SUPPORTING INFORMATION

Highly effective design strategy for the heterogenisation of chemo- and enantioselective organocatalysts

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Background

We have previously shown that mesoporous silica supports are highly amenable to the immobilisation of metal diamine complexes.[1] Both covalent and non-covalent anchoring strategies yielded higher activities and selectivities than their homogeneous counterparts, clearly demonstrating the merits of heterogenisation.

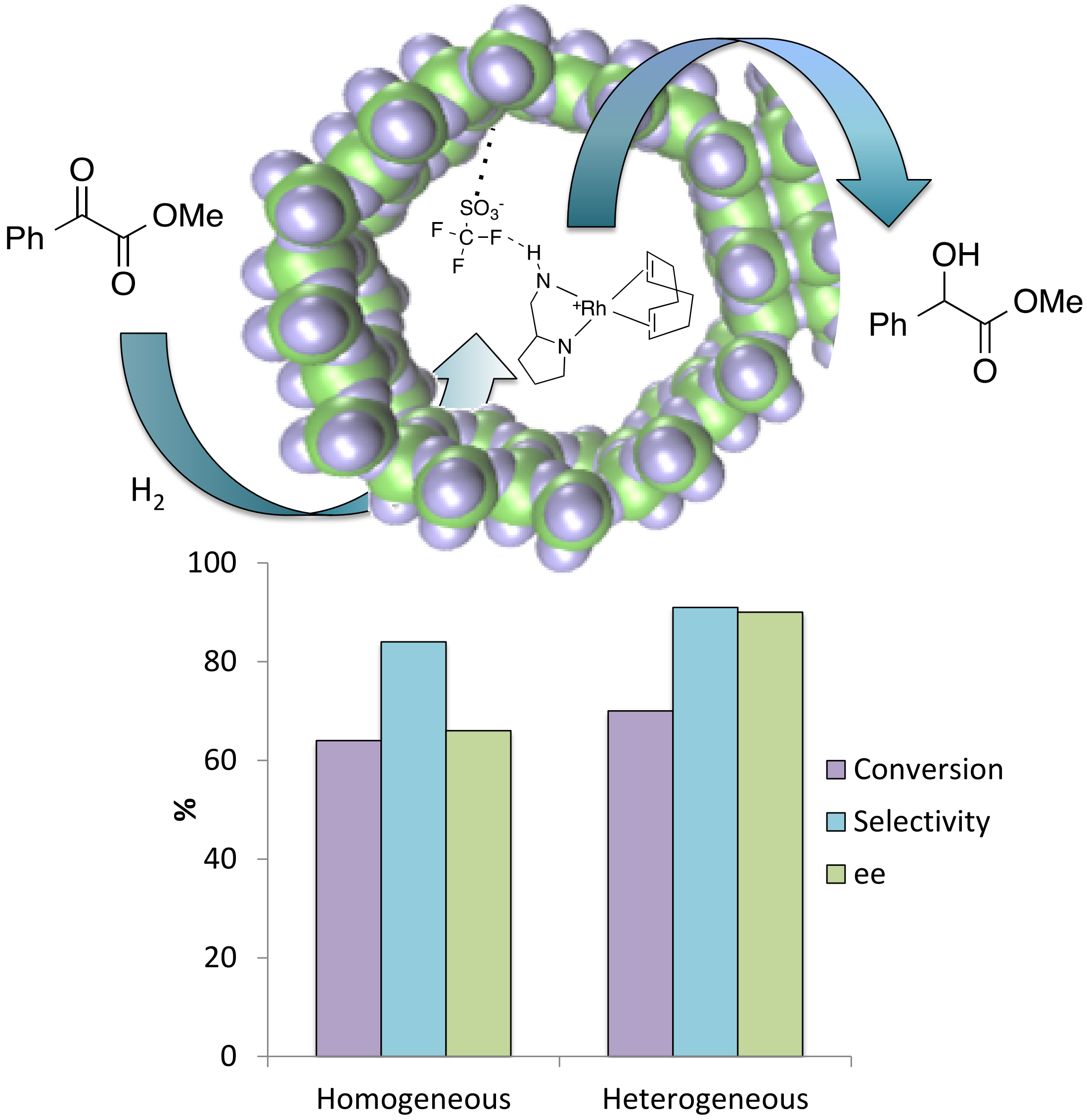


Figure S1: Upon immobilisation, Rh-diamine complexes display enhanced activity and selectivity compared to their homogeneous analogues.[1]

