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Prolinamide bridged silsesquioxane as an efficient, eco-compatible and recyclable chiral organocatalyst†‡

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A new organic–inorganic hybrid silica material derived from a bis-silylated prolinamide by sol–gel methodology has been successfully applied as a supported organocatalyst in asymmetric aldol and Michael reactions. Our immobilized system presents similar performances to homogeneous prolinamides and added advantages of easy recovery and good recyclability. It fits green chemistry requirements as the reactions are performed in water, at room temperature, with low catalyst loadings (2–16 mol%).

Introduction

Asymmetric molecular catalysis is a powerful tool for the stereoselective synthesis of highly valuable chiral building blocks.[1] This field has experienced exponential progress in the recent years due to the efficient development and application of organic molecules as catalysts in a wide range of transformations where new carbon–carbon bonds are formed without any metallic species.[2]

Mimicking the very efficient biocatalysts, small molecules such as simple, naturally abundant, and low cost amino-acids have been shown to be able to induce chirality for a broader range of reactions and substrates. Among them L-proline has traditionally been the most frequently used organocatalyst in enantioselective reactions such as aldolisations, Michael additions, Robinson annulations or Mannich reactions.[3] In addition to L-proline, substituted prolinamides have successfully been designed as asymmetric organocatalysts.[4] Moreover, many of these derivatives show not only higher reactivity, diastereo- and enantioselectivities, but they also allow performing reactions under aqueous or solvent-free conditions, improving the greenness of the process.[5]

However, the preparation of more complex organocatalysts usually involves several steps. Besides, the reactions often require high catalyst loadings (up to 30 mol%) and tedious purification of the products. Thus the recycling of the catalyst remains 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.[6] In this way, proline derived organocatalysts have been anchored to organic polymers (polystyrene, polyethyleneglycol) and to cyclodextrins.[7] Zeolites and mesoporous silica have also been reported as inorganic supports using grafting methods[6b,8] or cogelification with tetraethoxysilane (TEOS).[6a,9]

Hybrid silica materials are attractive supports for organocatalysts as they have been successfully used to entrap enzymes with enhanced efficiency.[10] Indeed, they combine the advantages of a silica matrix such as high surface area, thermal and mechanical stability and chemical inertness with the properties of the organic precursor.[6b,11] The most commonly used routes to immobilize homogeneous catalysts as silica materials are the surfactant-assisted sol–gel synthesis, or the grafting on a mesostructured silica,[12] which allow a high and 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. However, the use of large amounts of template molecules and the energy needed for their removal are limiting factors for their use as supports in the context of sustainable chemistry.[13] Bridged silsesquioxanes[14] represent an interesting class of organosilicas, obtained by the sol–gel process from bridged organosilanes, where the inorganic network is directly built around the organic fragments. These materials feature an inherently high homogeneity and the best possible loading of organic groups, but most often they suffer from a low porosity. However, recent examples have evidenced excellent catalytic properties in several reactions, despite their low surface areas.[6b,15]

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† Dedicated to the memory of Professor Rafael Suau.
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The recent advent of asymmetric organocatalysis[2] prompted us to investigate a bridged silsesquioxane obtained from a new bis-silylated prolinamide precursor. Its structure is based on an aminoindane-derived prolinamide, previously described by Nájera's group[4a,b] as an efficient promoter of the direct aldol and Michael reactions. We report here its synthesis, its catalytic performances as well as its recyclability.

Results and discussion

Preparation of the bridged silsesquioxane M1

The synthesis of **M1** is summarized in Scheme 1. Prolinamide **1** was obtained from commercial *N*-benzyloxycarbonyl-4-*trans*-hydroxy-L-proline and (1*S*, 2*R*)-*cis*-1-amino-2-indanol. Subsequent treatment with 3-(isocyanatopropyl)triethoxysilane in the presence of NEt_3 provided the bis-silylated protected prolinamide **2**. After the removal of the protecting group by catalytic hydride transfer, precursor **3** was obtained with good overall yield. The supported organocatalyst **M1** was prepared by hydrolytic polycondensation of monomer **3** with a fluoride salt (TBAF) as catalyst.

Material **M1** was fully characterized by elemental analyses, CP-MAS ^{13}C and ^{29}Si solid state NMR (Fig. 1 and 2), IR, TGA, TEM and SEM microscopies and N_2-sorption measurements, which revealed its non-porous nature (no adsorption of N_2 was detected; see ESI‡). The hybrid material **M1** was found to contain 1.82 mmol of organocatalyst/g, according to nitrogen elemental analysis (see the experimental section). The solid state ^{29}Si NMR spectrum (Fig. 1) shows chemical shifts corresponding to T^2 and T^3 units at around −58 and −68 ppm resulting from the hydrolysis–condensation of the corresponding monomer **3**. This fact proved that no Si–C bond cleavage occurred during the hydrolysis process and was confirmed by the corresponding chemical shifts of the organic fragments in the ^{13}C solid state NMR (Fig. 2) with a typical peak at around 14 ppm characteristic of the C–Si bond.

