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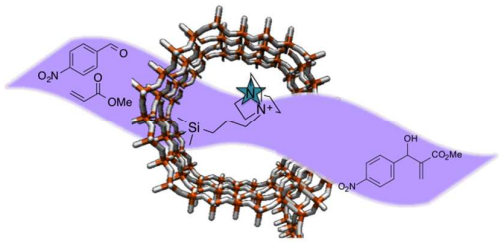
The covalent heterogenisation of cinchonine and 1,4-diazabicyclo[2.2.2]octane within a range of mesoporous silicas affords highly selective and active organocatalysts.



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

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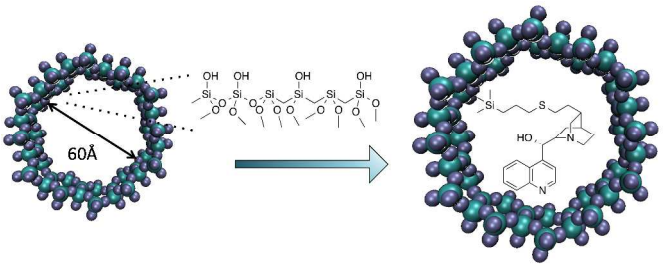
We have demonstrated that the covalent heterogenisation of two homogeneous organocatalysts, cinchonine and 1,4-diazabicyclo[2.2.2]octane, onto the inner walls of mesoporous silica supports results in highly active and selective solid catalysts that are easily recoverable and recyclable. We have further highlighted the efficacy of our design rationale and its amenability for tailoring the nature of the active site *via* meticulous choice of pore-aperture and hydrophobicity to create a superior heterogenised analogue for Michael addition and Baylis Hillman reactions. It is envisaged that this immobilisation strategy could be rationally extended to the heterogenisation of a plethora of organocatalysts.

The revitalisation of organocatalysis over the past decade has created a dynamic field in asymmetric organic synthesis.[1-3] The utilisation of simple and readily available organic entities to effectively catalyse demanding synthetic organic transformations, instead of the more traditional organometallic counterparts has inspired 'greener and more sustainable' routes to the synthesis of fine-chemicals. These catalysts are typically homogeneous in nature and are relatively easy to functionalise and manipulate to enable the formation of specific enantioselective carbon-carbon bonds. However, despite the strong prospects and potential implications, the deployment of functionalised organocatalysts has had limited applications within the chemical and pharmaceutical industries. As such, significant research emphasis has been placed in rendering these catalysts more amenable to industrial utilisation. [4, 5]

The most prominent deficiencies and challenges associated with adoption of organocatalysts for large-scale chemical processes can be inherently associated with their homogeneous nature and relative modest stabilities. Agglomeration and aggregation of the active sites often leads to a higher mole% of catalyst being required and difficulties in catalyst separation. Heterogenisation of these active organic entities, therefore, promises to be a viable method to alleviate the above shortcomings. To the purist, it could be considered as adding extra unnecessary steps to the synthetic procedure. However, the design of a versatile and effective heterogeneous organocatalyst with isolated single-sites[6-8] will facilitate improvements in activity, selectivity and recoverability, the benefits of which will far outweigh that of its homogeneous counterparts. Despite the above, there are very few reports[9-15] of immobilised organocatalysts that are capable of mimicking the levels of activity and selectivity usually prevalent in the homogenous systems. Hence there is a pressing need for the development of a design rationale that could serve as a basis for anchoring homogeneous organocatalysts in a more robust fashion.

We,[16-19] and others[20-25] have previously shown that mesoporous silica supports are highly amenable to both the covalent and electrostatic immobilisation of organometallic catalysts (Fig. S1 ESI). This is owing to their defined pore apertures and pendant silanol groups that are amenable for facile functionalisation and manipulation. [11, 26-29] However, despite the significant progress made with elegant anchoring strategies of the organometallic species[30-34] their industrial application has been limited due to the use of expensive metal precursors and harmful reagents.[21,30,31,35,36] Therefore it is highly desirable, both in terms of economic viability and sustainability, to apply the design rationale evoked from these systems to the more benign and practical organocatalysts.



Scheme 1: Schematic outlining the functionalisation of mesoporous silica with cinchonine.