Experimental

General

Chemicals and solvents were supplied by Fisher, Sigma Aldrich, Fluka and Merck Novabiochem. Fumed silica purchased from Aldrich, 250 Å, 150 Å, 60 Å, and 30 Å Grace-Davison silica employed without the need for calcination and of particle sizes 75-150µm for all porous supports.

^{1}H NMR spectra were recorded on Bruker Advance AV-300 at ^{1}H frequencies of 300.130. Spectra were recorded in $CDCl_3$ and DMSO at room temperature with TMS serving as internal standard ($\delta = 0$) and were used to calculate conversion and chemoselectivities for the Michael addition reaction. To calculate enantioselectivities for the Michael addition reaction HPLC (Agilent Technologies 1120 LC) was ran on a CHIRALCEL OJ and AD-H columns using UV detection. Perkin Elmer Clarus 480 with an Elite 5 column was used to calculate conversion and selectivities for the Baylis Hillman reaction.

Thermogravimetric analyses (TGA/DTG) of materials were performed under argon flow (100 ml min^{-1}) with a SETSYS Evolution TGA-DTA/DSC thermobalance, heating from 40 to 1000 ^{o}C at 5 ^{o}C min^{-1}.

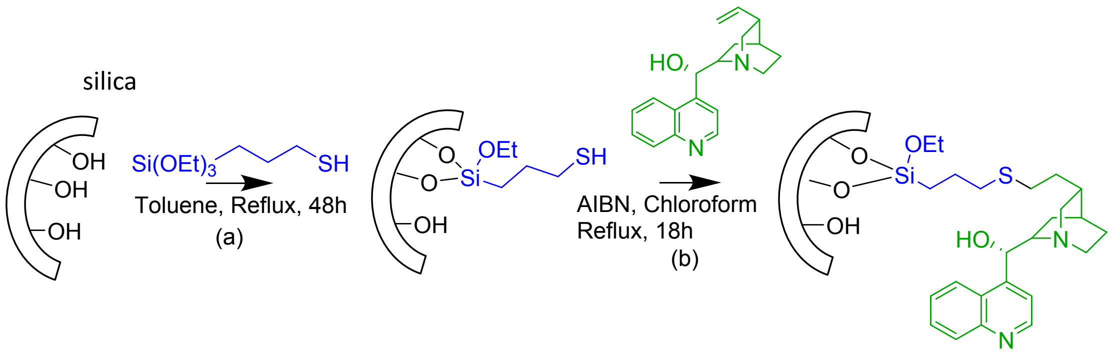
N_2 physisorption measurements were carried out at 77K in the relative pressure range from 1 x 10^{-6} to 1 P/P_0 by using a Quantachrome Autosorb1MP/TCD instrument. Prior to the analysis, the samples were outgassed at 453 K for 3 h (residual pressure lower than 10^{-6} Torr). Specific surface areas were determined using the Brunauer–Emmett–Teller equation, in the relative pressure range from 0.01 to 0.1 P/P_0. Pore size distributions were obtained by applying the DFT method and using the desorption branch of the N_2 physisorption isotherm.

FTIR spectra of self-supporting pellets were collected under vacuum conditions (residual pressure $<10^{-5}$ Torr; 1 Torr = 133.33 Pa) using a Bruker Equinox 55 spectrometer equipped with a pyroelectric detector (DTGS type) with a resolution of 4 cm^{-1}.