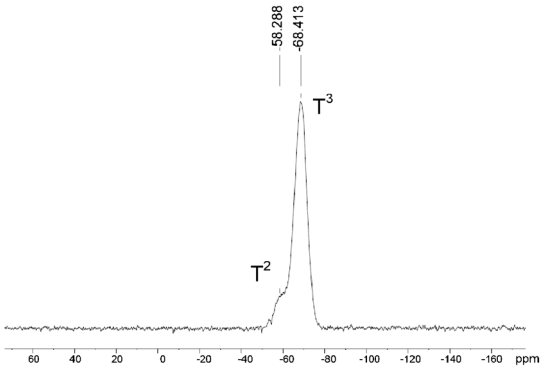


Fig. 1 ^{29}Si solid state NMR of **M1**.

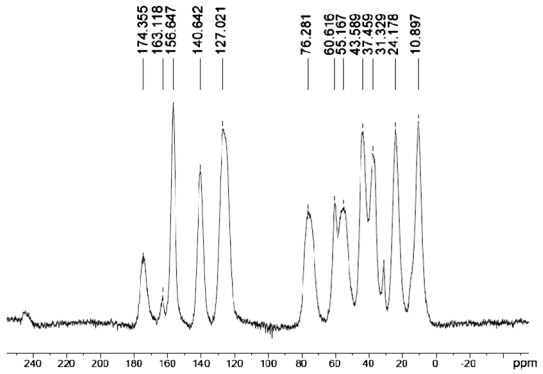
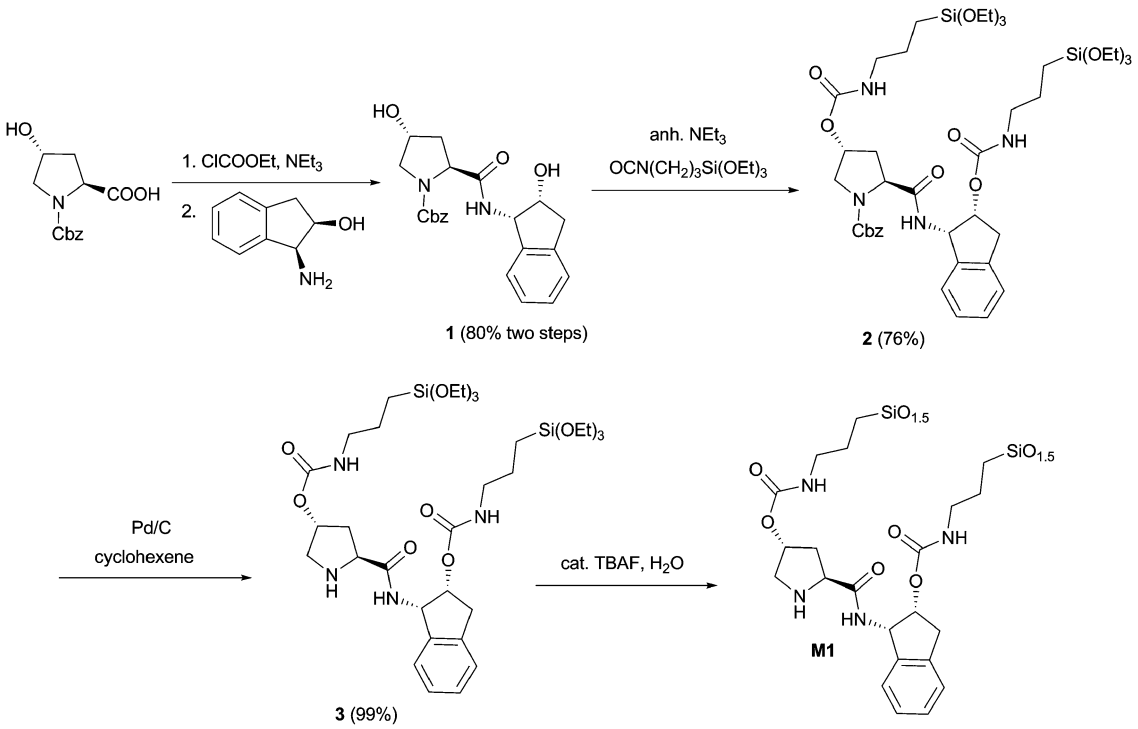


Fig. 2 ^{13}C solid state NMR of **M1**.



