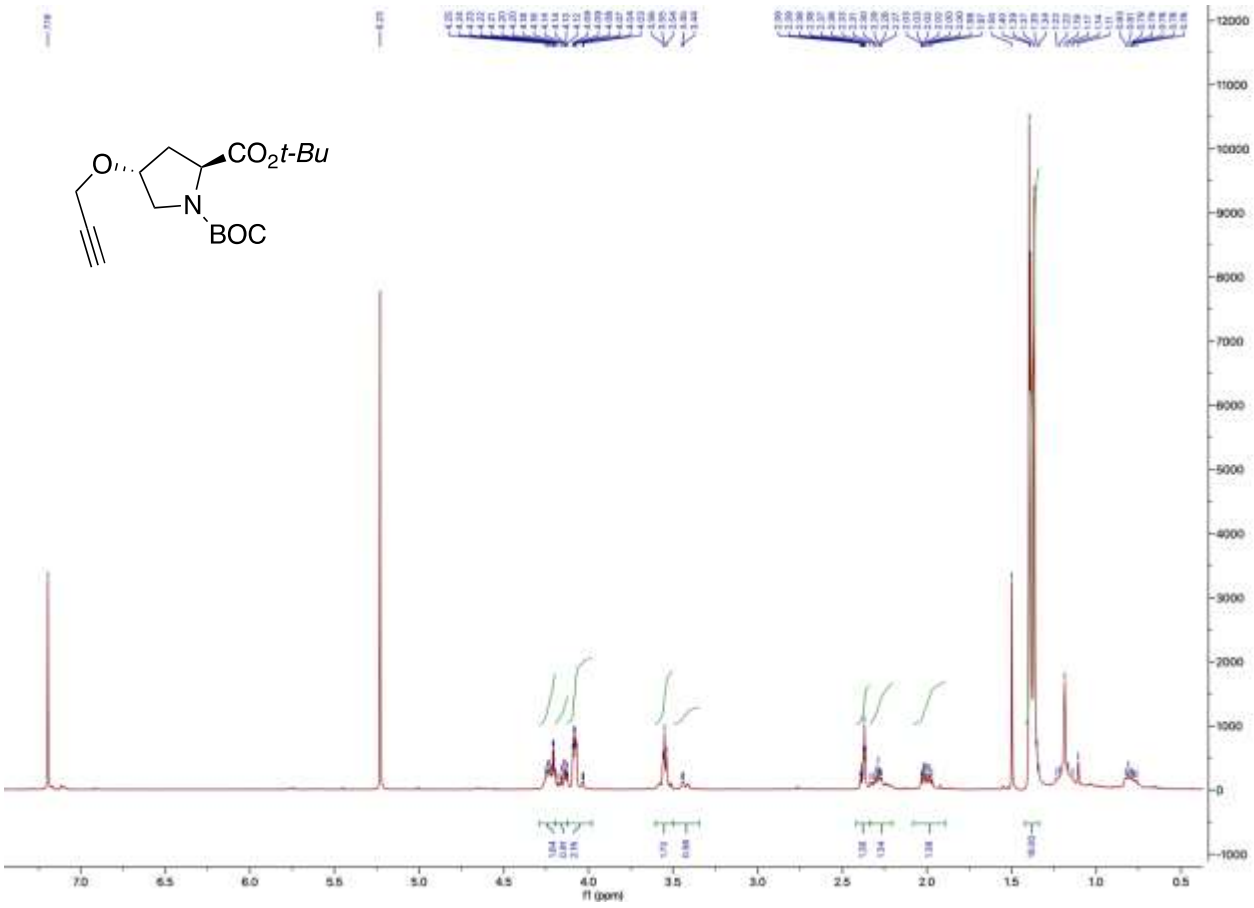


MW 287.17	MW 24	MW 120	MW 327.2
1 eq	60 % w/w	1.5 eq	**Y = 515 mg**
1.724 mmol	mineral oil	2.59 mmol	1.57 mmol
500 mg	1.5 eq	d = 1.39 g/mL	**91 %**
	2.59 mmol	311 mg	
	104 mg	**224 µL**	

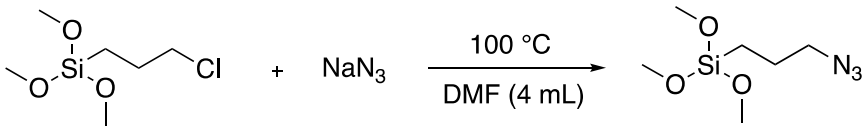
NaH and pentane (5mL) were added in a 25ml round bottom flask; the suspension was stirred in order to remove the mineral oil for 5 min; pentane was removed and DMF (5 mL) added.