Solid-state ^{13}C spectra were recorded at 100.56 MHz using a Varian VNMRS spectrometer and a 6 mm (rotor o.d.) magic-angle spinning probe. They were obtained using cross polarisation with a 1 s recycle delay, 1 ms contact time, at ambient probe temperature (~25 °C) and at a sample spin-rate of 6.8 kHz. Between 1400 and 5000 repetitions were accumulated. Spectral referencing was with respect to an external sample of neat tetramethylsilane (carried out by setting the high-frequency signal from adamantane to 38.5 ppm). Silcon-29 spectra were recorded on the same instrument and probe at 79.44 MHz. Direct-excitation spectra were recorded following a 6.2 µs pulse with either a 120 (459 repetitions) or 240 s (150 repetitions) recycle delay and at a spin-rate of 6.8 kHz. Cross-polarisation spectra were recorded using a 2 s recycle delay, 3 ms contact time, approximately 10,000 repetitions and at the same spin-rate. Spectral referencing was with respect to an external sample of neat tetramethylsilane (carried out by setting the high-frequency signal from tetrakis(trimethylsilyl)silane to -9.9 ppm).

Synthesis

Immobilisation of Cinchonine[2,3]



Scheme S1: Schematic of the functionalization of mesoporous silica with cinchonine.

60 Å Porous silica (5.00 g) was degassed at 200 °C for 2 h under vacuum and once cooled it was suspended in toluene (50 ml). 3-Mercaptotriethoxysilane (2.02 ml, 8.4 mmol) was added drop wise to the solution and subsequently heated at reflux for 24 h. The solid was filtered and washed with hot EtOH (2 x 20 ml) and CH_2Cl_2 (2 x 20 ml) before drying at 50 °C in air to give the thiol functionalized silica as a white powder.

Thiol functionalized silica (1.00 g) was added to a solution of cinchonine (0.22 g, 0.75 mmol) and 2,2'-azoisobutyronitrile (AIBN) (0.125 g, 0.75 mmol) in chloroform (20 ml). The solution was heated at reflux for 18 h. After this time, the solid filtered, washed with CH_2Cl_2 (2 x 20 ml) and soxhlet for 18 h with CH_2Cl_2. The product was dried under vacuum at room temperature to give an off white powder.

Thiol functionalization of hydrophobic mesoporous silica

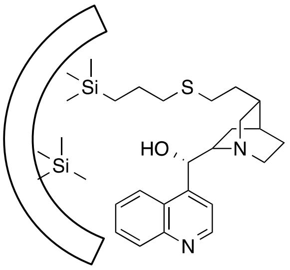


Figure S2: Hydrophobicity was introduced into the mesoporous silica via the methylation of pendant silanols.

60 Å Porous silica (1.00 g) was degassed at 200 °C for 2 h under vacuum and once cooled was suspended in toluene (30 mL). 3-Mercaptotriethoxysilane (0.048 ml, 0.2 mmol) was added drop wise to the solution simultaneously with methyltrimethoxysilane (0.14 ml, 1 mmol) and subsequently heated at reflux for 24 h. The solid was filtered and washed with hot EtOH (2 x 20 ml) and CH_2Cl_2 (2 x 20 ml) before drying at 50 °C in air to give the thiol functionalized silica as a white powder.

Immobilisation of DABCO[4]

Mesoporous silica (5g) was degassed for 2 hours at 200°C. It was then suspended in toluene (50ml), 3- chloropropyltriethoxysilane (0.1ml) was added drop wise and triethylamine (0.01ml) was added. The suspension was stirred under reflux at 120°C for 48 hours. The reaction was then cooled, the silica was collected via filtration and washed by soxhlet extraction technique.

The propyl chloride functionalised silica (2g) was suspended in acetone (60ml) and DABCO (1g) was added. It was stirred under reflux for 36 hours before being washed via soxhelt extraction.

Catalysis

Typical catalytic Michael addition:

Cinchonidine functionalised mesoporous silica (0.05 g) or cinchonidine (0.006mmol) was added to a solution of *N*-benzylmaleimide (111 mg, 0.6 mmol) and ethyl-2-oxocyclopentanecarboxylate (0.095 ml, 0.64 mmol) in CH_2Cl_2 (1.5 ml) and stirred for 5 h at room temperature. The solid catalyst was removed by filtration, washed with CH_2Cl_2 (5 ml) and concentrated to provide a conversion based NMR analysis and stereoselectivity calculated by HPLC.