Scheme 1 Synthesis of bis-silylated monomer **3** and hybrid material **M1**.

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Catalytic activity and recyclability of the hybrid material M1 in the aldol reaction

The activity of this new hybrid material was then evaluated in the direct asymmetric aldol reaction between *p*-nitrobenzaldehyde and cyclohexanone, which is typically used as a benchmark for these reactions.

Initial catalytic tests were performed in water using different catalyst loadings and reaction temperatures, and the presence of *p*-nitrobenzoic acid as an additive was also evaluated (Table 1). Good diastereo- and enantioselectivities were achieved (*dr* 4/1, *ee* up to 76%). Furthermore, complete conversion was obtained within 24 h in all cases, except when using 2 mol% of **M1** (Table 1, entry 1), although selectivity was not affected. After filtration and evaporation of volatiles, compound **4** was isolated in excellent yields as a diastereomeric mixture. Interestingly, with lower loading of our hybrid catalyst **M1**, we obtained quite similar results to those reported with the homogeneous prolinamide[4a] (Table 1, entry 7).

It is noteworthy that although **M1** displays non-detectable porosity, similar TON and TOF are achieved compared with the homogeneous systems. We believe that the catalytic events take place at the external surface of the particles and that most of the prolinamide entities remain non-accessible inside the bulk material. Furthermore, unlike homogeneous systems, **M1** proceeds without the use of any acid cocatalyst. Indeed, in our hands, the use of *p*-nitrobenzoic acid did not improve the selectivity results (Table 1, compare entries 2 and 3). Lower temperature did not affect the selectivity either (Table 1, entry 5), whereas the use of water was critical, and under solvent-free conditions the reaction did not proceed.

Material **M1** bears a carbamate moiety in the indenyl ring, instead of the hydroxyl of Nájera's prolinamide **5b**. The latter functional group has a significant effect on selectivity, since both *ee* and *dr* are lower for Nájera's prolinamide **5a** (Table 1, entry 7) than for **5b** (Table 1, entry 8). Nevertheless the carbamate moiety did not display the same positive effect regarding the performance of a homogeneous non-silylated bis-carbamate prolinamide analogue **6** (Fig. 3, Table 1, entry 10)‡ which showed comparable activity and selectivity with respect to **5a**, but lower than those obtained with **5b**. The comparison of *ee* achieved with **M1** and **6** did not reveal significant differences; therefore the immobilization of the catalyst did not imply any drawback in terms of selectivity. Furthermore, the addition of *p*-nitrobenzoic acid as a cocatalyst did not seem to have a positive effect on the selectivity for the supported catalyst **M1**, whereas in the case of Nájera's prolinamide this additive is necessary to increase both the reaction rate and selectivity in those reactions involving an enamine pathway (entries 7–9, Table 1).[4a,b]

With these considerations in mind we set the optimal conditions and carried out recycling experiments (Table 2).

Supported catalyst **M1** proved to be reusable for 5 runs with excellent yields and good *dr* and *ee*, using a very simple experimental procedure. The reaction was performed in water at room temperature without additives and 16 mol% of **M1** (this loading seems to provide the best balance between performance and the amount of the catalyst used).

The newly developed experimental protocol was then applied to other aromatic aldehydes as acceptors, and also an intramolecular reaction was tested with triketone **9** (Table 3). In all cases the reaction afforded the desired aldol product in good yields and **M1** could be recycled. Clear asymmetric induction was observed with acceptors such as benzaldehyde and 2-chlorobenzaldehyde, even though it implied an increase in the reaction times and a drop in both *dr* and *ee*, 3/1 (*anti*/*syn*) and 51–57% respectively (Table 3, entries 1–4).

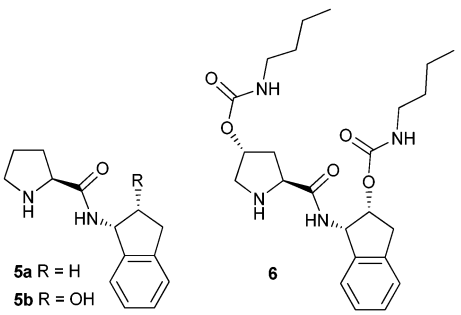
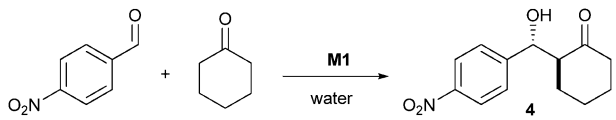


Fig. 3 Nájera's prolinamides and a homogeneous non-silylated bis-carbamate prolinamide analogue.

