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PAPER

Recyclable silica-supported prolinamide organocatalysts for direct asymmetric Aldol reaction in water†‡

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Asymmetric organocatalytic materials based on a prolinamide scaffold have been synthesized according to different synthetic routes from a monosilylated precursor: simple or surfactant-assisted co-condensation and grafting on preformed mesostructured silica. The catalytic properties of these materials have been compared for direct asymmetric aldol reactions. The best catalytic material results from a simple co-condensation without structure-directing agent. Simple and green conditions are used for the aldol reaction, the process being performed in water at room temperature, with relatively low amounts of supported organocatalysts and in the absence of an acid co-catalyst. Good recyclabilities are observed without the need for catalyst regeneration, with enantioselectivities (ee up to 92%) higher than that of the parent homogeneous catalysts.

Introduction

Asymmetric organocatalysis is currently considered a fundamental and powerful tool for the stereoselective synthesis of enantiomerically enriched compounds.[1] Although the use of non-metallic catalysts for the acceleration of organic reactions has been known for more than a century, the recent development and efficient application of a wide range of small chiral organic molecules as catalysts to facilitate chemical transformations in a selective manner, has led to a rediscovery of the concept and to widespread progress in this field over the last decade.[2–11]

The aldol reaction is one of the most useful organic transformations leading to the formation of new C–C bonds, with the creation of one or more stereogenic centers. The asymmetric direct aldol reaction, involving a ketone in a non-activated form as nucleophile, is one of the most studied types of synthesis in the field of asymmetric organocatalysis.[12,13] Mimicking the type I aldolases, which function *via* an enamine pathway, small molecules such as the naturally abundant and low cost aminoacid L-proline or some other proline derivatives have been shown to act as effective organocatalysts for enantioselective aldolisations.[2–13] Amongst the proline derivatives, substituted prolinamides bearing other stereogenic centers have successfully been designed as asymmetric organocatalysts for C–C bond forming processes, showing high activities, diastereo- and enantioselectivities.[14–18] Moreover, they also allow reactions to be carried out in aqueous conditions, improving the sustainability of the process.[19]

Organocatalysts offer some advantages over transition-metal based catalysts, such as robustness, ready availability, non-toxicity, inertness towards moisture and oxygen, simple handling and storage, in addition to providing easy experimental procedures under non-inert conditions and precluding any metal contamination in the final products. This is in accordance with sustainable and environmentally friendly processes. However, the preparation of more complex organocatalysts may involve several steps. Besides, the reactions often require high catalyst loadings (up to 30 mol%) and tedious purification of the products. Thus, an easy separation, recovery and recycling of the catalyst remain a scientific challenge of economic and environmental relevance. One of the most widely used strategies for this purpose consists in immobilising the homogeneous catalyst on an insoluble support, with the advantages of easy handling, clean separation of the products and the catalyst by filtration, and facile recovery and reuse of the latter.[20–25] In this way, proline-derived organocatalysts have been anchored to different organic (polystyrene,[26–29] polyethyleneglycol,[30] cyclodextrines[31]) or inorganic supports (zeolites and mesoporous silica), either by grafting methods[24,32,33] or cogelification with tetraethoxysilane (TEOS).[23,34,35]

The formation of hybrid silica materials is attractive as a means to achieve supported organocatalysts. Such materials combine the advantages of a silica matrix such as high surface

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‡ This article is dedicated to Prof. Miguel A. Miranda on the occasion of his 60th birthday.

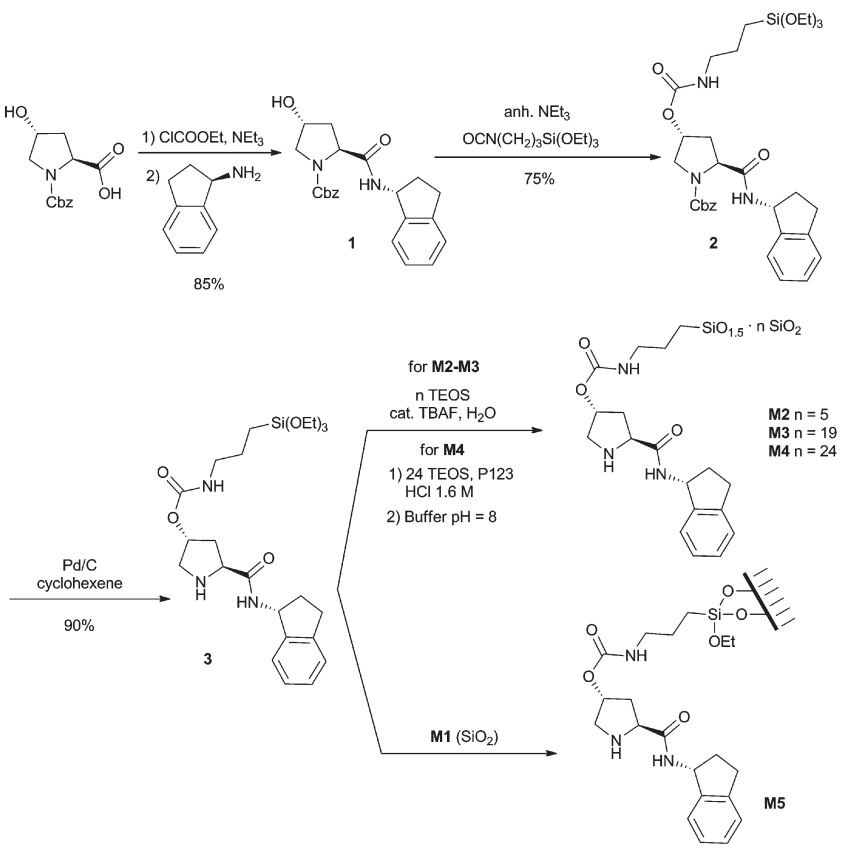
area, thermal and mechanical stability and chemical inertness with the properties of the organic precursor.[24,36–38] In addition, they have been successfully developed using the sol–gel process to entrap enzymes with enhanced efficiency.[39,40] Indeed the sol–gel hydrolytic condensation of organo-alkoxysilanes[41] is a convenient method for the preparation of organosilica materials with targeted properties.[42,43] Moreover, the surfactant-assisted sol–gel synthesis or the grafting on a mesostructured silica[44,45] are commonly employed routes for the synthesis of mesostructured organosilicas with a controlled loading of the active fragment on the support, preserving the organic part in the silica framework due to the strong Si–C covalent bonding. Materials with high surface areas and large pore sizes, favouring an easy accessibility of the organic functions in addition to the possible diffusion of the solvent–soluble reactants within the insoluble solid, appear attractive for their development and uses, particularly for liquid–solid phase catalytic reactions.