The crude intermediate di-*ter*t-butyl (2*S*,4*R*)-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 (2*S*,4*R*)-4-(prop-2-yn-1-yloxy)pyrrolidine-1,2-dicarboxylate



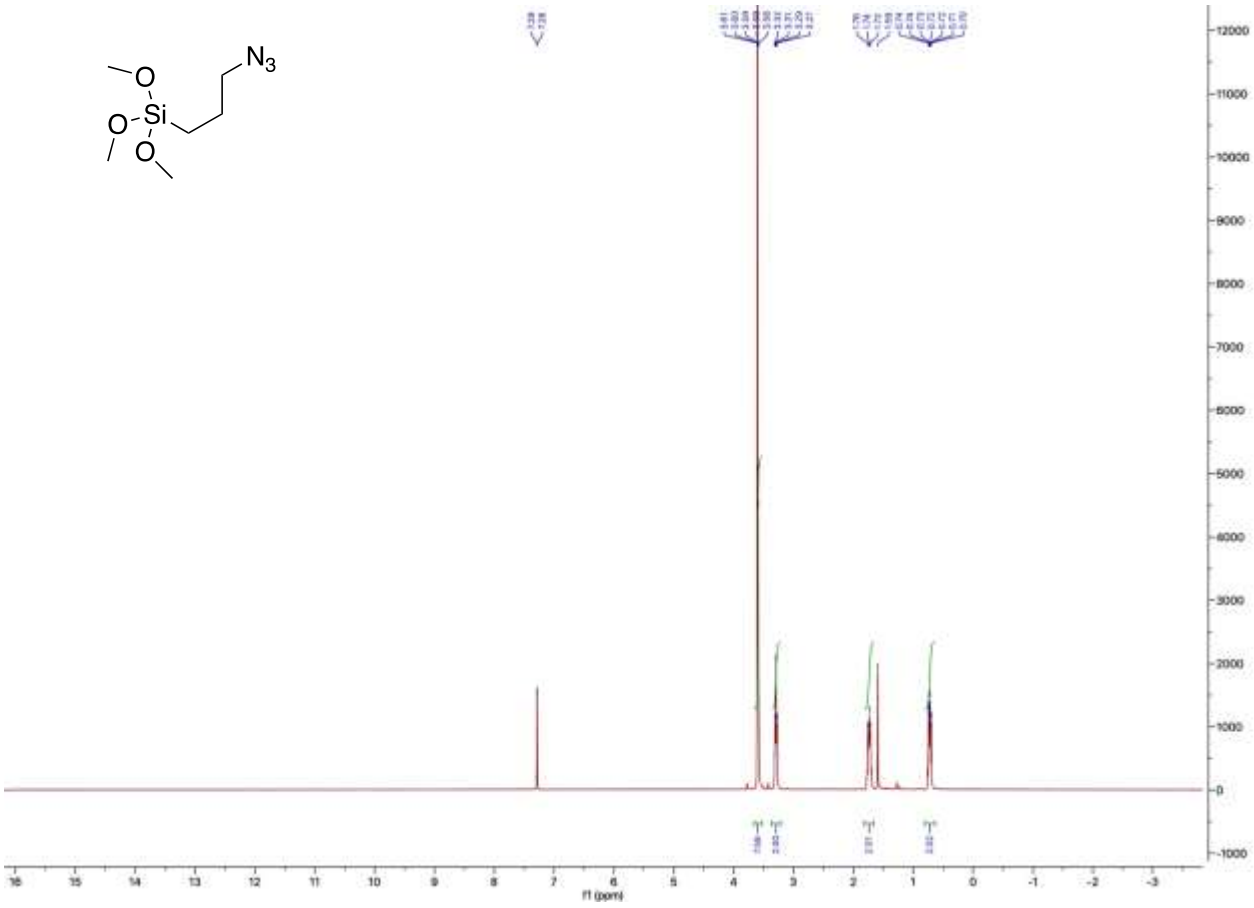
Synthesis of (3-azidopropyl)trimethoxysilane



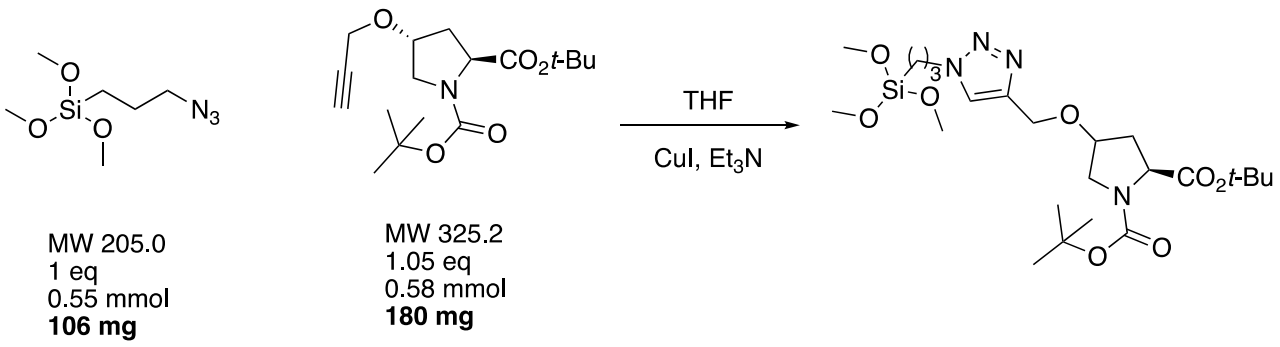
MW 198.05	MW 65.01	MW 205.0
1 eq	1.5 eq	**Y = 1.2 g**
6.61 mmol	9.915 mmol	5.89 mmol
d=1.09	**644 mg**	**89 %**
1.31 g		
1.2 mL		