Typical catalytic Baylis Hillman Reaction

4 nitrobenzaldehyde (0.8 mmol) and mesitylene (0.056ml) were added to MeOH (1ml) and stirred until a homogeneous solution was obtained. Methyl acrylate (1.6mmol) and catalyst (homogeneous: 0.3mol% or heterogeneous catalyts: 50mg) were added and the solution was stirred for 5 days at room temperature in a sealed 2 ml vial. All products were analysed via GC Clarus 480 with a FID detector using an elite 5 column. Products and substrates were quantified the calibration method with mesitylene as a standard.

Calculations

Michael Addition:

Conversions and chemoselectivites were calculated via ^{1}H NMR:

$$Conversion\ (\%) = \frac{Integration\ of\ products\ x100\%}{Integration\ of\ products\ + Integration\ of\ residual\ starting\ material}$$

$$Selectivity\ (\%) = \frac{Integration\ of\ individual\ product\ x100\%}{Integration\ of\ all\ products}$$

$$Turnover\ number\ (\%) = \frac{moles\ of\ substrate\ converted}{moles\ of\ catalyst}$$

Stereoselecivity was calculated form HPLC:

$$Enantioselectivity\ (\%) = \frac{R - S}{R + S} \times 100\%$$

Errors associated with measuring conversion are dependent on the accuracy of the NMR spectroscopy technique and the integration related with each proton signal. For our purposes, the hydrogen atoms are not acidic or readily exchangeable, therefore the measured conversion is expected to be within ± 3 % error. Chemoselectivity is determined in the exact same way (*via* NMR) so an identical error is associated with this measurement. With repeat experiments and studying the range of ee's associated with homogeneous catalysis the error in enantioselectivity is primarily based on the error with the HPLC technique, this is ± 2 %.

Baylis Hillman Reaction

All products were analyses via GC Clarus 480 with a FID detector using an Elite 5 column. Products and substrates were quantified *via* the calibration method with mesitylene as the internal standard.

The reaction solution for assessing the carbon balance using mesitylene as the internal standard was composed of (methylacrylate is excluded from the calculations for simplicity as it was present in great excess):

Mesitylene: 0.0487g
4 nitrobenzaldehyde: 0.1207g

Response factor (RF) for 4 nitrobenzaldehyde: 0.5763
Response factor for product: 0.3395

Performing an identical procedure to the one above, the following exemplar GC data was obtained at RT after 3 days with the heterogeneous catalyst:

Molecule	**Area**
Mesitylene	1447859.98
4 nitrobenzaldehyde	1180149.55
Product	259316.09
Others	0

Table S1: Integrated peak areas of the reagents and products in the Mortia Baylis Hillman reaction taken from the GC trace.

Rearranging the formula:

$$\frac{Peak\ Area_{reagent}}{Peak\ Area_{mesitylene}} = RF \times \frac{Moles_{reagent}}{Moles_{mesitylene}}$$

$$\frac{Peak\ Area_{reagent}}{Peak\ Area_{mestiylene}} \times \frac{Moles_{mesitylene}}{RF} = Moles_{reagent}$$

Gives: Using the equations and respons e factors above the moles the carbon balance can be confirmed to be within acceptable error.

Molecule	**Area**	**Moles**
Mesitylene	1447859.98	0.00040519
4 nitrobenzaldehyde	1180149.55	0.00057309
Product	259316.09	0.00021376
Others	0	0
Total moles		**0.00119204**

Table S2: Moles calculated using the calibration method of the reagents and products in the Mortia Baylis Hillman reaction.

$$Conversion\ (\%) = \frac{Initial\ moles\ of\ 4\ nitrobenzaldehyde - moles\ of\ 4\ nitrobenzaldehyde}{Intial\ moles\ of\ 4\ nitrobenzaldehyde}$$

$Conversion\ (\%) = 27.2\%$

$$Selectivity\ (\%) = \frac{Moles\ of\ product}{Moles\ of\ converted\ 4\ nitrobenzaldehyde} \times 100\%$$

$Selectivity\ (\%) = 100\%$

$$Mass\ balance\ (\%) = \frac{moles\ of\ 4\ nitrobenzaldehyde + moles\ of\ product\ + moles\ of\ others}{Intial\ moles\ of\ 4\ nitrobenzaldehyde}$$

$Mass\ balance\ (\%) = 98.5\%$

Both the reproducibility and carbon balance (>95mole%) are within accepted limits.