We have recently reported the catalytic performance and recycling profiles of a non-porous bridged silsesquioxane prepared from a bis-silylated prolinamide precursor.[46] Its structure was based on an aminoindane-derived prolinamide previously described by Nájera's group[14–16] as an efficient promoter of the direct aldol and Michael reactions. In this case, the prolinamide moiety was bound to the silica matrix *via* two different positions which may restrict the flexibility of the organic fragment involved in the catalytic reaction. With the aim of finding efficient and recyclable silica-supported prolinamides with enhanced selectivities, we undertook the preparation of several materials derived from a monosilylated precursor, which would afford a less rigid structure within the silica matrix. Moreover, the co-gelification of this organosilane with tetraethyl orthosilicate (TEOS) would provide porous materials with high surface area in contrast to the previously described non-porous silsesquioxane. The surfactant-assisted sol–gel and grafting methods have also been envisaged. We describe herein the preparation of the monosilylated precursor, the corresponding hybrid silica materials derived thereof under different experimental conditions and the catalytic performance and recyclability in the direct aldol reaction of these supported organocatalysts.

Results and discussion

Synthesis and characterization of the supported organocatalysts M2–M5

The monosilylated prolinamide precursor **3** and the silica materials **M2–M5** derived thereof were synthesized as summarized in Scheme 1. Aminoindane-derived prolinamide **1** was obtained from commercial *N*-benzyloxycarbonyl-4-*trans*-hydroxy-L-proline and (*R*)-2,3-dihydro-1*H*-inden-1-amine. Subsequent reaction of **1** with (3-isocyanatopropyl)triethoxysilane in the presence of NEt_3 provided the monosilylated protected prolinamide **2**. After the removal of the protecting group by treatment with cyclohexene and catalytic Pd/C, the organosilane **3** was obtained with good overall yield. From this precursor, four different hybrid silica materials were prepared by sol–gel



Scheme 1 Preparation of the supported organocatalysts **M2–M5**.

Table 1 Physical and spectroscopic data of **M2–M5**

	^{29}Si SSNMR				N_2-sorption measurements		N : Si ratio		
Mat.	T^3	Q^2	Q^3	Q^4	S_{BET} (m^2 g^{-1})	V_{pore} (cm^3 g^{-1})	Calc.[a]	Exp.[b]	Cat. loading (mmol g^{-1})[c]
M2	−66.9	−93.0	−102.0	−111.1	<5	—	0.50	0.43	1.19
M3	−67.7	−92.9	−102.9	−112.2	450	0.37	0.15	0.19	0.74
M4	−64.5	−92.0	−100.9	−107.4	300	0.21	0.13	0.12	0.46
M5	−57.7[d]	−92.7	−101.6	−109.8	360	0.83	0.18	0.12	0.50

[a] Theoretical N : Si ratio according to the stoichiometry of the starting precursors. [b] Experimental value of N : Si ratio according to the elemental analyses. [c] mmol Prolinamide g^{-1} material calculated from the N elemental analysis. [d] Value corresponding to a T^2 signal.

methodologies and grafting on a SBA-15 type mesostructured silica **M1**.[47] Organosilicas **M2** and **M3** were obtained by sol–gel co-condensation of **3** with different amounts of TEOS (molar ratios of 1 : 5 and 1 : 19 respectively) under nucleophilic conditions using a fluoride salt (TBAF) as catalyst. Template-assisted hydrolytic polycondensation of **3** with TEOS under acidic conditions (1.6 M HCl, P123 as structure directing agent, EtOH as co-solvent with several drops of DMF) afforded **M4** ([P123] : [TEOS] : [**3**] : [H_2O] : [HCl] : [EtOH] = 0.37 : 24 : 1.0 : 4390 : 126 : 106). The final suspension was stirred at 40 °C for 24 h and then left at 100 °C for 24 h without stirring. The surfactant was removed from the obtained solid by subsequent Soxhlet extraction with acidic ethanol and then the resulting material was treated with a phosphate buffer (pH = 8) to liberate the pyrrolidine amino group. Finally, the material **M5** was synthesized by anchoring the precursor **3** to a mesostructured silica **M1**[47] under standard conditions (in refluxing toluene for 24 h).

The materials were characterized by elemental analysis, ^{29}Si CP MAS solid state NMR, thermogravimetric analysis (TGA), transmission electron microscopy (TEM), scanning electron microscopy (SEM) and nitrogen-sorption measurements. The ^{13}C CP MAS solid state NMR (SSNMR) and IR were only recorded for **M2** as in the other materials the high dilution of the organic moiety in the hybrid silica precludes the observation of the corresponding signals. Some physical and spectroscopic data are given in Table 1.

N_2-sorption measurements revealed the non-porous nature of **M2**, probably due to the low molar ratio TEOS : **3** (5 : 1) used in the synthesis and to the voluminous organic fragment of the material.[48] A higher amount of TEOS resulted in appreciably high surface area in the case of **M3** and **M4**, respectively 450 and 300 m^2 g^{-1}. Both **M3** and **M4** present a characteristic type IV isotherm, showing a hysteresis loop with a relatively sharp distribution of mesopores (Fig. 1). While **M3** was simply prepared by the common sol–gel nucleophilic-catalyzed route as for **M2**, **M4** was synthesized with a neutral surfactant (P123) as structuring agent (Scheme 1) and was thus intended to be mesostructured. However, under the reaction conditions we used, it was not possible to obtain such a structured porosity as evidenced by its N_2-sorption isotherm (no H1–type hysteresis loop),[49] most probably due to the bulky organic part of the precursor **3**. This is confirmed by the powder X-ray diffractogram (Fig. 2), typical for a worm-like mesoporous organization and by the TEM micrographs.† Indeed it is known that mesostructured hybrid silica are more easily achievable with low organic-fragment derived organosilanes.[50] Whereas the microporous

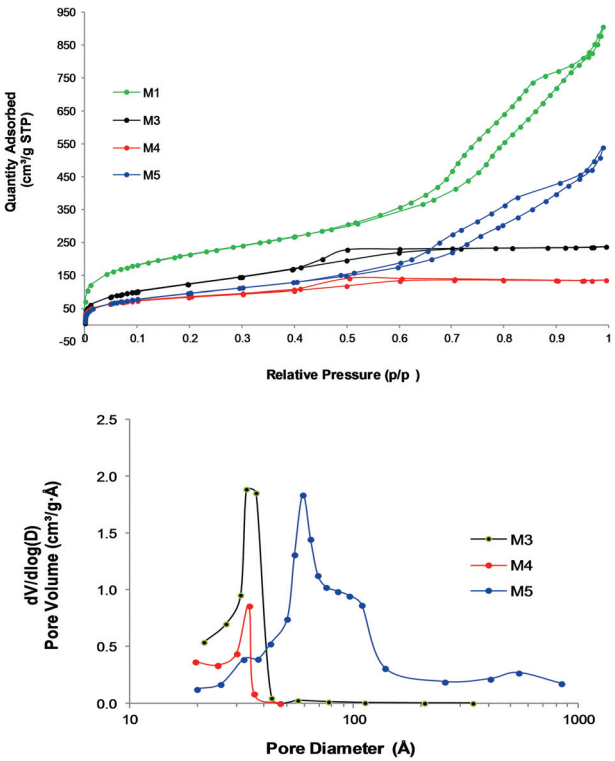


Fig. 1 N_2-sorption isotherm and pore size distribution of **M1**, **M3**, **M4** and **M5**.