In this work we have combined the design principles ascertained from the immobilisation of the metal diamine complexes[16-19] with an in-depth understanding of the mechanism of homogeneous base-catalysed reactions, to rationally design organic-inorganic hybrid catalysts (Scheme 1) that mimic the activity and selectivity seen in their corresponding homogeneous analogues. Herein, we report and demonstrate the viability of our design-application approach (Scheme 1), where subtle modifications[11,14, 37-40] to the hydrophobicity and pore aperture of the support facilitate improvements in catalytic activity and selectivity. More importantly, the design strategy that we have evolved requires minimal modification of the parent organocatalyst, which is vital in preserving its original activity and selectivity post heterogenisation. The covalent anchoring approach further ensures a more robust linkage with the pendant silanol groups of the support. Appropriate choice and fine-tuning of the organocatalyst itself (e.g. cinchonine, 1,4-diazabicyclo[2.2.2]octane (DABCO) – see later) can afford appropriate substrate and support binding sites, that futher enhances the accessibility of the active centre to reagents during catalysis. The synthetic methodologies that we have employed (as above) assist the creation of isolated single-sites,[6,7, 41] which not only facilitate advantageous interactions of the active centre with the support matrix, but simultaneously afford synergistic enhancements in catalytic output.

The base catalysed asymmetric Michael addition reaction is among the most widely studied C-C bond forming reactions and is extensively employed in fine chemical synthesis within the pharmaceutical and perfume industries (Fig. 1A). In order to develop a highly efficient enantioselective catalyst for the Michael addition, cinchonine was anchored covalently to the pendant silanol groups largely within the inner walls of mesoporous silicas (Scheme 1, Fig. 1 and Scheme S1 ESI). The environment and method of anchoring of the cinchonine catalyst was carefully considered. Cinchonine is a bifunctional organocatalyst: the quinuclidine moiety activates the nucleophile whilst the hydroxyl group activates the electrophile. Owing to the molecule's steric bulk, the organocatalyst is able to preferentially orientate the substrate to give exquisite stereo-control.[10-12] It is highly likely that the organic functional groups will be tethered at the surface and inside the pores randomly by utilising our strategy; but as evidenced by BET measurements these groups are predominantly found within the interior cavities of the mesoporous silica (Fig. S3 ESI). By securely anchoring this organocatalyst primarily onto the inner walls of mesoporous silica with the appropriate pore dimension (60Å) a constrained environment could be created within the pore; and it was envisaged that this sterically demanding void space in the vicinity of the active centre would afford enantioselective control that could mimic or exceed that of the homogenous analogue.[16,11]

The structural integrity of the heterogenised analogue (Het. Cinc. MS) was confirmed by using an array of structural and physico-chemical characterisation techniques (Fig. S3, Table S3 and Fig. S4 ESI).[42] The resulting heterogenised catalyst displayed enhanced turnover numbers and modest enantioselectivities when compared to that of the homogeneous analogue (Fig. 1B), with the added advantage of it being easily recyclable (Fig. S7 ESI and Fig. S8 ESI).

In order to further manipulate the performance of the heterogeneous cinchonidine catalyst, the pendant silanols of the mesoporous silica support were methylated to create a hydrophobic environment (Fig. 1B and Fig. S2 ESI).[11, 28] It has been hypothesised[12, 43, 44] that the hydrophobic coating would reduce the interactions between the reactants and pore walls thereby mitigating any diffusion limitations and subsequently increasing the activity of the catalyst. It was found that hydrophobic coating on the mesoporous silica resulted in progressively higher turnover numbers than the standard heterogenised catalyst (increased from 23 to 60), indicating that the active site was more accessible to the substrate (Fig. 1B). However, strikingly, the hydrophobic environment had a detrimental effect on the enantioselectivity of the catalyst, which decreased from 74% to 56%. It is highly likely that the hydrophobic groups alter the environment around the active sites in such a way that it restricts the preferential orientation[7,10] of the desired transition-state, which is responsible for the higher enantioselectivity.

To further validate the versatility of our design rationale, we extended the above methodology to another key transformation within the chemical industry; the Baylis Hillman reaction.[45-47] The highly atom efficient Baylis Hillman reaction is extremely significant as it produces products with high functionality. DABCO