SiO_2/ Cinchonine Volumetric analysis

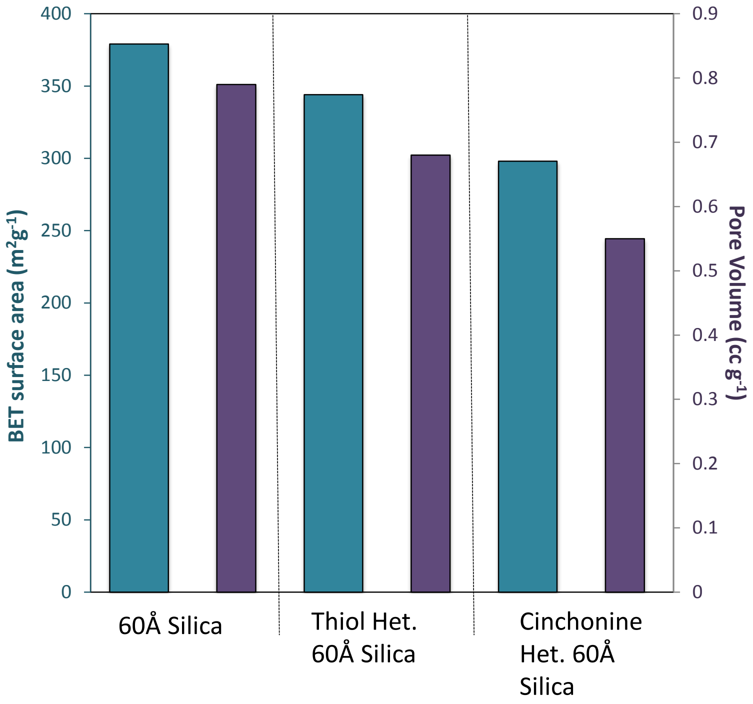


Figure S3 –BET surface area and pore volumes collected at 77K of plain SiO_2 60Å, Thiol Het. 60Å Silica and Cinchonine Het. 60Å Silica indicating the functionalised within the pores of the mesoporous silica

SiO_2/ Cinchonine FT-IR

Sample	**Wavenumber (cm^{-1})**	**Vibrating**	**Inference**
60Å Silica	3740 br.	Si-OH	Pendant silanols are available for functionalisation.
Thiol het. 60Å Silica	3740 br. 2982 2936 2982 2582 1395 1450	Si-OH C-H C-H C-H S-H C-H C-H	Evidence for the immobilisation of the thiol.
Cinchonine het. 60Å Silica	3740 br. 3400 2800-3000 br. 1500-1700 br.	Si-OH O-H C-H C=C and C=N	Lack of SH stretch indicates the thiol has been successfully coupled and presence of additional stretches between 1500 and 1700 cm^{-1} suggests successful immobilisation of the alkaloid.

Table S3 –FT-IR data of plain SiO_2 60Å, Thiol het. 60Å Silica and Cinchonine het. 60Å Silica confirming the presence of the cinchonine on the support.

SiO_2/ Cinchonine ^{29}Si CP/MAS NMR

Figure S4 –^{29}Si CP/MAS NMR of the cinchonine tether confirming the covalent link between the tether and the mesoporous silica support.