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

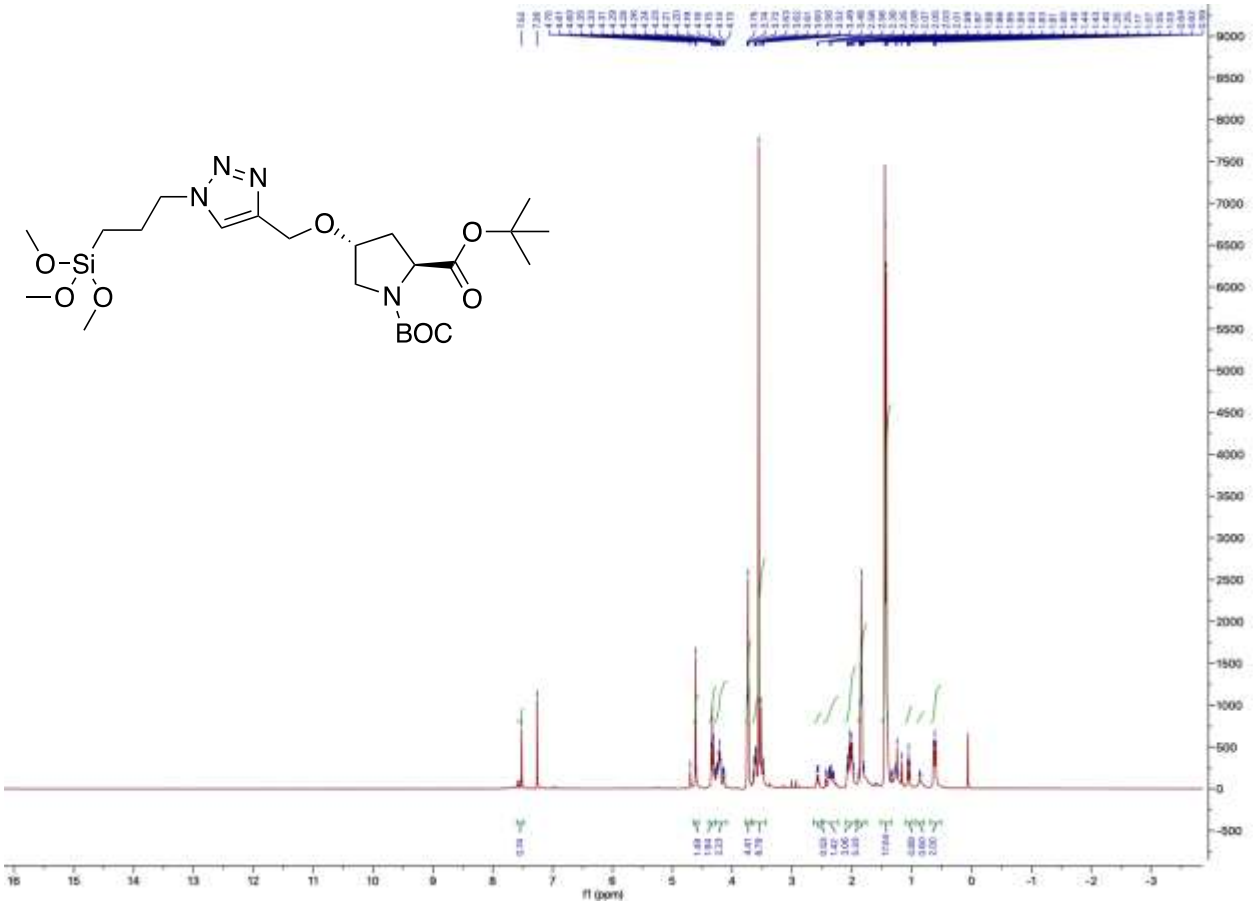


Synthesis of di-*tert*-butyl (2*S*,4*R*)-4-((1-(3-(trimethoxysilyl)propyl)-1H-1,2,3-triazol-4-yl)methoxy)pyrrolidine-1,2-dicarboxylate

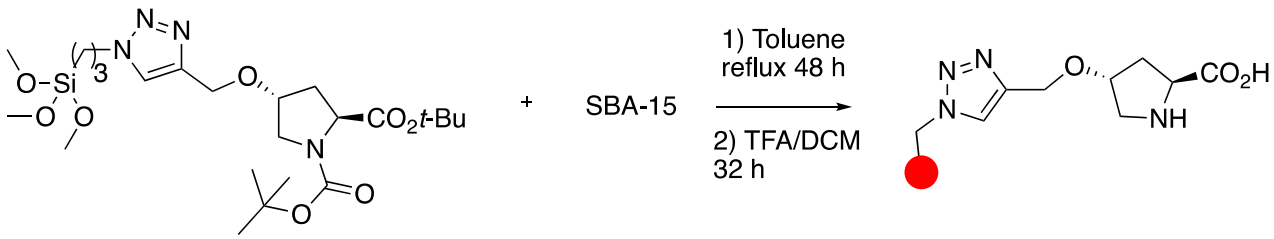


To a solution of (3-azidopropyl)trimethoxysilane (106 mg, 1 eq., 0.55 mmol) and di-*tert*-butyl (2*S*,4*R*)-4-(prop-2-yn-1-yloxy)pyrrolidine-1,2-dicarboxylate (180 mg, 1.05 eq., 0.58 mmol) in 5 mL of THF, TEA (Triethylamine, 150 µL, 1.1 mmol, 2 eq.) and copper iodide (2 mg, 0.011 mmol, 0.02 eq.) were 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_2N of the (3-azidopropyl)trimetoxysilane)), 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_3O), 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_2Si).