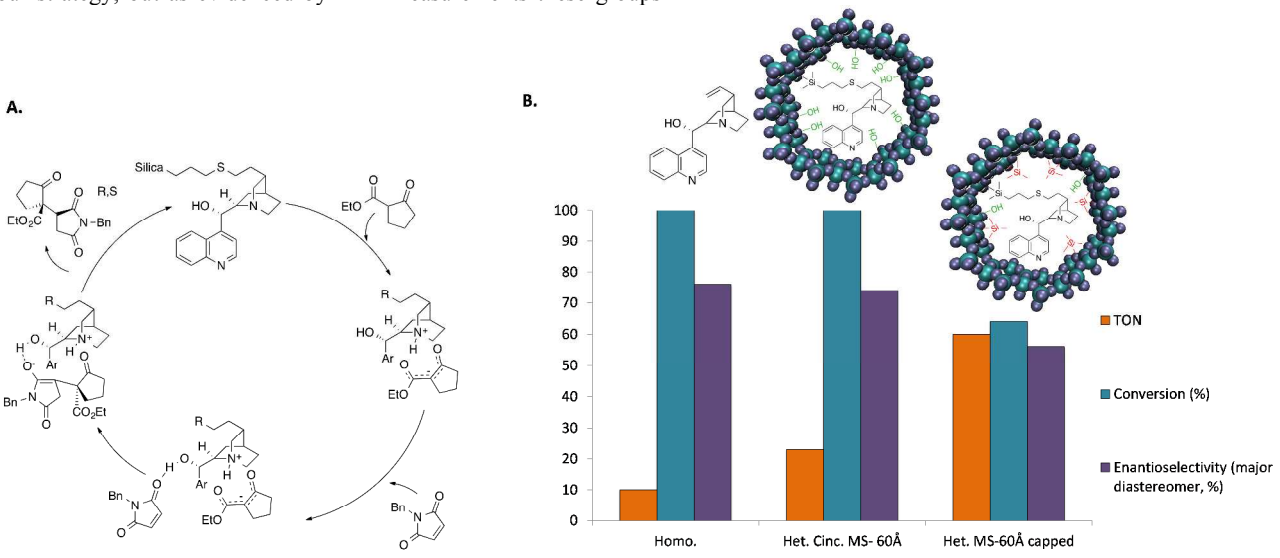
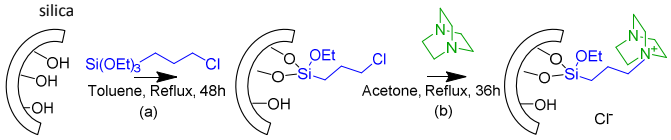


Figure 1: Mechanistic pathway of Michael addition (A) and **c**atalytic results comparing the homogeneous cinchonine to the heterogenised catalysts with varying degrees of hydrophobicity (B). Reaction conditions: N-benzylmaleimide (0.6mmol), ethyl-2-oxocylcopentanecarboxylate (0.64mmol) CH_2Cl_2 (1.5ml) and Het. Cinc. MS-60A/capped (50mg) or cinchonine (0.006mmol) stirred for 5h at room temperature.

was recognised as a suitable catalyst to anchor to the interior walls of the porous silica support, given its propensity for efficiently catalysing the Baylis Hillman reaction.[48-50] Prior to the immobilisation of an organocatalyst, it is imperative to consider the mechanism of the proposed reaction. DABCO activates the electrophile *via* its Lewis basic nitrogens. Therefore, in our methodology the tether was designed in such a fashion to ensure that the active site was readily accessible and available to participate in the reaction. We also deliberately kept the length of the tether short, as it was hypothesised[33] that the interactions between the pendant silanols on the support and substrate might assist the reaction (Scheme 2). DABCO was securely anchored onto a range of mesoporous silicas (Het. DABCO MS) with varying pore diameters (30, 60, 150, 250Å respectively) *via* a two-step procedure with a silica bound propyl chloride intermediate (Scheme 2).