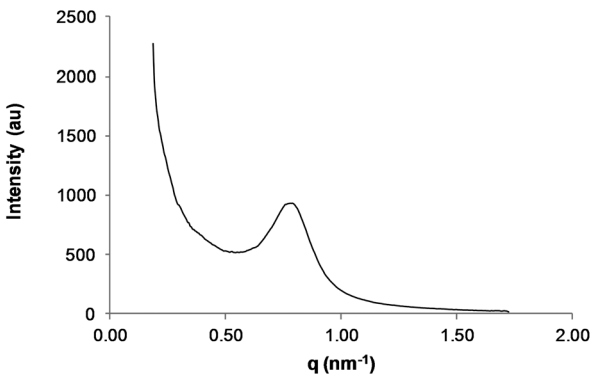


Fig. 2 PXRD pattern of **M4**.

contribution was found negligible for **M3**, a *t*-plot micropore area of 50 m^2 g^{-1} was found for **M4** (Fig. 1). Finally the organosilica **M5** maintained the isotherm profile of the parent

non-functionalized silica **M1** (Fig. 1), suggesting that the original mesostructure of **M1** had not been affected by the grafting process, as confirmed by TEM micrographs.† The BET surface area decreased significantly (from 740 for **M1** to 360 $m^2\ g^{-1}$ for **M5**) clearly indicating that precursor **3** had been successfully grafted on the surface of **M1** and thus somehow filling the pores.

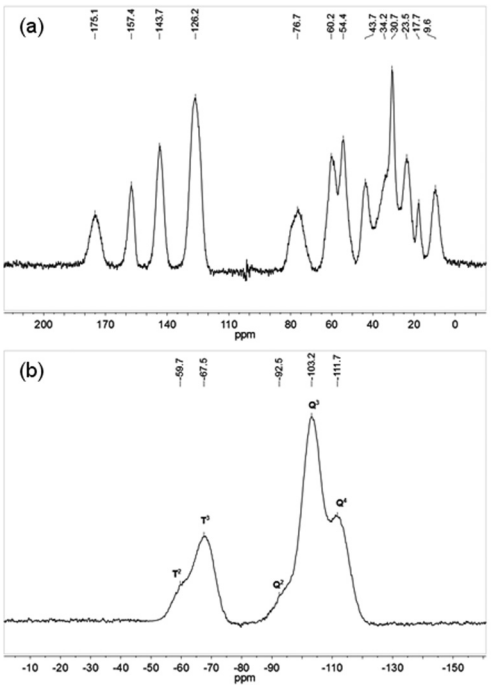


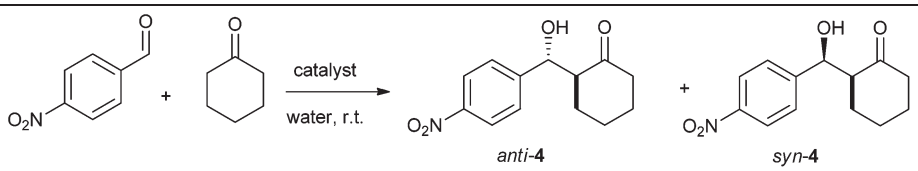
Fig. 3 (a) ^{13}C and (b) ^{29}Si NMR CP MAS spectrum of **M2**.

The presence of the organic ligand in the hybrid materials was ensured by the solid-state NMR spectra (^{29}Si and ^{13}C). The ^{29}Si CP MAS NMR spectra showed, in all cases, two groups of chemical shifts: T units from −57 to −68 ppm resulting from the hydrolysis and condensation of the organosilane **3**, and Q units ranging from −92 to −112 ppm formed from TEOS, as exemplified by the ^{29}Si CP MAS NMR spectrum of **M2** (Fig. 3b). Indeed, the presence of T peaks suggested that the integrity of the Si–C bond was maintained during the formation of the hybrid material, which was also confirmed in the case of **M2** by the ^{13}C solid state NMR spectrum (Fig. 3a), where a chemical shift appears at around 10 ppm indicative of the CH_2–Si bond. As shown by ^{29}Si solid state NMR spectra, the condensation is not complete for these materials and, hence, the experimental values of elemental analysis are not expected to match the theoretical ones.[51] For material **M3** the experimental N : Si ratio was slightly higher than the calculated one. Residual DMF remaining in the materials despite overnight drying under vacuum at 50 °C may account for the higher nitrogen content than was expected. A residual signal at 1657 cm^{-1} in the IR spectra can be attributed to the C═O vibration of both the prolinamide moiety and DMF. The catalyst loading was inferred from the nitrogen elemental analysis (Table 1).

Catalytic activity and recyclability of the supported organocatalysts M2–M5 in direct aldol reaction

The activity of the new hybrid silica materials was then evaluated *via* a typically used benchmark for the direct asymmetric aldolisations, namely the reaction between *p*-nitrobenzaldehyde

Table 2 Catalytic tests[a] with the supported organocatalysts **M2–M5** and some homogeneous analogues



Entry	Catalyst (mol%)	Additive[b] (mol%)	*t*	*T* (°C)	Conversion[c] (%)	dr[d] (*anti*/*syn*)	ee_{anti}[e] (%)
1	**M2** (1)	—	6 d	rt[f]	98	86/14	88
2	**M2** (5)	—	4 d	rt	97	83/17	86
3	**M2** (10)	—	7 h	rt	>99 (88)	86/14	86
4	**M2** (10)	—	6 d	5	80	84/16	86
5	**M3** (10)	—	7 h	rt	>99 (70)	81/19	88
6	**M3** (10)	10	16 h	rt	>99[g]	84/16	84
7	**M4** (10)	—	24 h	rt	>99 (97)	82/18	88
8	**M5** (10)	—	8 h	rt	>99 (98)	83/17	82
9	**M5** (10)	10	8 h	rt	>99	85/15	86
10[h]	**5a** (20)	20	3 h	rt	97	77/23	72
11[h]	**5b** (20)	20	3 h	rt	95	87/13	82
12	**5b** (20)	—	5.5 h	rt	99	83/17	70
13	**6** (10)	—	6 h	rt	>99	72/28	62
14	**6** (20)	20	3 h	rt	97	78/22	76
15	**7** (10)	—	5 h	rt	>99	81/19	70

[a] Reaction conditions unless otherwise stated: aldehyde (1 equiv.), cyclohexanone (5 equiv.), water (0.5 mL $mmol^{-1}$ aldehyde) and the indicated amount of the corresponding catalyst. [b] *p*-Nitrobenzoic acid. [c] Determined by ^1H-NMR spectroscopy. In brackets, isolated yield of the diastereomeric mixture after filtration. [d] Diastereomeric ratio determined by ^1H-NMR spectroscopy. [e] Enantiomeric excess determined by chiral HPLC. [f] rt Stands for temperatures between 22 and 25 °C. [g] 7% of this conversion corresponded to a side product (see text). [h] Data extracted from ref. 16.