^{1}H-NMR spectrum ($CDCl_3$) of di-*tert*-butyl (2*S*,4*R*)-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**



MW 530.7
0.55 mmol
290 mg

500 mg

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 SI2**).

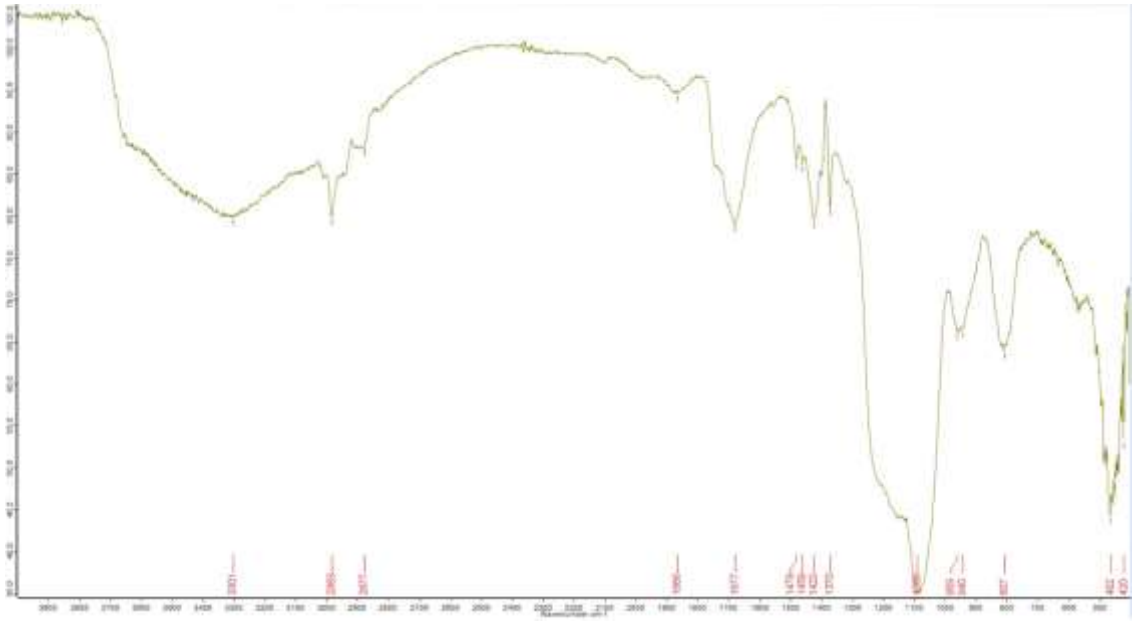


Figure SI2. FT-IR spectrum of the protected proline anchored onto SBA-15.

Table SI1. Elemental Analysis of protected proline anchored onto SBA-15

Element	%	Protected proline loading
C	13.09	0.545
H	2.07	
N	3.1	0.553

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).