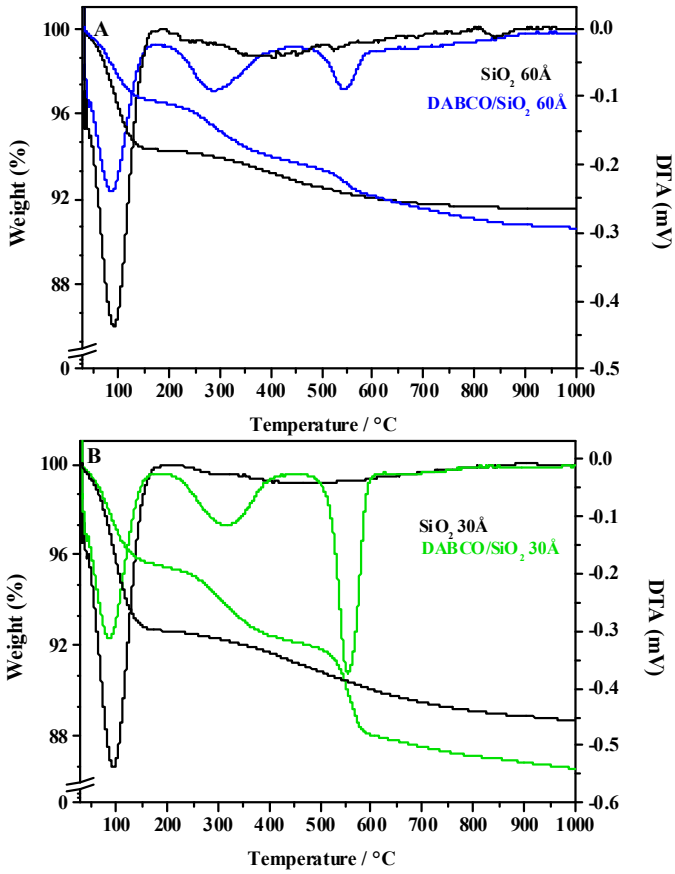
Scheme 2: Heterogenisation of DABCO onto mesoporous silica.[51]

In order to confirm the successful immobilisation of DABCO onto the mesoporous support a combination of characterisation techniques were deployed. Elemental analysis was used to verify the presence of the organocatalysts within the porous framework. The catalyst loading was calculated from the corresponding C, H, N contents. It was found that the catalyst loading was fairly consistent over the range of mesoporous silicas employed in our study, regardless of pore diameters (Table S4 ESI). The textural properties of the DABCO/mesoporous SiO_2 samples, measured by N_2 adsorption/desorption techniques at 77 K (Fig. S2, S4 and S5 ESI), are summarised in Table 1. Analogous to the cinchonine approach, it is again plausible that the DABCO organocatalyst will be randomly tethered on the external surface as well as within the internal pores of the mesoporous framework. Interestingly, the specific surface area (SSA), pore diameter and pore volume decreased when DABCO was anchored covalently to the mesoporous silica, indicating that the DABCO molecules have been largely confined to the inner walls of the mesoporous channels.

Table 1 Textural properties of the DABCO/Mesoporous SiO_2 catalysts.

Samples	SSA_{BET} (m^2 g^{-1})	Pore size (Å)	Pore volume (cm^3 g^{-1})
SiO_2 30Å	663	40	0.71
DABCO/SiO_2 30Å	277	35	0.48
SiO_2 60Å	467	70	0.82
DABCO/SiO_2 60Å	372	63	0.70

Thermogravimetric analysis (TGA) and their associated derivatives (DTA) enabled the thermal stability of the anchored DABCO moiety to be assessed (Fig. 2A and B). The initial weight loss between 100-150°C can be ascribed to the removal of physisorbed water, and this was apparent in both the mesoporous silica-bound DABCO and in its the pure silica analogue (Fig. 2). When DABCO is immobilised onto the mesoporous support, the weight loss due to the physisorbed water is less; this is indicative of the fact that the immobilisation of the organic moiety has occurred *via* the hydrophilic pendant silanol groups of the support. Additionally further weight loss features in the TGA/DTA of anchored DABCO/mesoporous SiO_2 at 250-350°C and 540-580°C are clearly discernible, which can be attributed to the decomposition



of the organic DABCO groups.

Figure 2: TGA and DTA curves of DABCO immobilised within mesoporous silica 60Å (A) and 30Å (B). In both cases, the corresponding blank mesoporous silica frameworks are provided for comparison.

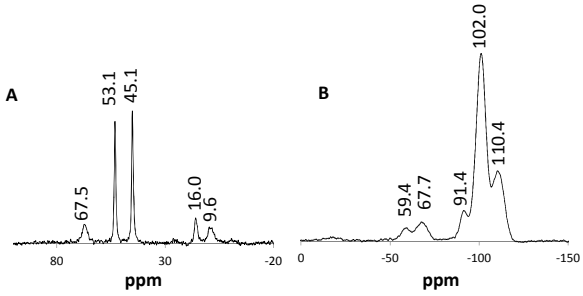


Figure 3: ^{13}C CP/MAS NMR (A) of the DABCO tether and the corresponding ^{29}Si CP/MAS NMR (B) spectra confirming the covalent link between the tether and the mesoporous silica support