and cyclohexanone to provide aldol **4** as a diastereomeric mixture (Table 2). Initial tests were conducted in water using different temperatures and loading of **M2** as catalyst (entries 1–4), complete conversion being achieved after 7 h with 10 mol % of catalyst at room temperature (entry 3). Lower temperature (5 °C, entry 4) or lower loading of catalyst (1 and 5 mol%, entries 1 and 2) resulted in a significant decrease of the reaction rate but the selectivity was not affected, similar diastereomeric ratios (dr) and enantiomeric excess (ee) being obtained in all cases. The catalytic tests with the other materials **M3–M5** were then performed with a 10 mol% catalyst loading at room temperature (entries 5–9). Complete conversions were observed between 7 and 24 h depending on the catalyst, with higher dilution of the organics in the silica matrix (**M4**) resulting in lower rates. From these results, it seems that the presence of regular or worm-like mesoporous structures (**M4, M5**) does not bring any significant advantage in activity or selectivity with respect to simple sol–gel co-condensation (**M2**, **M3**). Moreover the effect of *p*-nitrobenzoic acid as co-catalyst did not significantly improve either the activity or the selectivity (compare entries 5 and 6 for **M3** and entries 9 and 10 for **M5**). Remarkably, the crotonization compound[52] coming from a dehydration process was not formed in any case. The only side-product observed once, in small amount (**M3**, *p*-nitrobenzoic acid as additive, entry 6), was a diastereomeric mixture of the hemiacetal derived from the final aldol and *p*-nitrobenzaldehyde.[53]

For the sake of comparison, we have included in Table 2 the results reported[16] for Najéra's prolinamides **5a** and **5b** (Fig. 4) (entries 10–12) and those we obtained from **6** and **7** (Fig. 4)† (entries 13–15). Compound **7** bearing a carbamate moiety is a homogenous analogue of our supported organocatalysts. The other compounds would allow us to observe the effect of the presence of a hydroxyl group in the indenyl and pyrrolidine rings on the selectivity. The substitution of the free hydroxyl of **6** by a carbamate group in **7** displays a positive effect on the activity, diestereo- and enantioselectivity (compare entries 13 and 15) although the enantiomeric excess was similar or still lower than those obtained with **5b** containing a free hydroxyl in the indane fragment (compare entry 15 with entries 11 and 12).

It is worth pointing out that the supported organocatalysts **M2** and **M3** afforded TON (10) and TOF (1.4 h^{-1}) values for this aldol reaction comparable to those of homogeneous systems **5a–b**, **6** and **7** (TON = 4.9, 4.8, 10, 10, respectively) (TOF = 1.6, 1.6, 1.7 and 2.0 h^{-1}, respectively). Moreover, the organosilicas **M2–M5** prepared from the monosilylated precursor **3** exhibit higher enantioselectivities for the major diastereoisomer than these homogeneous prolinamides (compare entries 1–9 and 10–15 in Table 2) and also than the previously described non-porous bridged silsesquioxane derived from a bis-silylated prolinamide analogue.[46] This last observation seems to support our hypothesis about the relationship between the degree of flexibility of the immobilized organic moiety and the selectivity. But, undoubtedly, silica should be far from being a passive support[54] and higher activity or selectivity for silica-immobilized catalysts has been reported in some cases.[55,56] This synergetic effect may be explained in terms of confinement, which can trigger chemical discrimination and, in some cases, increase the selectivity. Confinement may also efficiently direct the stereochemical outcome through space constriction and molecular close contact.[23,57] For the dense material **M2**, confinement effects may not be observed and the role of the silica matrix in the selectivity enhancement remains unclear, although it could be attributed to some substrate-support interaction.

In the case of the non-porous material **M2** the catalytic events should take place at the external surface of the particles and therefore the whole process must be fast although only a small part of the catalyst is accessible by the substrates. On the other hand, for mesoporous materials **M3**, **M4** and **M5**, the catalytic sites located inside the pores should all be accessible at a fast or low rate. The smallest pore size (30–35 Å) and pore volume (0.21 $cm^3\ g^{-1}$) displayed by **M4** might account for the particularly low rate observed for **M4** compared to **M3** and **M5**. Indeed, the pores might be too narrow to allow a good diffusion of the substrates and the products within the material.

Following these encouraging results of activity and selectivity we tested the reusability of our supported organocatalysts for the mentioned direct aldol reaction in water at room temperature (Tables 3 and 4). Recycling of **M2** was performed with two catalyst loadings (5 and 10 mol%, entries 1–5 and 6–10 respectively

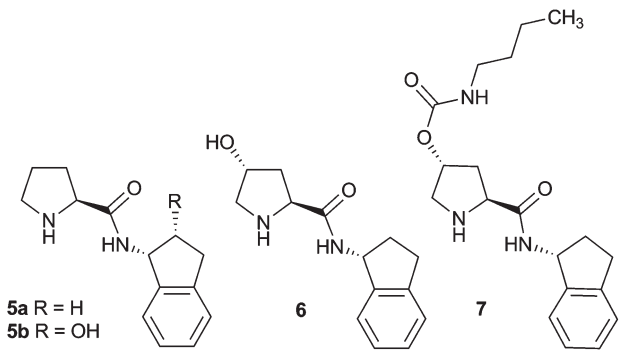


Fig. 4 Nájera's prolinamides **5a–b** and homogeneous non-silylated prolinamide analogues **6** and **7**.

Table 3 Recycling experiments[a] with **M2** in the direct asymmetric aldol reaction (see reaction in Table 2)

Entry	mol%	Cycle	*t*	Yield[b] (%)	dr[c] (*anti*/*syn*)	ee_{anti}[d] (%)
1	5	1	4 d	97[e]	83/17	86
2	5	2	5 d	92	82/18	86
3	5	3	6 d	91	81/19	76
4	5	4	7 d	95	82/18	80
5	5	5	8 d	94	80/20	86
6	10	1	24 h	88	86/14	86
7	10	2	16 h	95	86/14	74
8	10	3	16 h	88	83/17	86
9	10	4	16 h	97	85/15	86
10	10	5	16 h	95	84/16	80

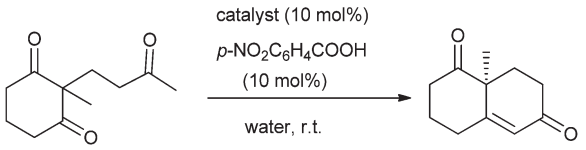
[a] Reaction conditions: room temperature, aldehyde (1 equiv.), cyclohexanone (5 equiv.), water (0.5 mL $mmol^{-1}$ aldehyde) and a catalytic amount of **M2**. After the time indicated, the reaction mixture was filtered and the catalytic material washed several times with AcOEt, dried under vacuum and directly used in the next cycle. [b] Unless otherwise stated: isolated yield of the diastereomeric mixture after filtration when achieving complete conversion. [c] Diastereomeric ratio determined by ^{1}H NMR spectroscopy. [d] Enantiomeric excess determined by chiral HPLC. [e] Conversion determined by ^{1}H NMR spectroscopy.