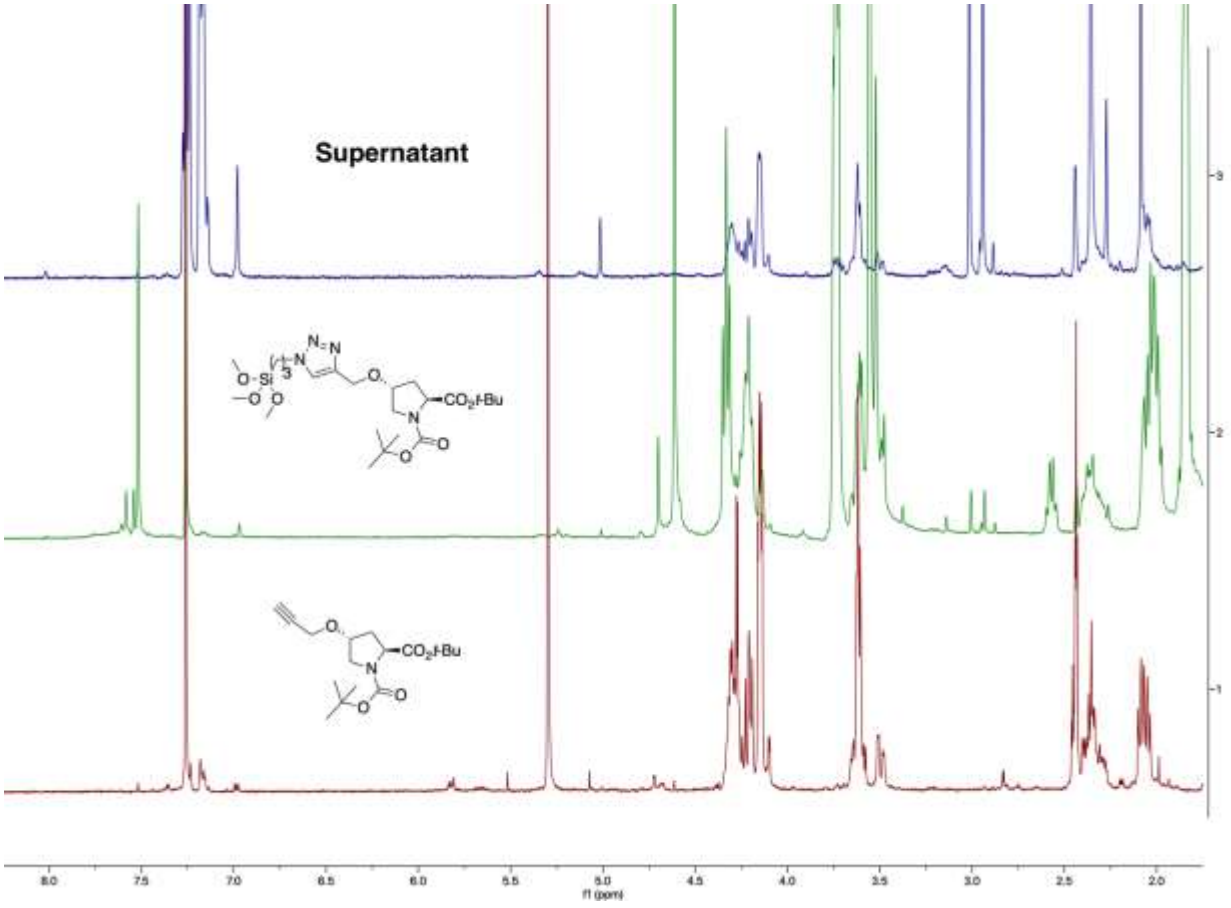


Figure SI3. Comparing of 1H NMR spectrum of supernant solution after reaction of anchoring with trimetoxysilicon functionalized protecting proline and propargyl functionalized protected proline.

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]

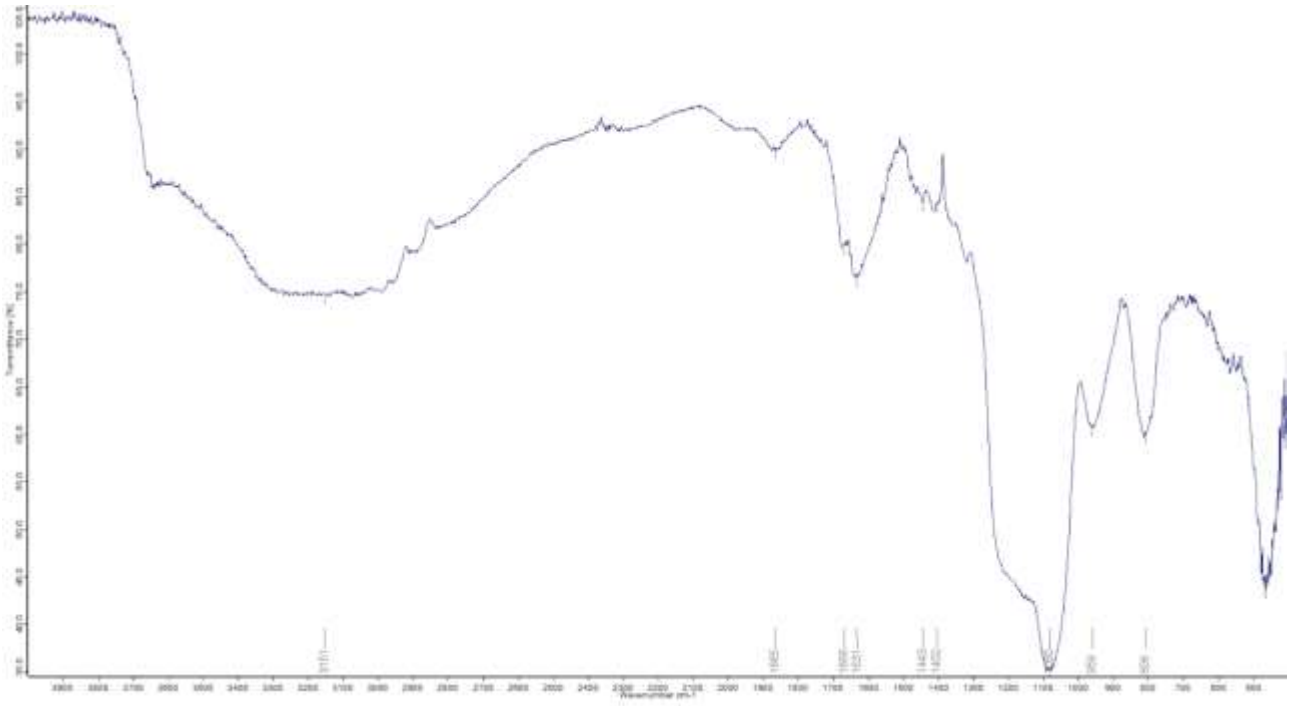


Figure SI4. FT-IR spectrum of the proline anchored onto SBA-15 (**4**).

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

Element	%	Protected proline loading
C	9.29	0.596
H	1.84	
N	3.36	0.600

Complete deprotection of both groups (BOC and *tert*-Butyl) is confirmed by EA (loading calculated for $C_{12}H_{22}N_4O_8Si$) 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 higly reproducible. We were able to prepare a new batch with similar catalyst loading (0.53 mmol g^{-1}) employing the reported procedure.