Table 1 Direct aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde catalyzed by **M1**: optimisation of the reaction conditions[a]



Entry	Catalyst (mol%)	Additive (p-$NO_2C_6H_4COOH$, mol%)	Time/h	T/°C	Yield[b] (%)	*anti*/*syn*[c]	ee_{ant}[d] (%)
1	**M1** (2)	—	144	22	97	78/22	70
2	**M1** (8)	—	16	22	90	86/14	70
3	**M1** (8)	5	8	22	99[e]	84/16	64
4	**M1** (16)	—	6	22	97	82/18	74
5	**M1** (16)	—	24	5	89	80/20	66
6	**M1** (24)	—	6	22	92	72/28	76
7	Nájera's prolinamide **5a**[f] (20)	20	3	22	97[e]	77/23	71
8	Nájera's prolinamide **5b**[f] (20)	20	3	22	95[e]	87/13	81
9	Nájera's prolinamide **5b** (20)	—	5.5	22	99[e]	83/17	70
10	**6** (10)	—	5	22	100[e]	82/18	73

[a] Reaction conditions: aldehyde (1 equiv.), cyclohexanone (5 equiv.), water (0.5 mL $mmol^{-1}$ aldehyde) and a catalytic amount of **M1**. [b] Isolated yield of a diastereomeric mixture after filtration when achieving complete conversion. [c] Determined by ^1H NMR spectroscopy. [d] Determined by chiral-phase HPLC. [e] Conversion. [f] Data extracted from ref. 4*a*.

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Table 2 Recycling experiments using **M1** (16 mol%) in water at 22 °C

Cycle	Time/h	Yield[a] (%)	*anti*/*syn*[b]	ee_{anti}[c] (%)
1	6	97	82/18	74
2	16	94	82/18	73
3	24	91	83/17	70
4	24	97	79/21	68
5	24	96	85/15	69

[a] Isolated yield of a diastereomeric mixture. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral-phase HPLC.

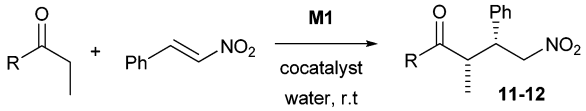
In the intramolecular reaction of **9** to obtain the Wieland–Miescher ketone, **10**, the use of *p*-nitrobenzoic acid as an additive was necessary to achieve good conversions in reasonable times, and moderate enantioselectivity (43% *ee*) was observed. In this particular case, the purification of the final compound required column chromatography, and remarkably, **M1** could be reused for 5 consecutive cycles (Table 3, entries 5–9). To the best of our knowledge, this is the first example of catalyst recycling in this Robinson annulation.

Catalytic activity and recyclability of the hybrid material M1 in the Michael reaction

Finally, the versatility of the catalytic system was evaluated by the Michael addition of 3-pentanone and butanone to *trans*-β-nitrostyrene (Table 4). In these reactions, addition of the co-catalyst was necessary for good conversions, which required longer reaction times. In agreement with previous results reported in the literature,[4b] the *syn* diastereomer was the major product obtained.

Similar enantioselectivity but lower diastereoselectivity was observed for the reaction with 3-pentanone to give **11** (up to 66% ee_{syn}, *anti*/*syn* 21/79, Table 4, entry 1) when compared with Nájera's prolinamide[4b] (95% conversion in 3 days, *anti*/*syn* 7/93, 64% ee_{syn}, MeOH as solvent and 20 mol% of the catalyst). More interesting is the use of butanone, which may give rise to regioisomers. The target compound **12** was obtained in a 1/4 *anti*/*syn* ratio and 66% *ee* for the *syn* isomer. In addition, the formation of the regioisomeric product was reduced to only 16% instead of the 40% described for the homogeneous prolinamide.[4b] Material **M1** could be recycled in both cases.

Table 4 Catalytic performance of **M1** in Michael addition[a]



Entry	Cycle	R	Time (days)	Conv.[b] (%)	*anti*/*syn*[b]	ee_{syn}[c] (%)
1	1	Et	5	**11** (97)	21/79	66
2	2	Et	7	**11** (60)	24/76	60
3	1	Me	7	**12** (99[d])	20/80	66
4	2	Me	7	**12** (40[e])	24/76	70

[a] Reaction conditions: *trans*-β-nitrostyrene (0.21 mmol), ketone (1.07 mmol), water (106 μL), *p*-$NO_2C_6H_4COOH$ (0.02 mol) and **M1** (0.035 mmol). [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral-phase HPLC. [d] 16% of the regioisomer observed. [e] 14% of the regioisomer observed.