Table 4 Recycling experiments[a] with **M3–M5** in the direct asymmetric aldol reaction (see reaction in Table 2)

Entry	Mat.	Cycle	*t*	Yield[b] (%)	dr[c] [*anti*/*syn*]	ee_{anti}[d] (%)
1	**M3**	1	7 h	70	81/19	88
2	**M3**	2	16 h	80	78/22	92
3	**M3**	3	16 h	93	81/19	92
4	**M3**	4	24 h	88	77/23	88
5	**M3**	5	30 h	70	79/21	86
6	**M4**	1	1 d	97	82/18	88
7	**M4**	2	3 d	98	82/18	82
8	**M4**	3	5 d	92	84/16	86
9	**M5**	1	8 h	75	83/17	80
10	**M5**	2	16 h	93	82/18	92
11	**M5**	3	16 h	83	76/24	88
12	**M5**	4	20 h	91	71/29	86
13	**M5**	5	24 h	87	68/32	80

[a] Reaction conditions: room temperature, aldehyde (1 equiv.), cyclohexanone (5 equiv.), water (0.5 mL $mmol^{-1}$ aldehyde) and supported organocatalyst (10 mol%). After the time indicated, the reaction mixture was filtered and the catalytic material washed several times with AcOEt, dried under vacuum and directly used in the next cycle. [b] Isolated yield of the diastereomeric mixture after filtration when achieving complete conversion. [c] Diastereomeric ratio determined by ^1H NMR spectroscopy. [d] Enantiomeric excess determined by chiral HPLC.

Table 5 Catalytic performance[a] of **M2**, **M3** and **M5** in the intramolecular asymmetric aldol reaction with triketone **8**



8 **9**

Entry	Mat.	Cycle	*t* (d)	Yield[b] (%)	ee[c] (%)
1	**M2**	1	2	61	44
2	**M2**	2	2	87	52
3	**M2**	3	3	80	46
4	**M2**	4	5	90	46
5	**M2**	5	5	78	48
6	**M3**	1	2	60	42
7	**M3**	2	2	59	42
8	**M3**	3	3	58	44
9	**M3**	4	4	62	33
10	**M3**	5	5	72	40
11	**M5**	1	2	82	48
12	**M5**	2	2	83	44
13	**M5**	3	3	78	44
14	**M5**	4	4	60	26
15	**M5**	5	5	87	24

[a] Reaction conditions: room temperature, water (0.5 mL $mmol^{-1}$ substrate), supported organocatalyst (10 mol%), *p*-nitrobenzoic acid as co-catalyst (10 mol%). After the time indicated, the reaction mixture was filtered and the catalytic material washed several times with AcOEt and MeOH, dried under vacuum and directly used in the next cycle. [b] Isolated yield after chromatography on silica gel, the conversion was complete at the indicated time. [c] Enantiomeric excess determined by chiral HPLC.

in Table 3). Selectivity was maintained upon recycling up to 5 runs in both cases. With 5 mol% of **M2** the reaction proceeds slowly and some decrease in the reaction rate was observed in successive runs whereas with 10 mol%, the reactions ran faster with the same conversion rate even after 5 runs.

Organosilicas **M3–M5** also proved to be reusable in the same aldol reaction using a 10 mol% catalyst loading, up to three or five runs being carried out for each material batch (Table 4). An increase of the reaction times required for complete conversion was observed upon recycling but, interestingly, high selectivities were retained. We should emphasize that the developed procedure is very simple and environmentally friendly (aqueous media, room temperature, no acid co-catalyst, relatively low loadings of supported catalyst compared with the corresponding homogeneous catalysts and which can be recovered easily by simple filtration, avoiding chromatography separation from the diastereomeric aldol mixture, reuse of the catalyst).

Finally, the catalytic performance and recyclability of hybrid silica materials **M2**, **M3** and **M5** were also assayed for the intramolecular aldol reaction with triketone **8** in water at room temperature (Table 5). In this particular reaction, the use of *p*-nitrobenzoic acid as additive (10 mol%) and column chromatography of the reaction crude mixture were required to achieve Wieland-Miescher ketone **9** in good isolated yields. Although moderate asymmetric induction was obtained (ee up to 52%), all three materials could be reused for 5 consecutive cycles, without a significant decrease in enantioselectivity for **M2** and **M3** upon recycling. To the best of our knowledge, there are few recent reports for the catalyst recycling in this Robinson annulation.[46,58]

Conclusions

In summary, the immobilisation of a monosilylated prolinamide derivative **3** has been achieved according to three routes: (i) common nucleophilic-catalyzed sol–gel hydrolysis-condensation with two different molar ratios of TEOS:**3** (5 and 19) affording a non-porous **M2** and a mesoporous **M3** hybrid materials respectively; (ii) with a neutral surfactant as structure-directing agent affording a worm-like mesoporous material **M4** and (iii) grafting of **3** on a SBA-15 silica, **M1**, yielding preserved mesostructured **M5**. The evaluation tests of these catalysts together with related homogeneous catalysts (**5a**, **5b**, **6** and **7**) in the direct intermolecular aldol reaction show that the immobilized catalysts, though less reactive, allow reproducibly a better selectivity than the homogeneous ones. Interestingly, increasing the porosity does not affect neither the yield nor the selectivity although the reaction rate was slower for the non-porous catalyst **M2**. Moreover, the presence of additives which was beneficial in the case of the homogeneous catalysts did not improve the selectivity at all. These immobilized catalysts are furthermore easily recovered by simple filtering and could be re-used up to five times with similar performance as for the first runs. Finally the intramolecular asymmetric aldol reaction with triketone **8** was successfully realized and although the selectivity was moderate in this case, these catalysts could also be recycled at least three times. Interestingly, these results demonstrate that a sol–gel material obtained by simple co-condensation of an organosilane and a silica source without using any structure-directing agent can be as efficient as the related mesostructured materials **M4** and **M5**, which are both obtained using an important amount of

surfactant. Efficient catalysts can thus be obtained without the use of any template, which require tedious extraction processes or calcination for their elimination. It is also worth mentioning that these reactions were performed exclusively in water as solvent without a co-catalyst and result in easier isolation of the product and good recycling of the catalyst. Greener materials and synthetic procedures will result from the development of such approaches.