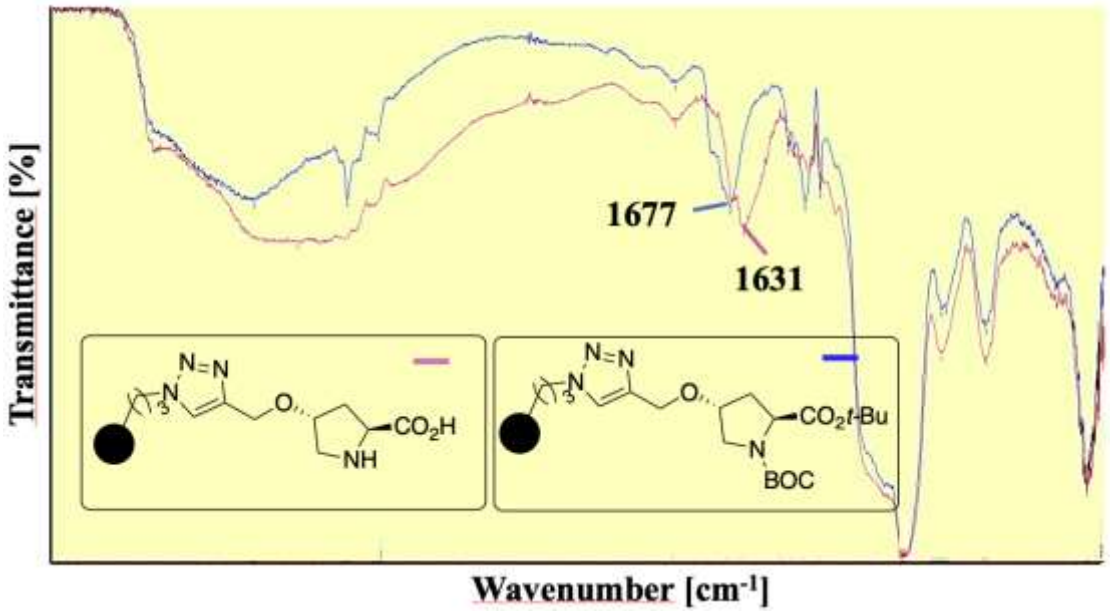


Figure SI5. FT-IR spectra of protected proline (blue) and proline (purple) both anchored onto SBA-15 (**4**).

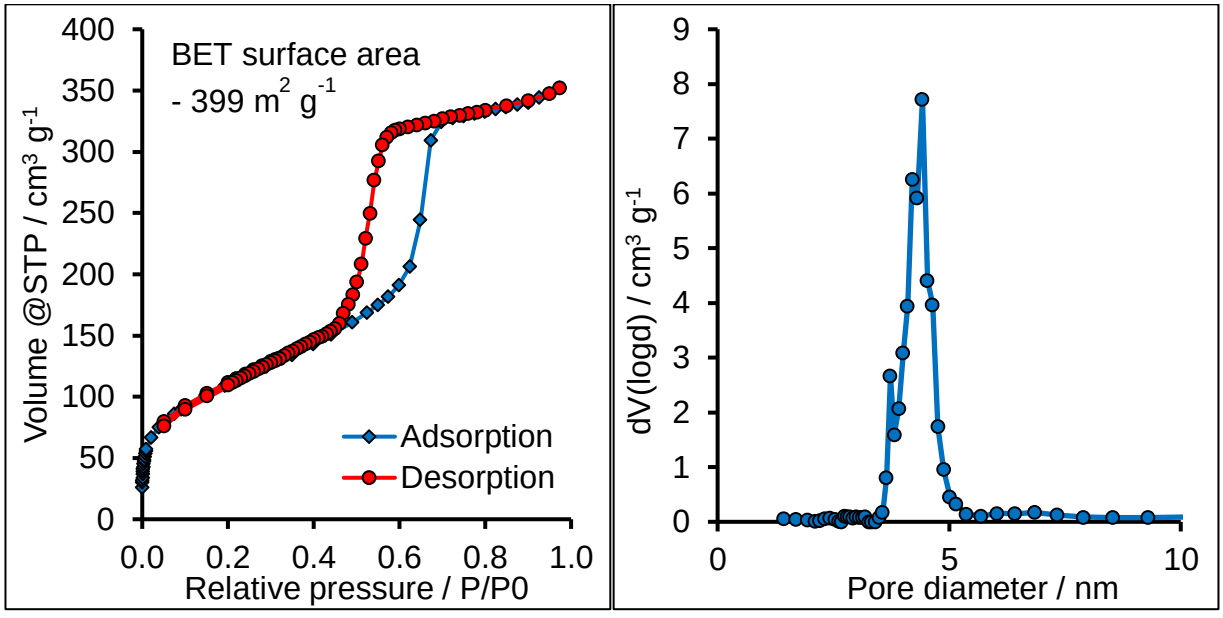


Figure SI6. Nitrogen porosimetry isotherm (left) and BJH pore size distribution (right).

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 NH_4Cl 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 $MgSO_4$ and concentrated in vacuo after filtration.