CP/MAS NMR spectroscopy[14, 52] was also employed to investigate the integrity of the DABCO propyl (Scheme 2) tether on the support post immobilisation (Fig. 3). In particular, the ^{13}C CP/MAS NMR confirmed the presence of the DABCO tether in our anchored catalysts (Fig. 3A). It was reassuring that the five expected signals, which can be assigned to $SiCH_2$ (9.6 ppm), $-CH_2$ (16.0

ppm), CH_2-N (67.5 ppm) and DABCO (45.1 and 53.1 ppm), were prominently detected in our anchored catalysts. Furthermore, the covalent linkage between the tether and support was substantiated using ^{29}Si CP/MAS NMR (Figure 3B). The broad signal around 60 ppm is indicative of a Si-C covalent bond. The peak is broad owing to the combinations of $XSi(OSi)_3$, $XSi(OSi)_2OR$ and $XSi(OSi)OR_2$ binding modes. More significantly, the presence of two distinct bands, one centred at -59.4 ppm and the other at -67.7 ppm was evident, and these can be readily assigned to T^2 ($(SiO)_2SiX(OR)$) and T^3 ($(SiO)_3SiX$) species respectively. The signals at -91.4, -102.0 and -110.4 ppm are due to the tetrahedral silicon atoms comprising the framework of the mesoporous silica: these can be readily ascribed to Q^2 ($Si(OH)_2(OSi)_2$), Q^3 ($Si(OH)(OSi)_3$) and Q^4 ($Si(OSi)_4$) species, respectively.

The heterogenised DABCO catalysts were further characterised by FT-IR spectroscopy to confirm the presence of the organic DABCO moiety (Figure 4). The band at 1470 cm^{-1} can be assigned to the CH_2 bending modes of the DABCO species (curves **b** and **d**) in the heterogenised catalysts; this band was conspicuous in its absence in the corresponding FTIR spectra of PropylCl/SiO_2 (curves **a** and **c** of the mesoporous silica support containing just the tether)[15] In addition, the presence of a band at 3745cm^{-1} indicates that there is a fraction of pendant silanol groups that are still available for further functionalisation of the catalyst, providing ample scope for further manipulation of catalyst loading, if required. However it is important to note that our design strategy relies upon the creation of well-defined and isolated active centres that are amenable to detailed characterisation at the molecular level, as their homogeneous counterparts, for enabling structure-property relationships. Therefore saturation of the pendant silanols with the organocatalyst is not desirable in the creation of isolated single-sites, which form the loci for the generation of enhanced catalytic turnovers (see Fig. 5).

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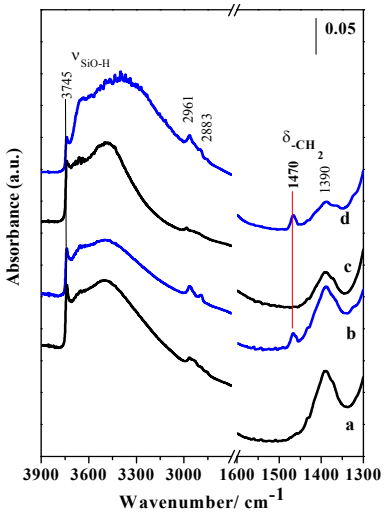

Figure 4: FT-IR spectra of the DABCO organocatalyst anchored on mesoporous silica 60Å (curve **b**) and 30Å (curve **d**). The corresponding propylCl/SiO_2 60Å (curve **a**) and PropylCl/SiO_2 30Å (curve **c**) are provided for comparison (non-immobilised supports). All samples have been outgassed at room temperature

It was indeed revealing that in the Baylis Hillman reaction (Fig. 5A) the anchored DABCO organocatalyst displayed higher activity and selectively than its homogeneous counterpart (Figure 5B) whilst retaining heterogeneity (Fig. S9 ESI), further vindicating the merits of our design approach. Our results also indicated that the choice of pore aperture is also critical for regulating the activity and selectivity, and should be carefully considered in the design rationale. Interestingly it was found that a smaller pore aperture resulted in higher activities; the turnover numbers progressively increased as the environment around the organocatlyst became more confined (Fig. 5B). DABCO was also immobilised on additional mesoporous silica supports with larger pore apertures (250 Å and 150 Å) following the same procedure as previously outlined (Scheme 2), it was discovered that if the pore aperture was too large (> 150 Å) no appreciable activity was observed. These preliminary results also provide valuable evidence that the majority of the active sites are indeed located within the inner walls of the mesoporous support and are crucial in modulating the activity (Figure 5) and enantioselectivity (Figure 1).[18] Our design strategy therefore provides complementary benefits from a catalytic perspective; where covalent anchoring of homogeneous organocatalysts to the inner walls of an appropriately tuned pore aperture can result in enhancements both in catalytic activity (turnover) and retention of selectivity (stereo- and enantioselectivity).[37-40]