Experimental

General

The ^{1}H and ^{13}C NMR spectra in solution were recorded on Bruker DRX-250 MHz, DPX-360 MHz or AVANCE-III 400 MHz and are referenced to solvent signals ($CDCl_3$: δ = 7.26 ppm; DMSO-d_6: δ = 2.50 ppm). The ^{29}Si and ^{13}C CP MAS solid state NMR spectra were obtained from a Bruker AV400WB; the repetition time was 5 s with contact times of 5 ms. These NMR instruments belong to the Servei de Ressonància Magnètica Nuclear of the Universitat Autònoma de Barcelona or to the University of Montpellier II. From the Servei d'Anàlisi Química of the Universitat Autònoma de Barcelona the following experimental data were acquired: infrared spectra (IR), specific rotation ($[\alpha]_D$) and high-resolution mass-spectrometry (HRMS). IR was recorded with a Bruker Tensor27 with an ATR Golden Gate. Specific rotation values were obtained at 22 °C in a JASCO J-175 polarimeter at 589.6 nm and they are given in 10^{-1} ° cm^2 g^{-1}. HRMS were determined using a *microTOF-Q* instrument with direct injection of the sample. Elemental analyses were done by Serveis Científico-Tècnics of the Universitat de Barcelona. Elemental analyses of C, N and H were performed using an elemental analyser EA-1180 CE Instrument of Thermo Fisher Scientific with BBOT as an internal standard. The content of Si was determined by ICP in a Perkin-Elmer Optima 3200RL instrument. Melting points were determined using a Koffler-Reichert apparatus and were not corrected. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (chiral columns Daicel Chiralpak AD-H and Daicel Chiralpak IC) with a Waters 2960 instrument using a UV photodiode array detector. At the Institut Charles Gerhardt Montpellier, surface areas were determined by the Brunauer–Emmet–Teller (BET) method from N_2 adsorption–desorption isotherms obtained with a Micromeritics ASAP2020 analyzer after degassing samples for 30 h at 55 °C under vacuum. The pore diameter distribution was calculated by the BJH method. Thermogravimetric analysis of hybrid materials was done at Institut de Ciència dels Materials de Barcelona (ICMAB) using a STA 449 F1 Netzsch instrument under atmospheric conditions. When required, experiments were carried out with standard high vacuum and Schlenk techniques. Chromatographic purifications were performed under N_2 pressure using 230–400 mesh silica gel (flash chromatography). *N*-Benzyloxycarbonyl-4-*trans*-hydroxy-L-proline 98%, (*R*)-(−)-1-aminoindane 97%, ethyl chloroformate 98%, (3-isocyanatopropyl)triethoxysilane 95%, *n*-butylisocyanate 98%, tetrabutylammonium fluoride (TBAF, 1 M solution in anhydrous THF), *p*-nitrobenzaldehyde 98%, *p*-nitrobenzoic acid 99%, Pd/C 10 wt%, tetraethyl orthosilicate 98%, Pluronic P123 and dry DMF were purchased from Sigma-Aldrich. Cyclohexene 99% and cyclohexanone 99% were obtained from Merck. All reagents and analytical grade solvents were used as received except the (3-isocyanatopropyl)triethoxysilane 95%, which was distilled under vacuum prior to use. Dry solvents and reagents were obtained following standard procedures: 1,2-dichloroethane, pentane, triethylamine were distilled over CaH_2; THF and Et_2O over Na/benzophenone and ethanol was distilled from Mg/I_2. Distilled and deionized water (*MilliQ*) was used for the sol–gel process. Triketone **8**[58,59] and mesostructured non-functionalized silica **M1**[47] were prepared according to a previously described procedure. Compounds **4** and **9** were previously described and their spectral and analytical data were consistent with literature values.[14]

(2*S*,4*R*)-Benzyl-2-[(*R*)-2,3-dihydro-1*H*-inden-1-ylcarbamoyl]-4-hydroxypyrrolidine-1-carboxylate, 1

Commercial *N*-Cbz-4-*trans*-hydroxy-L-proline (2.17 g, 8.00 mmol) and NEt_3 99.5% (1.12 mL, 0.726 g cm^{-3}, 8.00 mmol) were dissolved in THF (30 mL) and the solution cooled to 0 °C with an ice bath. At this temperature ethyl chloroformate 98% (0.765 mL, 1.14 g cm^{-3}, 8.00 mmol) was added dropwise and the resulting mixture was stirred at 0 °C for 30 min. Then the (*R*)-(−)-1-aminoindane (1.10 g, 8.00 mmol) was added slowly at 0 °C. The mixture was stirred for 1 h at 0 °C, overnight at room temperature and 3 h at reflux. After this time, the mixture was cooled to room temperature and diluted with AcOEt (20 mL). The precipitated ammonium salt was filtered. The filtrates were concentrated under reduced pressure and the residue was recrystallized from AcOEt–methanol to furnish **1** as a white solid (2.59 g, 85%). Mp 178–179 °C; $[\alpha]_D$ +84.1° (*c.* 0.56 in EtOH); IR ν_{max} (ATR)/cm^{-1} 3459 and 3285 (OH and NH), 3024 (Csp^2-H), 2974, 2939 and 2883 (Csp^3-H), 1688 and 1651 (C═O) cm^{-1}; δ_H (400 MHz, DMSO-d_6, rotamers mixture, aprox. 60/40) 8.38 (1H, m, CON*H*), 7.39–6.91 (9H, m, 9H, H_{Ar}), 5.41 (0.4H, t, *J* 7.2, CONHC*H*), 5.30 (0.6H, t, *J* 8.0, CONHC*H*), 5.12 (2H, m, PhCH_2O), 4.43 (2H, m, C*H*OH and NC*H*CO), 3.66 (1H, m, Cbz-NC*H*H), 3.61–3.55 (1H, m, Cbz-NCH*H*), 3.00–2.93 (1H, m, NHCHCH$_2$C*H*H), 2.89–2.78 (1H, m, NHCHCH$_2$CH*H*), 2.51–2.36 (1H, m, NHCHC*H*HCH$_2$), 2.26–2.10 (1H, m, HOCHC*H*HCH), 2.09–2.03 (1H, m, HOCHCH*H*CH), 1.90–1.71 (1H, m, NHCHCH*H*CH$_2$), the signal of the OH was not observed due to exchanges with water of the deuterated solvent; δ_C (100 MHz, DMSO-d_6, rotamers mixture, aprox. 60/40) 173.5, 173.3, 155.5, 155.4, 143.0, 142.9, 142.8, 142.7, 136.7, 128.1, 127.7, 127.5, 127.4, 127.3, 126.2, 126.0, 124.1, 124.0, 123.8, 69.4, 68.7, 66.9, 66.8, 59.4, 58.9, 55.3, 54.8, 54.4, 47.6, 39.6, 38.5, 32.8, 32.7, 29.6; ESI-HRMS: calcd for $C_{22}H_{24}N_2O_4 + Na^+$: 403.1628; found: 403.1630.