Conclusions

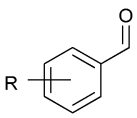
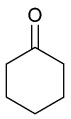
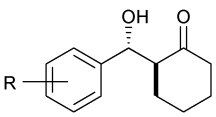
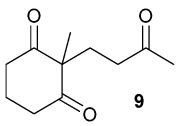
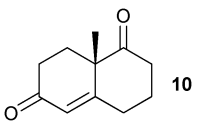
In summary, we have presented the first hybrid silica material derived from a bis-silylated prolinamide by sol–gel methodology, without TEOS addition, which has been applied as a supported recyclable asymmetric organocatalyst in aldol and Michael reactions. Using relatively low catalyst loading for a supported organocatalyst, a simple, efficient and environmentally friendly procedure has been developed in aqueous media, no acid additives being required in some cases. Despite its very low porosity, this material exhibits performances similar to those found for homogeneous organocatalysts. Further studies are currently in progress to find hybrid silica materials with improved catalytic activities and selectivities, as well as to broaden their applications in other asymmetric transformations.

Experimental

General

The ^{1}H, ^{13}C NMR spectra in solution were recorded on Bruker DXP-250 MHz, DXP-360 MHz, AVANCE-II 400 MHz or AVANCE 600 MHz. The CP-MAS ^{29}Si and ^{13}C solid state NMR spectra were obtained from a Bruker AV400WB; the repetition time was 5 s with contact times of 5 ms. All NMR

Table 3 Aldol reaction with other substrates catalysed by hybrid silica material **M1**[a]

Entry	Cycle	Time (days)	Product (yield[b], %)	*anti*/*syn*[c]	*ee*[d] (%)	Acceptor	Donor	Product
1	1	7	**7** (96)	63/37	50			 **7** R = H **8** R = 2-Cl
2	1	3	**8** (>99)[e]	72/28	52			
3	2	5	**8** (99)[e]	68/32	51			
4	3	7	**8** (>99)[e]	69/31	57			
5[f]	1	1	**10** (74)	—	43			 **10**
6[f]	2	3	**10** (68)	—	34			
7[f]	3	3	**10** (71)	—	33			
8[f]	4	3	**10** (81)	—	27			
9[f]	5	4	**10** (79)	—	27			

[a] Reaction conditions: aldehyde (1 equiv.), ketone (5 equiv.), water (0.5 mL $mmol^{-1}$ aldehyde), *p*-$NO_2C_6H_4COOH$ (10 mol%) and **M1** (16 mol%). [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Enantiomeric excess of the *anti*-diastereomer determined by chiral-phase HPLC. [e] Conversion determined by ^{1}H NMR. [f] Triketone, water (0.5 mL $mmol^{-1}$), **M1** (16 mol%) and *p*-$NO_2C_6H_4COOH$ (10 mol%), purification by flash chromatography.

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instruments belong to the "*Servei de Ressonància Magnètica Nuclear*" of the Universitat Autònoma de Barcelona. From the "*Servei d'Anàlisi Química*" of Universitat Autònoma de Barcelona the following experimental data were acquired: infrared spectra (IR), specific rotation (ORD) and high-resolution mass-spectrometry (HR-MS). IR was recorded with a Bruker Tensor27 with an ATR Golden. Specific rotation values $[\alpha]_D$ were obtained in a JASCO J-175 polarimeter at 589.6 nm and they are given in 10^{-1} deg cm^2 g^{-1}. HR-MS were determined using a *microTOF*-Q instrument with direct injection of the sample. Elemental analyses were done by the *Serveis Científico-Tècnics* of the *Universitat de Barcelona*. Elemental analyses of C, N and H were performed using an elemental analyser EA-1108 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, Daicel Chiralpak IC, Daicel Chiralcel OD) with a Waters 2960 instrument using a UV photodiode array detector. At the *Institut Charles Gerhardt* of 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 average pore diameter 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%, (1*S*, 2*R*)-(−)-*cis*-1-amino-2-indanol 99%, ethyl chloroformate 98%, 3-(isocyanatopropyl)triethoxysilane 95%, *n*-butylisocyanate 98%, tetrabutylammonium fluoride (TBAF, 1 M solution in anhydrous THF), *p*-nitrobenzaldehyde 98%, 3-pentanone 98%, *trans*-*β*-nitrostyrene 98%, *p*-nitrobenzoic acid 99%, Pd/C 10% wt 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 just before use. Dry solvents and reagents were obtained following standard procedures: 1,2-dichloroethane, pentane and triethylamine were distilled over CaH_2, THF and Et_2O over Na/benzophenone, and ethanol was distilled over Mg/I_2. Distilled and deionized water (*MilliQ*) was used for the sol–gel process. Triketone **9** was prepared according to a previously described procedure.[16]