SiO_2/DABCO Volumetric analysis

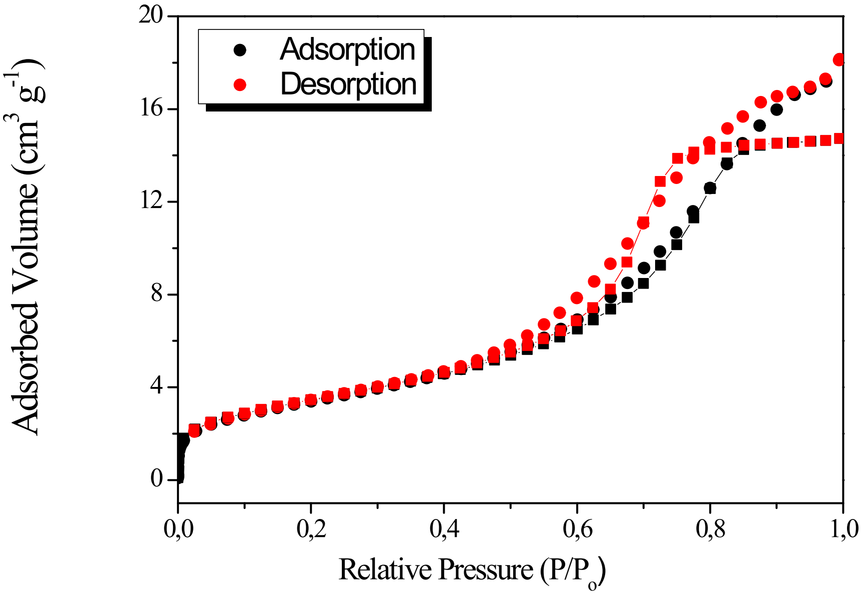


Figure S5 – N_2 adsorption/desorption isotherms at 77K of plain SiO_2 60Å (■) and DABCO/SiO_2 60Å (●)

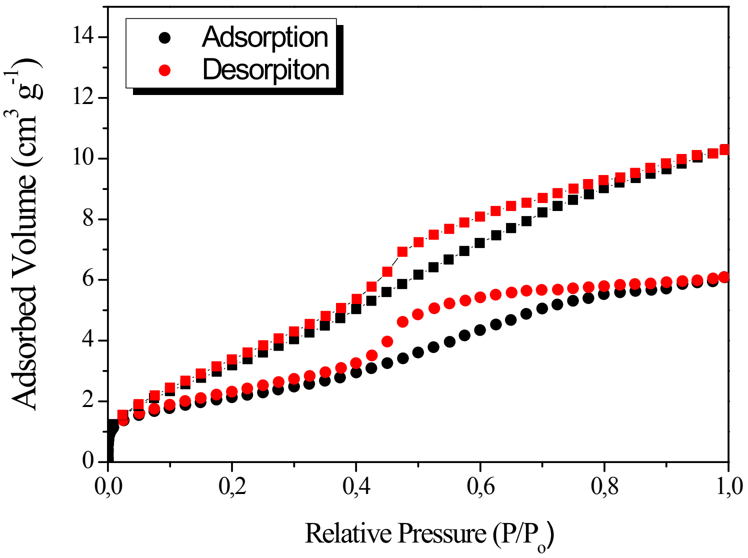


Figure S6 – N_2 adsorption/desorption isotherms at 77K of plain SiO_2 30Å (■) and DABCO/SiO_2 30Å (●)

CHN Elemental Analysis:

Elemental analysis was deployed to confirm the presence and loading of DABCO on the structure. A limitation of this technique is that it will detect all C, H, N present regardless of whether it is associated with the covalently bound organocatalysts, non-bound species or organic solvents. To minimise any possible conflicts all prepared catalysts were washed *via* soxhlet extraction technique to remove any adsorbed species and no nitrogen containing solvents were used. The loading of the catalyst on the support was determined via this formula:

$$n_{active\ nitrogen}/_{g} = \left(\frac{x(\%)}{100 \times 14\ (\frac{g}{mol}) \times 2}\right)$$

Catalyst	Active Nitrogen (mmol/g)
Cinchonine Functionalised 60 Å Silica	
Cinchonine Het	0.26
Cinchonine Het phobic	0.06
DABCO Functionalised Silica	
DABCO Het 30 Å Silica	0.26
DABCO Het 60 Å Silica	0.31
DABCO Het 150 Å Silica	0.31
DABCO Het 250 Å Silica	0.31

Table S4: Calculated loading (mmol/g) of organocatalysts onto the mesoporous silica frameworks.

Catalyst recycle and leaching test

Heterogeneous cinchonine was successfully recycled retaining high turnover numbers and enantioselectivity.