(2*S*,4*R*)-Benzyl-2-[(*R*)-2,3-dihydro-1*H*-inden-1-ylcarbamoyl]-4-[3-(triethoxysilyl)propylcarbamoyloxy]pyrrolidine-1-carboxylate, 2

A few drops of dry DMF were added to a stirred suspension of **1** (1.18 g, 3.09 mmol) in dry $ClCH_2CH_2Cl$ (15 mL) at 70 °C under an inert atmosphere, until a homogeneous solution was obtained. Then freshly distilled (3-isocyanatopropyl)-

triethoxysilane (1.30 mL, 0.999 g cm^{-3}, 5.21 mmol) and dry NEt_3 (0.45 mL. 0.726 g cm^{-3}, 3.22 mmol) were added and the mixture was stirred at 80 °C under inert atmosphere of Ar for 48 h. After this time, the volatiles were removed under vacuum and the excess of isocyanate was distilled off. The residue was dissolved in the minimum amount of dry THF. The product precipitated upon addition of dry Et_2O. The solid was filtered off and purified by flash chromatography (silica gel, hexane–AcOEt 1 : 2) to afford **2** as a white solid (1.50 g, 75%). Mp 107–109 °C; R_f 0.11 (hexane–AcOEt 1 : 2); $[\alpha]_D$ = +0.2° (*c.* 1.0 in EtOH); IR ν_{max} (ATR)/cm^{-1} 3290 (NH), 3066 (NH), 2973 and 2883 (Csp^3-H), 1688 (C═O), 1651 (C═O); δ_H (360 MHz, DMSO-d_6, rotamers mixture, aprox. 50/50) 8.42 (0.5H, d, *J* 8.2, CONH), 8.40 (0.5H, d, *J* 8.0, CONH'), 7.39–6.90 (10H, m, H_{Ar} and OCONH), 5.24 (1H, m, NHCH), 5.10 (3H, m, PhCH_2 and CHOH), 4.31 (1H, m, NCHCO), 3.73 (6H, q, *J* 6.8, OCH_2CH_3), 3.64 (1H, dd, *J* 12.2 *J* 4.5, Cbz-NCHH), 3.55 (1H, m, Cbz-NCHH), 2.93 (3H, m, OCONHCH_2 and NHCHCHH), 2.79 (1H, m, NHCHCHH), 2.36–2.29 (2H, m, OCHCHHCHCO and NHCHCH_2CHH), 2.10 (1H, m, NCHCHH), 1.75 (1H, m, HNCHCH_2CHH), 1.44 (2H, m, NHCH$_2$CH_2), 1.14 (9H, t, *J* 6.8, OCH_2CH_3), 0.52 (2H, m, CH_2Si); δ_C (100 MHz, DMSO-d_6, rotamers mixture, aprox. 50/50) 171.3, 171.0, 155.5, 153.9, 153.8, 144.0, 142.9, 142.7, 136.9, 136.8, 128.4, 128.3, 127.8, 127.7, 127.5, 127.3, 127.2, 126.3, 126.2, 124.4, 124.3, 124.2, 123.9, 72.4, 71.6, 66.1, 58.7, 58.1, 57.7, 53.7, 53.1, 43.0, 37.3, 36.0, 32.8, 29.7, 7.2. ESI-HRMS: calcd for $C_{32}H_{45}N_3O_8Si$ + Na^+: 650.2868; found: 650.2860.

(3*R*,5*S*)-5-[((*R*)-2,3-Dihydro-1*H*-inden-1-yl)carbamoyl] pyrrolidin-3-yl (3-(triethoxysilyl)propyl)carbamate, 3

Compound **2** (2.45 g, 3.90 mmol) and cyclohexene (2.00 mL, 0.814 g cm^{-3}, 19.6 mmol) were dissolved in dry EtOH (35 mL). Then Pd/C 10% (0.51 g, 0.48 mmol) was added and the mixture stirred at reflux under an inert atmosphere. When TLC showed that all starting material was consumed (about 1 h), the reaction was cooled to room temperature and filtered through Celite®. The filtrates were concentrated under vacuum to afford **3** as a solid (1.72 g, 90%). Mp 150–152 °C; $[\alpha]_D$: +40.3° (*c.* 1.29 in EtOH); IR ν_{max} (ATR)/cm^{-1} 3297 (NH), 2972, 2926, 2881 (Csp^3-H), 1698 (C═O), 1658 (C═O); δ_H (360 MHz, DMSO-d_6) 8.16 (1H, d, *J* 8.7, CONH), 7.24–7.09 (5H, m, H_{Ar} and OCONH), 5.26 (1H, m, CONHCH), 4.99 (1H, br,NHCH$_2$CHO), 3.73 (7H, m, OCH_2CH_3 and NHCHCONH), 3.04 (1H, dd, *J* 12.0 *J* 4.8, NHCHH), 2.95 (3H, m, NHCH and OCONHCH_2), 2.84–2.74 (2H, m, NHCHCH_2CH$_2$), 2.38 (1H, m, NHCHCH$_2$CHH), 2.06 (1H, m, NHCH(CO)CHH), 1.94 (1H, m, NHCH(CO)CHH), 1.82 (1H, m, NHCHCH$_2$CHH), 1.44 (2H, m, OCONHCH$_2$CH_2), 1.14 (9H, t, *J* 6.8 Hz, OCH$_2$CH_3), 0.51 (2H, m, SiCH_2). the signal of the NH of the pyrrolidine ring was not observed, probably due to exchanges with water present in the deuterated solvent; δ_C (100 MHz, DMSO-d_6) 173.0, 155.9, 144.0, 142.9, 127.4, 126.4, 124.5, 123.6, 75.4, 59.5, 57.8, 53.3, 52.7, 42.9, 37.4, 32.9, 29.7, 23.0, 18.2, 7.2; ESI-MS *m*/*z* (%) 494.2 (100) [M + H^+], 316.2 (8.7) [M-$CH_2Si(OEt)_3$]$^+$; ESI-HRMS calcd for $C_{24}H_{39}N_3O_6Si$ + Na^+: 516.2500; found: 516.2499.

Preparation of hybrid material M2

To a stirred solution of **3** (0.324 g, 0.661 mmol) and TEOS (0.750 mL, 0.940 g cm^{-3}, 3.31 mmol) in anhydrous DMF (4 mL) at 40 °C, *MilliQ* water (273 μL, 15.2 mmol, H_2O/EtO = 1) and a commercial solution of 1 M TBAF in anhydrous THF (40.0 μL, 0.040 mmol, 1 mol% F with respect to Si) were added. The resulting solution was stirred for 10 min at 40 °C, then the stirring was stopped and the mixture was cooled to room temperature. After 1 h a gel was formed which was left to age at room temperature for 5 days. At that time, the gel was crushed, filtered off and washed with water (2 × 7 mL), EtOH (2 × 7 mL) and acetone (2 × 7 mL). The solid was dried overnight at 50 °C under vacuum (0.7 mbar) affording **M2** (0.483 g) as a pale yellow solid. S_{BET} < 5 m^2 g^{-1} (non-porous material); TGA (air, 20 to 700 °C) residual mass 56.86%; IR ν_{max} (ATR)/cm^{-1} 3292 (NH), 1655 (C═O), 1521, 1246, 953, 765; ^{13}C CP MAS NMR (100.6 MHz) δ 175.1, 143.6, 126.6, 76.8, 60.4, 54.5, 43.7, 34.4, 30.6, 23.9, 18.1, 14.3, 9.8; ^{29}Si CP MAS NMR (79.5 MHz) δ −66.9 (T^3), −93.0 (Q^2), −102.9 (Q^3), −111.0 (Q^4); elemental anal. found: N 4.99, C 28.03, H 3.54, Si 22.8 (1.19 mmol prolinamide g^{-1} material); calcd for $C_{18}H_{24}N_3O_3SiO_{1.5}$·5$SiO_2$ N 6.15, C 31.66, H 3.54, Si 24.68 assuming total condensation. The hydrolysis and condensation is never complete in these hybrid materials.