Syntheses

(2*S*, 4*R*)-Benzyl 4-hydroxy-2-((1*S*, 2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-ylcarbamoyl)pyrrolidine-1-carboxylate, 1. *N*-Benzyloxycarbonyl-4-*trans*-hydroxy-L-proline (2.12 g, 7.98 mmol) and NEt_3 99.5% (1.20 mL, 0.726 g cm^{-3}, 8.56 mmol) were dissolved in THF (60 mL) and the solution was cooled to 0 °C with an ice bath. At this temperature ethyl chloroformate (0.770 mL, 1.319 g cm^{-3}, 9.17 mmol) was added dropwise and the resulting mixture was stirred at 0 °C for 30 min. Then (1*S*, 2*R*)-(−)-*cis*-1-amino-2-indanol (1.20 g, 7.98 mmol) was added slowly at 0 °C. The mixture was stirred for 1 h at 0 °C overnight at room temperature and 3 h under reflux. After this, the mixture was cooled to room temperature and diluted with AcOEt (20 mL). The precipitated ammonium salt was filtered. Filtrates were concentrated under reduced pressure and the residue recrystallized in AcOEt/MeOH, thus obtaining the pure product **1** as a white solid (2.53 g, 80%). Mp 175–176 °C; $[\alpha]_D$: −16.5 (*c*. 0.06 in MeOH). IR ν_{max} (ATR)/cm^{-1} 3429 (OH), 3293 (NH), 3072 and 3025 (=CH), 2938 (CH), 1682 and 1654 (CO), 1557 (ar C–C), 1466, 1428, 1359, 1180, 1132, 1083, 1052, 978, 732; δ_H (600 MHz, DMSO-d$_6$, rotamers mixture) 2.06–2.00 (1H, m, OCCHCH_2), 2.14–2.10 (0.5H, m, OCCHCH_2), 2.21–2.17 (0.5H, m, OCCHCH_2), 2.80 (0.5H, d, *J* 7.2 Hz, CCH_2CHOH), 2.83 (0.5H, d, *J* 7.2, CCH_2CHOH), 3.08–3.01 (1H, m, CCH_2CHOH), 3.44–3.39 (1H, m, NCH_2), 3.52 (0.5H, dd, *J* 11.1, *J* 4.8, NCH_2), 3.55 (0.5H, dd, *J* 11.1, *J* 4.2, NCH_2), 4.34–4.29 (1H, m, NCH$_2$C*H*OH), 4.43–4.37 (1H, m, NHCHC*H*OH), 4.52 (0.5H, t, *J* 12.0, NCHCO), 4.57 (0.5H, t, *J* 7.8, NCHCO), 4.95 (0.5H, d, *J* 7.8, OH), 5.02 (0.5H, d, *J* 4.2, OH), 5.16–5.05 (3H, m, PhCH$_2$, OH), 5.17 (0.5H, dd, *J* 9.0, *J* 5.4, OCNHC*H*), 5.21 (0.5H, dd, *J* 8.4, *J* 4.8, OCNHC*H*), 6.91 (0.5H, d, *J* 7.2, H$_{Ar}$), 7.00 (0.5H, t, *J* 7.8, H$_{Ar}$), 7.56–7.14 (8H, m, H$_{Ar}$), 8.01–7.99 (1H, two d, *J* 8.4, *J* 9.0, OCN*H*); δ_C (62.5 MHz, DMSO-d$_6$, rotamers mixture) 26.5, 39.8, 40.6, 40.7, 41.0, 56.2, 56.6, 58.6, 58.8, 60.2, 60.8, 68.3, 68.8, 70.1, 70.8, 73.7, 74.0, 125.4, 125.7, 126.0, 127.7, 127.8, 128.7, 128.9, 129.0, 129.1, 129.5, 137.9, 138.0, 141.6, 141.9, 142.1, 156.7, 157.0, 175.1, 175.4; ESI-MS: calc. for $C_{22}H_{24}N_2O_5Na$: 419.1577, found: 419.1580.