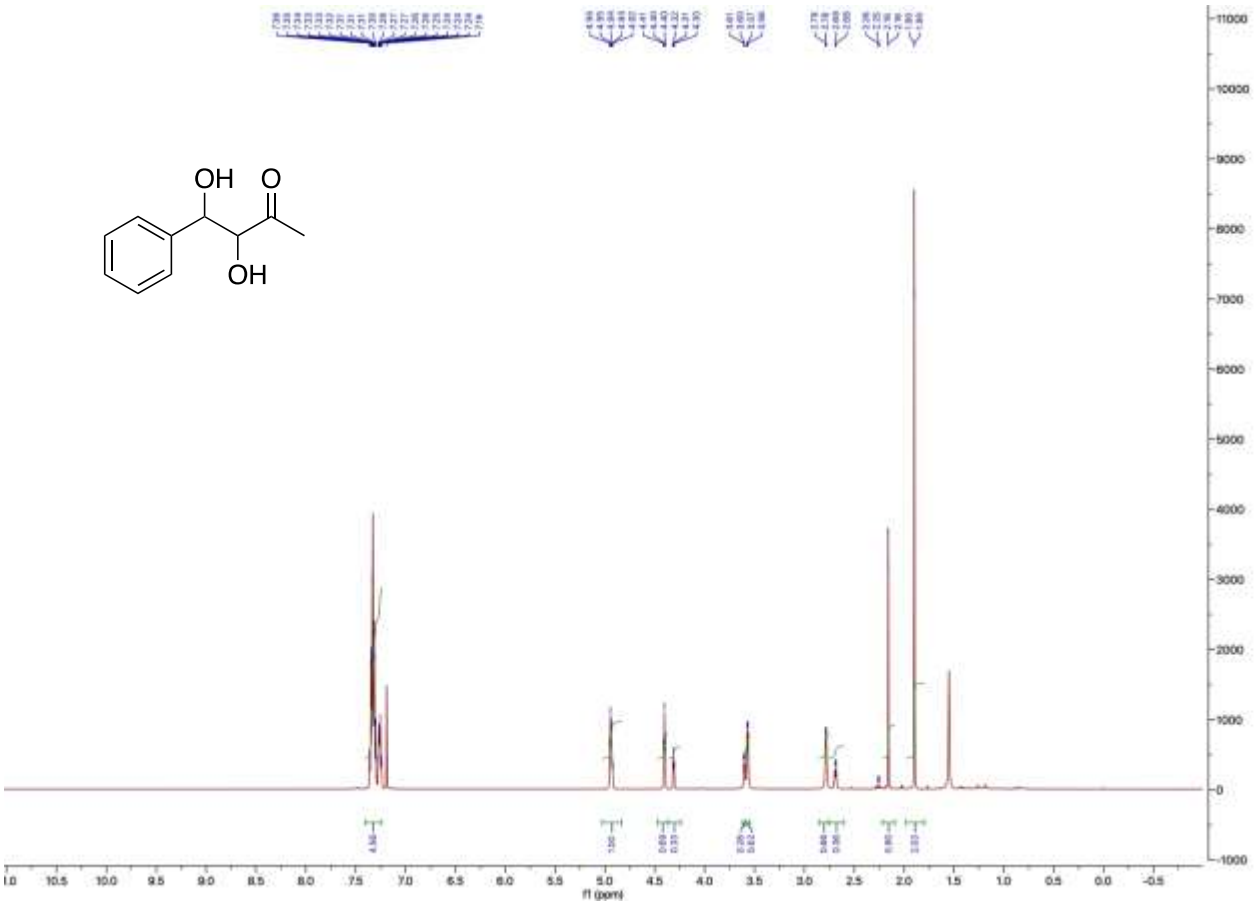
2) Heterogenous

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 NH_4Cl 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 $MgSO_4$ and concentrated in vacuo after filtration.

For each reaction: 1 mL of internal standard (durene) in $CDCl_3$ was added to the reaction mixture to evaluate the conversion. Conversion and *dr* were determined by ^{1}H-NMR of the crude reaction mixture.

^{1}H NMR (500 MHz, $CDCl_3$, 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, CH_3), 1.90 (s, 3H, CH_3).

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)


OH
O
OH
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
f1 (ppm)

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

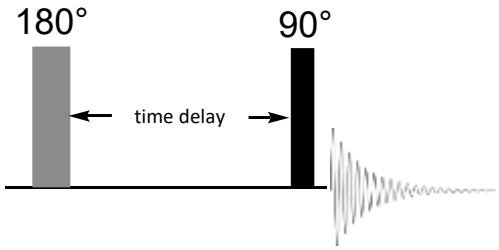


Figure SI7. Rappresentation of inversion recovery sequence employed to measure the T_1.

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

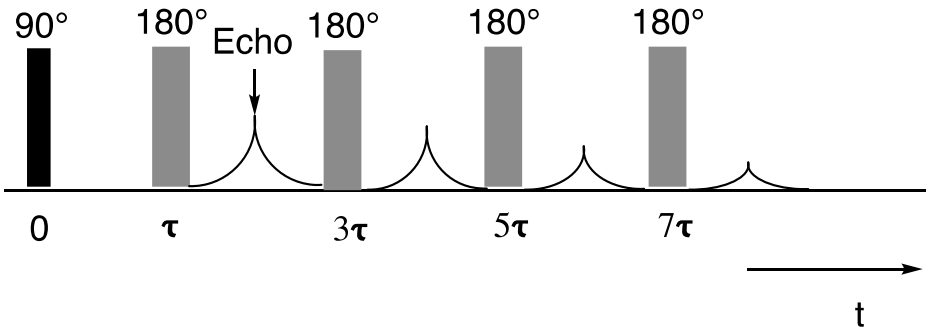


Figure SI8. Rappresentation of CPMG sequence employed to measure the T_2.