Preparation of hybrid material M3

To a stirred solution of **3** (0.499 g, 1.01 mmol) and TEOS (4.40 mL, 0.940 g cm^{-3}, 19.5 mmol) in anhydrous DMF (10 mL) at room temperature was added a solution of *MilliQ* water (1.50 mL, 83.3 mmol, H_2O/EtO = 1) and TBAF (1 M in anhydrous THF, 0.220 mL, 0.220 mmol, 1 mol% F with respect to Si) in anhydrous DMF (10 mL). The resulting solution was stirred for 10 min at room temperature then the stirring was stopped; after 10 min a gel was formed, which was left to age at room temperature for 6 days. At that time, the gel was crushed, filtered off and washed with water (2 × 10 mL), ethanol (2 × 10 mL) and acetone (2 × 10 mL). The final solid was dried overnight at 50 °C under vacuum (0.7 mbar) affording **M3** (1.73 g) as a white solid. S_{BET} 455 m^2 g^{-1}; pore diameter distribution centered around 30–40 Å, average pore diameter (4V/A, BET): 32 Å, pore volume: 0.37 cm^3 g^{-1}; TGA (air, 20 to 700 °C) residual mass 72.5%; ^{29}Si CP MAS NMR (79.5 MHz) δ −58.7 (T^2), −67.7 (T^3), −92.9 (Q^2), −102.9 (Q^3), −112.2 (Q^4); elemental anal. found: N 3.09, C 14.07, H 2.05, Si 32.2 (0.74 mmol prolinamide g^{-1} material); calcd for $C_{18}H_{24}N_3O_3$-$SiO_{1.5}$·19SiO_2 N 2.77, C 14.26, H 1.60, Si 37.05 considering complete condensation.

Preparation of hybrid material M4

In a 250 mL round bottom flask equipped with magnetic stirrer, P-123 (1.76 g, 0.30 mmol) was dissolved in aqueous HCl (1.6 M, 64.0 mL, 102 mmol) at 40 °C. When the solution was homogeneous, TEOS (3.50 mL, 0.940 g cm^{-3}, 19.6 mmol) was added and the resulting suspension was stirred for 20 min at 40 °C. At that time, a solution of **3** (0.400 g, 0.81 mmol) in a minimum amount of EtOH (*ca.* 5 mL, some drops of DMF were

necessary to completely dissolve **3**) was added and the final suspension stirred at 40 °C for 24 h. Then a reflux condenser was coupled to the flask, the stirring was stopped and the mixture was heated at 100 °C for 24 h. The mixture was cooled down to room temperature, then filtered and the solid was washed with water (3 × 30 mL), EtOH (3 × 30 mL) and acetone (3 × 30 mL). It was continuously extracted with acidic EtOH (10 v/v% conc. HCl–EtOH) for 4 days using a Soxhlet apparatus. After this time, the solid was treated with a phosphate buffer (pH = 8) until the filtrates reached pH 8. The final solid was dried overnight at 50 °C under vacuum (1.0 mbar) and finally **M4** (0.955 g) was obtained as a white solid. S_{BET} 300 m^2 g^{-1}; pore diameter distribution centred around 30–35 Å, average pore diameter (4V/A, BET): 28 Å, pore volume: 0.21 cm^3 g^{-1}; TGA (air, 20 to 700 °C) residual mass 75.4%; ^{29}Si CP-MAS NMR (79.5 MHz) δ −57.1 (T^2), −64.5 (T^3), −92.0 (Q^2), −100.9 (Q^3), −107.4 (Q^4); PXRD max at 0.781 nm^{-1}, repeating distance $2\pi/q_{max}$ = 8.05 nm (worm-like); elemental anal. found: N 1.93, C 9.56, H 1.92, Si 33.0 (0.46 mmol prolinamide g^{-1} material); calcd for $C_{18}H_{24}N_3O_3SiO_{1.5}\cdot 24SiO_2$ N 2.31, C 11.90, H 1.33, Si 38.65 considering complete condensation.

Preparation of hybrid material M5

In a 100 mL round bottom flask equipped with a Dean-Stark apparatus, compound **3** (0.262 g, 0.536 mmol) and non-functionalized mesostructured silica **M1**[47] 0.529 g, 8.81 mmol) were refluxed in dry toluene (50 mL) for 24 h. After this time the suspension was filtered. The solid was washed with EtOH (3 × 20 mL), acetone (3 × 20 mL) and CH_2Cl_2 (3 × 20 mL), then dried overnight at 50 °C under vacuum (1.0 mbar) affording **M5** as a white solid (0.603 g). S_{BET} 360 m^2 g^{-1}; pore diameter distribution centred around 50–100 Å, average pore diameter (4V/A, BET): 92 Å, pore volume: 0.83 cm^3 g^{-1}; TGA (air, 20 to 700 °C) residual mass 77.98%; ^{29}Si CP MAS NMR (79.5 MHz) δ −52.9 (T^1), −57.7 (T^2), −92.7 (Q^2), −101.6 (Q^3), −109.8 (Q^4); elemental anal. found: N 2.12, C 12.90, H 1.59H, Si 34.1 (0.70 mmol prolinamide g^{-1} material); calcd considering complete grafting N 2.95, C 16.86, H 2.05, Si 35.48.

Typical procedure for catalytic test in intermolecular aldol reaction with supported organocatalyst

In a vial, cyclohexanone (110 μL, 0.947 g cm^{-3}, 1.07 mmol, 5 equiv.), *milliQ* water (106 μL, 0.5 mL $mmol^{-1}$ aldehyde) and the catalytic amount of the supported catalyst were stirred together for 20 min at the temperature indicated in the tables. After this time, the *p*-nitrobenzaldehyde (0.033 g, 0.214 mmol, 1 equiv.) was added and the mixture was stirred for the time and temperature indicated in the tables. Then the crude mixture was diluted with AcOEt and filtered. The insoluble catalytic material was washed several times with AcOEt and the combined filtrates were concentrated under vacuum. If some residual cyclohexanone remained, the residue was washed with pentane and filtered off to afford a white solid. From this solid, diastereomeric *anti*: *syn* ratio, isolated yield of the mixture and enantiomeric excess for the major *anti* diastereomer (ee_{anti}) were determined. The catalytic material was dried under vacuum and directly used in the next cycle.

Typical procedure for catalytic test in intramolecular aldol reaction with supported organocatalyst

A mixture of triketone **8** (0.042 g, 0.215 mmol, 1 equiv.), *milliQ* water (0.5 mL $mmol^{-1}$ ketone), *p*-nitrobenzoic acid (0.10 equiv) and the catalytic amount of the supported organocatalyst was stirred in a vial at room temperature until ^{1}H NMR showed complete conversion of triketone. Then the crude mixture was diluted with AcOEt and filtered. The insoluble catalytic material was washed several times with AcOEt and MeOH and the combined filtrates were concentrated under vacuum. Purification by flash chromatography afforded compound **9** as an oil (hexane–AcOEt, from 9 : 1 to 7 : 3). The catalytic material was dried under vacuum and directly used in the next cycle.

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