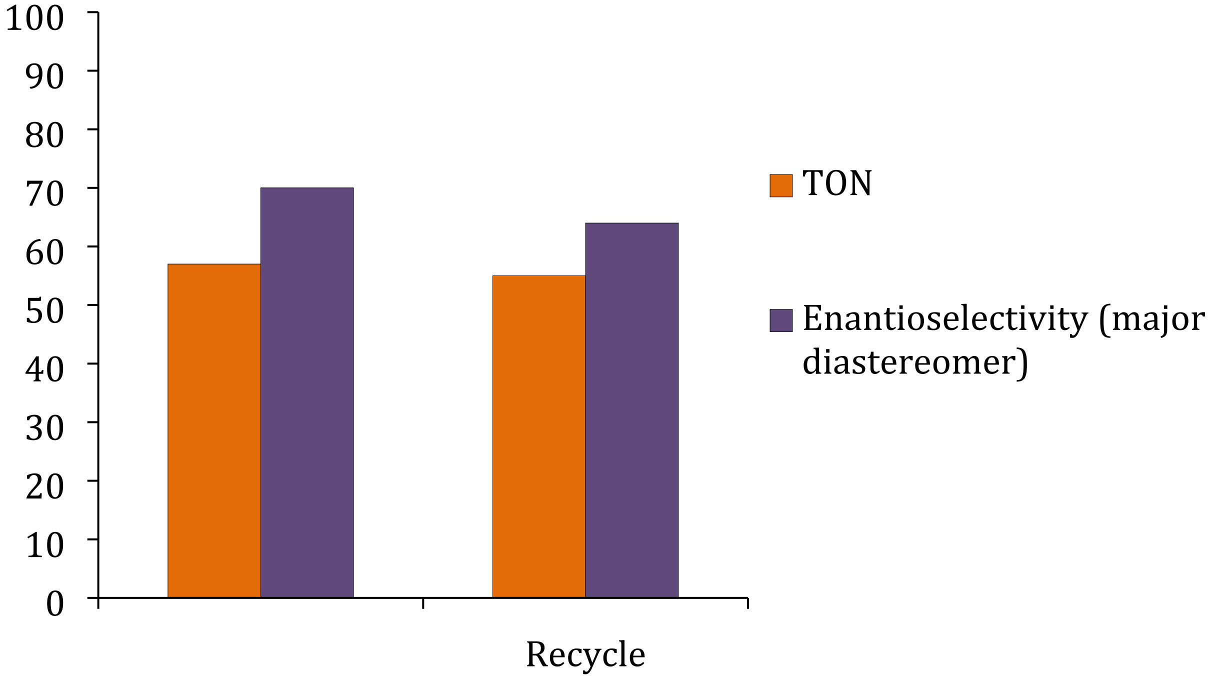


Figure S7: Recycle of heterogeneous catalysts in the Michael addition.

Conversion after removal of the catalyst for both the Baylis Hillman reaction and Michael reaction was monitored and indicated minimal leaching.