(2*S*, 4*R*)-Benzyl 4-(3-(triethoxysilyl)propylcarbamoyloxy)-2-{(1*S*, 2*R*)-2-[3-(triethoxysilyl)propylcarbamoyloxy]-2,3-dihydro-1*H*-inden-1-ylcarbamoyl}pyrrolidine-1-carboxylate, 2. Some drops of dry DMF were added to a stirred suspension of **1** (1.50 g, 3.77 mmol) in dry $ClCH_2CH_2Cl$ (5 mL) at 70 °C under inert atmosphere, until a homogeneous solution was obtained. Then, freshly distilled 3-(isocyanatopropyl)triethoxysilane (3.80 mL, 0.990 g cm^{-3}, 15.2 mmol) and dry NEt_3 (1.20 mL, 0.726 g cm^{-3}, 8.60 mmol) were added and the mixture was stirred at 80 °C under an inert atmosphere of Ar for 48 h. Then volatiles were removed under vacuum and the excess of isocyanate was distilled off (0.03 mbar, 65 °C). The residue was dissolved in a minimum amount of dry THF and the product precipitated upon addition of dry diethyl ether. The solid was filtered under a nitrogen atmosphere and washed with dry pentane to give **2** as a pale brown powder (2.56 g, 76%). Mp 208–210 °C; $[\alpha]_D$ +55.2 (*c*. 0.58 in EtOH); IR ν_{max} (ATR)/cm^{-1} 3319 and 3290 (NH), 2973, 2927 and 2884 (CH), 1687 and 1656 (CO), 1534, 1279, 1258, 1232, 1074 (SiO), 954, 767 and 734 (SiC); δ_H (400 MHz, DMSO-d$_6$, rotamers mixture) 0.51 (4H, *pseudo* t, *J* 8.4 Hz, CH_2Si), 1.14 (18H, t, *J* 7.0, OCH$_2$CH_3), 1.44 (4H, m, CH_2CH$_2$Si), 2.40–2.11 (2H, m, OOCNCHCH_2), 2.93 (5H, m, OCONHCH_2, NHCHCHCH_2), 3.17 (1H, m, NHCHCHOHCH_2), 3.53 (2H, m, NCH$_2$),

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3.57 (12H, q, *J* 7.0, OCH_2CH_3), 4.50 (1H, m, OCCHN), 5.09 (3H, m, $PhCH_2$, $NHCHCHOCH_2$), 5.32 (1H, m, NCH_2CHO), 5.40 (1H, m, NHCH), 6.83–6.73 (1H, m, H_{Ar}), 7.08–7.04 (0.5H, m, H_{Ar}), 7.26–7.18 (4H, m, H_{Ar}, OCONH), 7.37–7.30 (4.5H, m, H_{Ar}), 8.13 (1H, m, OCNH); δ_C (100 MHz, DMSO-d_6, rotamers mixture) 7.6, 8.9, 18.6, 19.0, 23.4, 25.6, 36.0, 36.2, 43.5, 45.8, 53.2, 53.6, 55.8, 56.5, 58.1, 66.6, 67.4, 72.2, 72.9, 75.1, 75.4, 79.7, 124.3, 124.6, 125.1, 127.0, 127.1, 127.7, 127.9, 128.2, 128.3, 128.8, 128.9, 137.2, 137.3, 140.5, 141.2, 141.7, 154.4, 156.0, 156.1, 162.8, 171.8, 172.1; ESI-MS: calc. for $C_{42}H_{66}N_4O_{13}Si_2Na$: 913.4057, found: 913.4059.

(2*S*, 4*R*)-Benzyl 4-[3-(triethoxysilyl)propylcarbamoyloxy]-2-{(1*S*, 2*R*)-2-[3-(triethoxysilyl)propylcarbamoyloxy]-2,3-dihydro-1*H*-inden-1-ylcarbamoyl}pyrrolidine-1-carboxylate, 3. Compound **2** (0.048 g, 0.054 mmol) and cyclohexene (0.030 mL, 0.811 g cm^{-3}, 0.29 mmol) were dissolved in dry EtOH (4 mL). Then Pd/C 10% (0.016 g, 0.015 mmol Pd) was added and the mixture stirred at reflux under an inert atmosphere. After 1 h (TLC monitoring) all starting material was consumed, the reaction mixture was cooled to room temperature and filtered under nitrogen. Filtrates were concentrated under vacuum to give product **3** as a sticky white solid (0.041 g, 99%). $[\alpha]_D$ −10.7 (*c*. 0.59 in EtOH); IR ν_{max} (ATR)/cm^{-1} 3308br, 2972, 2928 and 2882 (CH), 1687 and 1651 (CO), 1534, 1256, 1165, 1074 (SiO), 953, 775 (SiC); δ_H (250 MHz, DMSO-d_6) 0.52 (4H, m, CH_2Si), 1.15 (18H, t, *J* 7.0 Hz, OCH_2CH_3), 1.44 (4H, m, CH_2CH_2Si), 2.05 (1H, m, $NHCH_2CHCH_2$), 2.16 (1H, t, *J* 7.2, $NHCH_2CHCH_2$), 2.93 (6H, m, $OCONHCH_2$, $NHCHCHCH_2$), 3.19 (1H, d, *J* 4.4, $NHCHCHCH_2$), 3.3 (1H, under H_2O peak, $NHCH_2$), 3.74 (12H, q, *J* 7.0, OCH_2CH_3), 3.88 (1H, t, *J* 7.9, NHCHCO), 5.03 (1H, m, $NHCH_2CH$), 5.36 (1H, m, OCNHCH), 5.46 (1H, m, NHCHCH), 7.37–7.09 (6H, m, OCONH, H_{Ar}), 8.19 (1H, d, *J* 8.8 Hz, OCNH); δ_C (62.5 MHz, DMSO-d_6) 7.6, 18.6, 23.3, 23.4, 37.4, 37.8, 43.4, 53.0, 55.2, 58.1, 59.8, 75.6, 75.9, 79.7, 123.7, 125.3, 127.2, 128.2, 140.4, 141.9, 156.0, 156.2, 173.7; ESI-MS calc. for $C_{34}H_{60}N_4O_{11}Si_2Na$: 779.3689; found: 779.3685.