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 SI9**) and (**Figure SI10**) [2] to estimate T_1 and T_2, respectively.

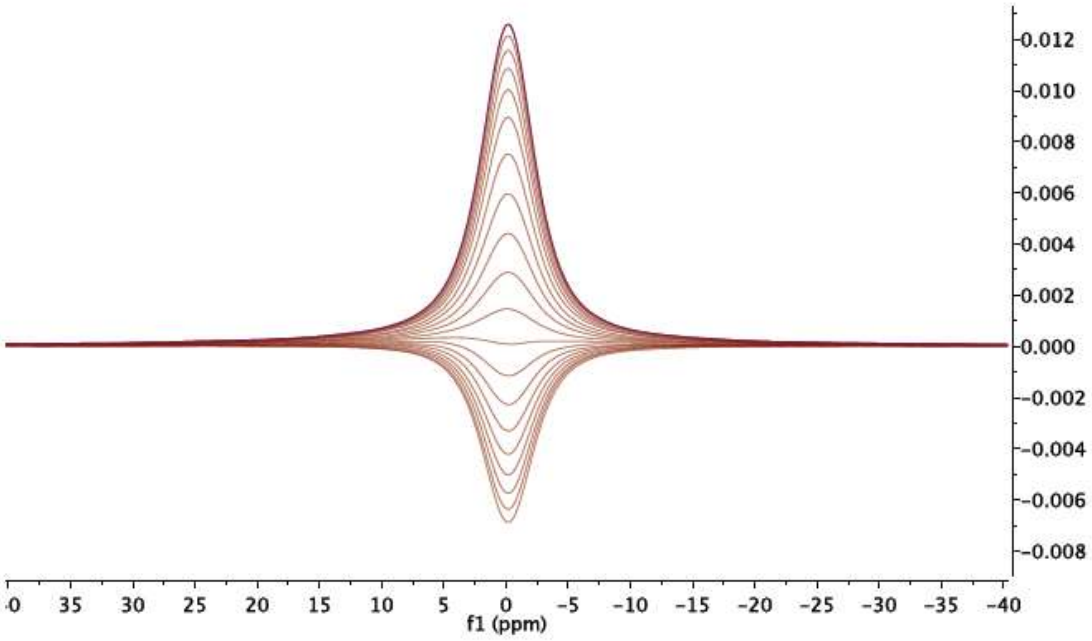


Figure SI9. FIDs (IR) of cyclohexane in the catalyst, after phasing and baseline correction, plotted *vs* time to obtain the T_1 value.

$$M_z = M_0(1 - 2e^{-\frac{t}{T_1}}) \quad (1)$$

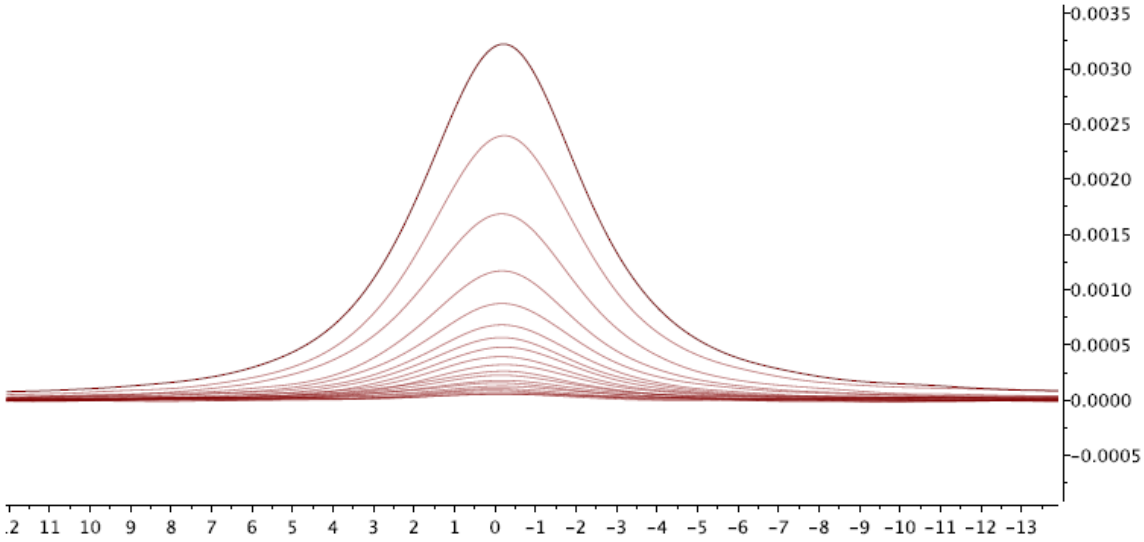


Figure SI10. FIDs (CPMG) of cyclohexane in the catalyst, after phasing and baseline correction, plotted *vs* time to obtain the T_2 value.

$$M_{xy} = M_0 e^{-\frac{t}{T_2}} \quad (2)$$

References

[1] P. Kasaplar, C. Rodriguez-Escrich and M. A. Pericàs, *Org. Lett.*, 2013, **15**, 3498.

[2] A. Gowda, J. Seo, C. K. Ranaweera, and S. V. Babu, *ECS J. Solid State Sci. Technol.*, 2020 9 044013.