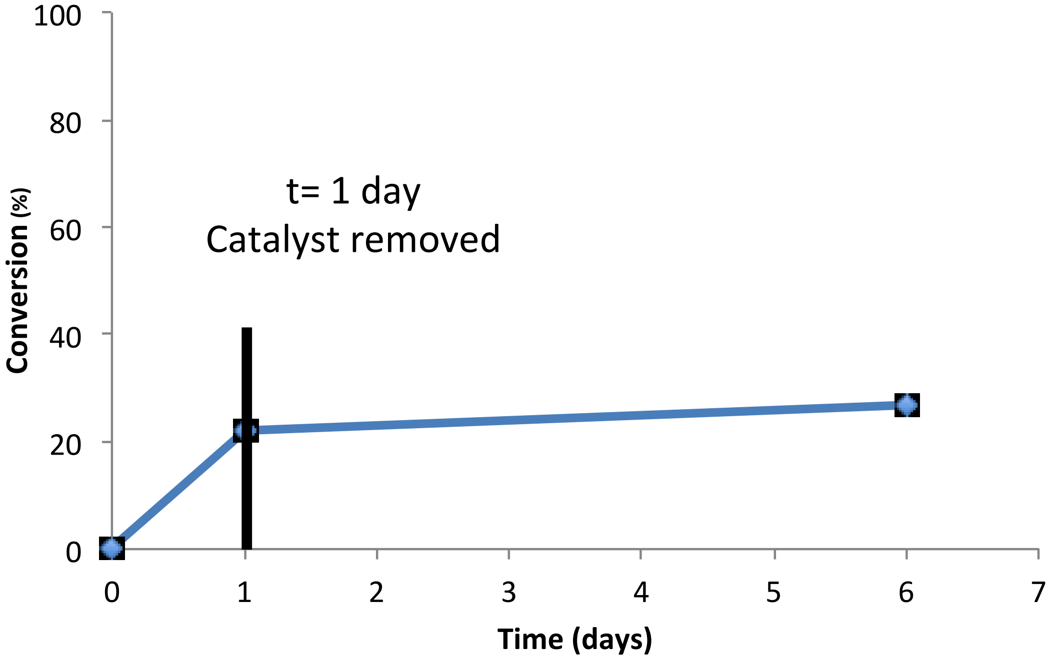


Figure S8: Conversion after removal of heterogenised catalyst from the Michael addition reaction indicating minimal leaching.

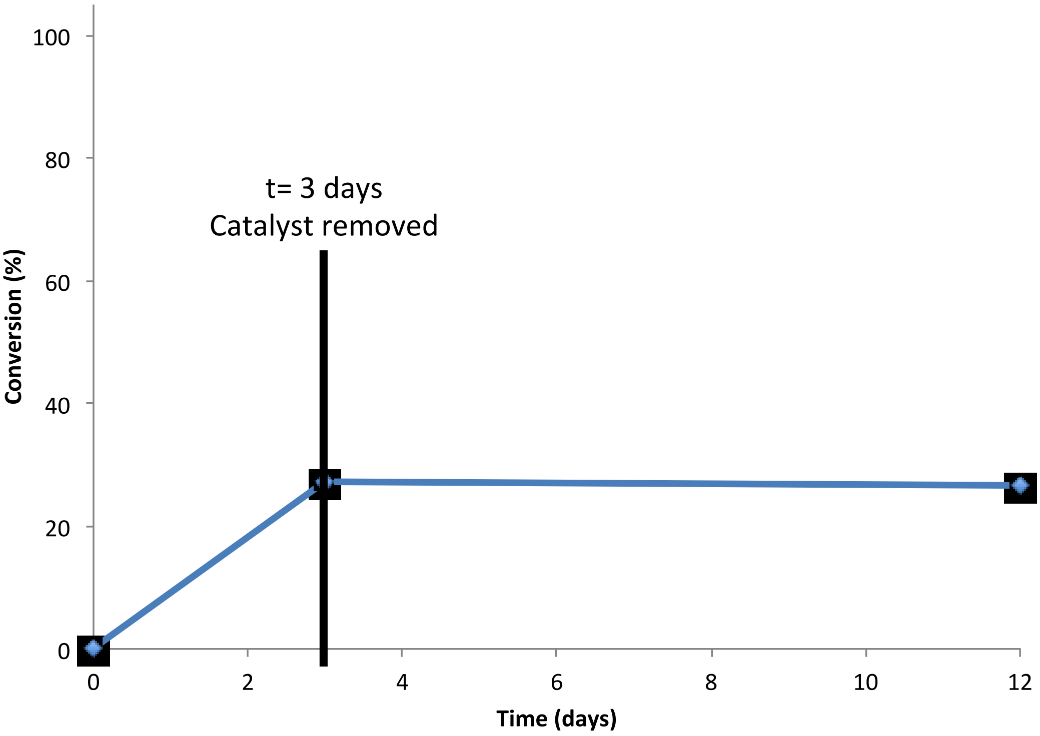


Figure S9: Conversion after removal of heterogenised catalyst from the Mortia Baylis Hillman reaction indicating no leaching.

References

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3. G. Sartori, A. Armstrong, R. Maggi, A. Mazzacani, R. Sartorio, F. Bigi and B. Dominguez- Fernandez, *J. Org. Chem.*, 2003, **68**, 3232-3237.
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