Preparation of material M1. To a solution of **3** (1.48 g, 1.95 mmol) in anhydrous DMF (6 mL) at 40 °C was added under stirring *MilliQ* water (206 μL, 11.4 mmol, H_2O/EtO = 1) and a commercial solution of 1 M TBAF in anhydrous THF (40 μL, 0.04 mmol, 1 mol% F^- with respect to Si). The resulting solution was stirred for 10 min at 40 °C, then the stirring was stopped and the mixture cooled to room temperature. After 2 h a gel was formed which was aged at room temperature for 5 days. After that, the gel was crushed, filtered and washed with water (2 × 5 mL), ethanol (3 × 5 mL) and acetone (2 × 5 mL). The final solid was dried overnight under vacuum (0.7 mbar) at 50 °C and finally **M1** (1.02 g) was obtained as a pale yellow solid. S_{BET}: <5 m^2 g^{-1} (non-porous material); IR ν_{max} (ATR)/cm^{-1} 3309br (NH), 2934br (CH), 1694br and 1657br (CO), 1512br, 1247br, 1100br, 1035br, 645br; ^{29}Si CP-MAS NMR (79.5 MHz) δ −58.3 (T^2), −68.4 (T^3); ^{13}C CP-MAS NMR (100.6 MHz) δ 174.4, 163.1, 156.7, 140.6, 127.0, 76.3, 60.6, 55.2, 43.6, 37.5, 31.3, 24.2, 10.9; elemental anal. Found: N 10.21, C 45.15, H 6.01, Si 10.40%. Calc. for $C_{22}H_{30}N_4O_8Si_2$: N 10.49, C 49.44, H 5.62, Si 10.49% assuming total condensation. N/Si: found 1.97; calc. 2.00. The hydrolysis and condensation are never complete in these hybrid materials.

Catalytic testing

Typical procedure for catalytic test in intermolecular aldol reaction with heterogeneous organocatalyst, M1. In a vial, cyclohexanone (5 equiv.), *MilliQ* water (0.5 mL $mmol^{-1}$ aldehyde) and a catalytic amount of material **M1** (1.82 mmol g^{-1}, the number of equivalents indicated in the tables) were stirred together for 20 min at the temperature indicated in the tables. After this, the aldehyde (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 to afford a white solid. From this solid, *anti*:*syn* ratio, isolated yield of the mixture and *ee* were determined. The catalytic material was dried under vacuum and directly used in the next cycle. Compounds **4**, **7** and **8** have been previously described and their spectral and analytical data were consistent with literature values.[4a]‡

Typical procedure for catalytic test in intramolecular aldol reaction with heterogeneous organocatalyst, M1. A mixture of triketone **8** (1 equiv.), water (0.5 mL $mmol^{-1}$ ketone), *p*-nitrobenzoic acid (0.10 equiv.) and material **M1** (1.82 mmol g^{-1}, 0.16 equiv.) 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. After column chromatography of the residue on silica gel using hexane/AcOEt (solvent gradient, from 9/1 to 7/3), pure compound **10** was obtained as oil. The catalytic material was dried under vacuum and directly used in the next cycle. Compound **10** has been previously described and their spectral and analytical data were consistent with literature values.[4a]‡

Typical procedure for catalytic test in the Michael reaction with heterogeneous organocatalyst, M1. In a vial, ketone (5 equiv.), *MilliQ* water (0.5 mL $mmol^{-1}$ *trans*-β-nitrostyrene), material **M1** (1.82 mmol g^{-1}, 0.16 equiv.) and *p*-nitrobenzoic acid (0.10 equiv.) were stirred together for 20 min. After this, *trans*-β-nitrostyrene (1 equiv.) was added and the mixture was stirred at room temperature for the time indicated in Table 4. Then the 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. From the resulting solid, conversion, *anti*:*syn* ratio and *ee* were determined. The catalytic material was dried under vacuum and directly used in the next cycle. Compounds **11** and **12** have been previously described and their spectral and analytical data were consistent with literature values.[4b,17]‡

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