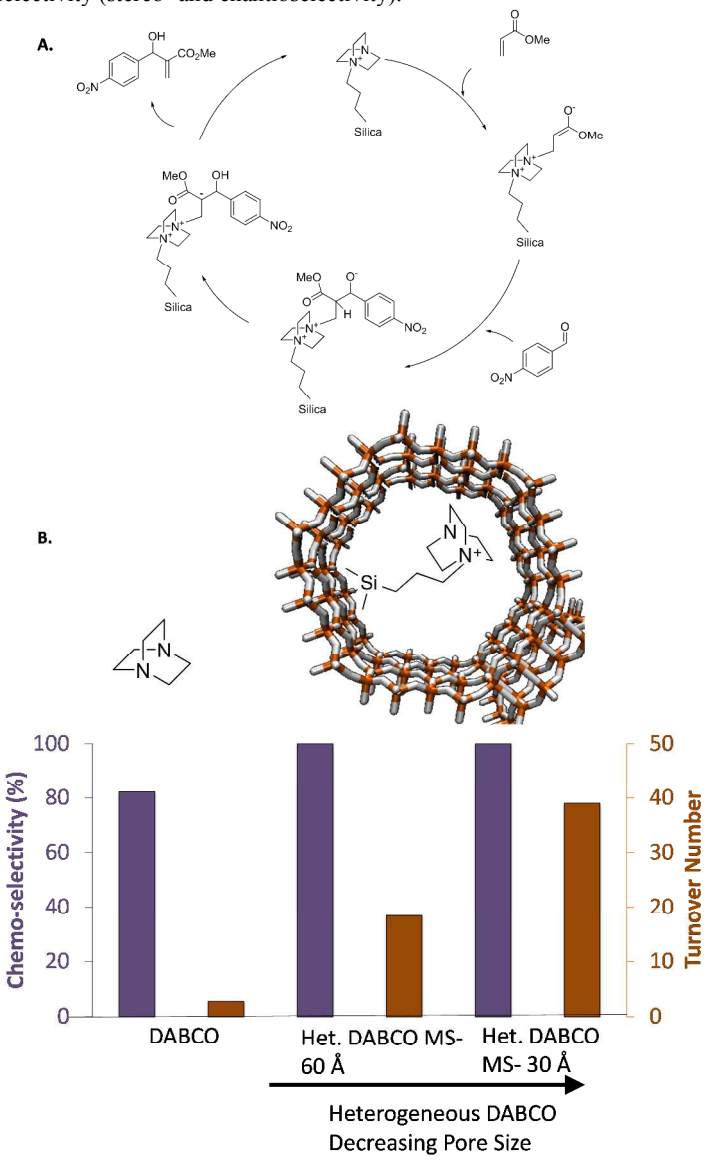

Figure 5: Proposed mechanism of MBH reaction (A) and catalytic performance of the homogeneous DABCO catalyst with its

heterogenised analogues (Het. DABCO. MS) confined within a wide-range of pore apertures (B). Reaction conditions: 4 nitrobenzaldehyde (0.8mmol), methyl acrylate (1.6mmol), MeOH (1ml) and homogeneous (0.3mol%) or heterogeneous (50mg) were stirred at room temperature for 5 days.

We have shown in this preliminary study that homogeneous organocatalysts can be covalently anchored and immobilised onto the inner walls of mesoporous silicas containing a wide-range of pore apertures and surface properties. The design approach that we have adopted facilitates the immobilisation of the active centres in a site-isolated fashion that serves to enhance catalytic turnovers and resulting enantioselectivities, compared to their corresponding homogeneous analogues. Through dextrous manipulation of the synthetic protocols, the active centres can be predominantly located within the interior confines of the mesoporous silica framework, which in combination with the degree of hydrophobicity of the support can suitably influence and modulate the catalytic activity and stereoselectivity. Through the use of appropriate characterisation tools, the nature of these discrete single-sites can be probed at a molecular level that can in future facilitate the establishment of structure-property relationships, which would further aid the design of more versatile and recyclable homogeneous organocatalysts that are amenable to industrial implementation.

Notes and references

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†Solid-state NMR spectra were obtained at the EPSRC UK National Solid-state NMR Service at Durham.
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