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Efficient synthesis of supported proline catalysts for asymmetric aldol reactions

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Proline has been grafted onto silica supports in a single step by reacting trans-4-hydroxy-L-proline with chloropropyl tethers, without the use of protecting groups for the proline amine and carboxylic acid functional groups. The resulting catalysts have been characterised to show that grafting is through reaction with the 4-hydroxy group. The catalysts have been tested in an asymmetric aldol reaction, and shown to be both more active and more enantioselective than equivalent catalysts prepared using a protection/deprotection route for the proline grafting step.

Introduction

Enantiomerically-pure substances are high added-value chemicals and have been employed in a diverse range of research fields, including flavour and aroma chemicals,[1, 2] nonlinear optical devices,[3, 4] agricultural chemicals[5] and the manufacture of pharmaceuticals.[6] Many modern drug substances are chiral and contemporary regulatory requirements demand high levels of enantiopurity in clinical trials. There has, therefore, been a long-standing interest in synthetic methods which deliver non-racemic products, and there has been a recent rapid development in catalytic enantioselective synthetic methodologies.

The majority of methods reported to date have involved homogeneous systems.[7, 8] There has been recent interest in the use of proline-derived chiral catalysts, and the original seminal observations of an asymmetric annelation processes[9, 10] have been greatly expanded in scope more recently.[11-13] Proline (Figure 1a) is bifunctional, with carboxylic acid and amine functionalities. These two functional groups can, in principle, act in concert in cooperative acid/base mechanisms, or can act sequentially, catalysing tandem reaction steps.

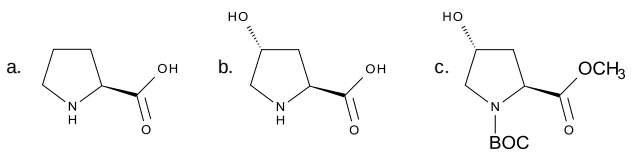
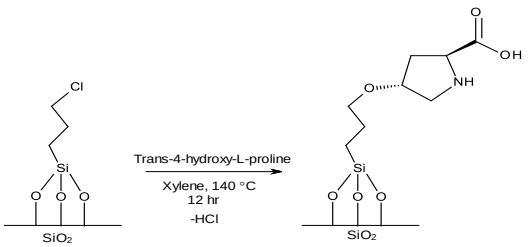


Fig. 1 a) L-proline, b) trans-4-hydroxy-L-proline, c) N-Boc-trans-4-hydroxy-L-proline methyl ester.

Significant advantages in terms of catalyst separation and recovery can be delivered if proline-derived organocatalysts are immobilized on solid supports, and a number of catalysts of this type have been reported, mainly using polymer-mounted systems.[14-16] However, silica is a more attractive support material because of its thermal and mechanical stability as well as its chemical inertness, and there are several examples of proline-bearing silica materials in the literature (including MCM-41,[17, 18] SBA-15,[19] silica gel,[17] and zeolites[20]). The first report of the use of proline–grafted silica to catalyse asymmetric aldol synthesis appeared in 2003.[17]

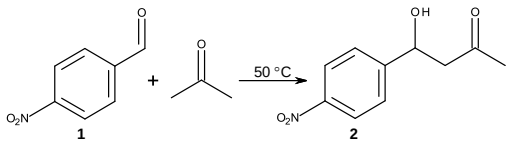
The majority of the reported methods to prepare silica-supported proline catalysts describe relatively complex, multi-step syntheses of the solid catalysts, incorporating protection/deprotection steps for the two functional groups on the proline. Typically, 4-hydroxy-L-proline is used as the starting material (Figure 1b). Protection of the secondary amine is achieved with t-butyloxycarbonyl (Boc), and the carboxylic acid is protected by esterification (Figure 1c). A recent publication reporting the use of unprotected proline in the preparation of a polymer-supported proline organocatalyst[21] has stimulated the work described in this paper, in which a silica gel surface is functionalised with proline, bypassing the protection/deprotection steps. The object has been to support proline on silica in a single step using trans-4-hydroxy-L-proline, by reacting a chloro alkyl tether on the silica with the hydroxy group on the proline. We aim to show how this can be achieved without compromising the catalytic properties (and associated enantioselectivity) of the two functional groups (Scheme 1).



Scheme 1 Reaction between (3-chloropropyl) trimethoxysilane bound to a silica surface and trans-4-hydroxy-L-proline.

The effect of the physical nature of the support is also investigated, by basing catalysts on an ordered mesoporous silica (MCM-41, 1000 m^2 g^{-1}) and on two commercial amorphous silica gels.

The catalysts are tested in a direct asymmetric mixed aldol reaction, between 4-nitrobenzaldehyde (1) and acetone (Scheme 2). In this reaction, acetone reacts with L-proline to generate a chiral enamine, which then adds to the aldehyde C=O bond, leading eventually to the (S)-configured aldol. The reaction proceeds via an intermediate chiral iminium, which liberates the (S)-aldol product, regenerating the proline catalyst.[11]



1 2

Scheme 2 Cross-aldol reaction between 4-nitrobenzaldehyde (1) and acetone to give the aldol product (2).

Experimental

Materials and instrumentation

Tetraethyl orthosilicate (TEOS, 98%), (3-chloropropyl)trimethoxysilane, trans-4-hydroxy-L-proline, N-Boc-trans-4-hydroxy-L-proline, trifluoroacetic acid (99%), N-Boc-trans-4-hydroxyproline methyl ester, cetyltrimethylammonium bromide (CTABr) as a structure directing agent for synthesis of MCM-41, and two commercial mesoporous silica gels (SiO_2 (H), with surface area 516 m^2 g^{-1} and average pore diameter 4.6 nm, and SiO_2 (L), with surface area 312 m^2 g^{-1} and average pore diameter 11 nm) were all purchased from Aldrich and used as received. All reagents for the catalytic tests were also purchased from Aldrich and used as received.

Powder X-ray diffraction (XRD) patterns were measured on a Rigaku Miniflex diffractometer over a 2θ range of 1.5°–10° with a step size of 0.05° and a counting time of 30 s $degree^{-1}$. The N_2 adsorption–desorption isotherms were measured at 77 K on a Micromeritics ASAP-2020, after evacuation at 423 K for 5 h. Surface areas were calculated by the BET method from the adsorption branch and pore size distributions were determined from the desorption branch using the BJH method. Thermogravimetric analysis (TGA) was carried out using a Perkin-Elmer thermobalance. The materials were heated to 150 °C and held at this temperature for 2 h to ensure evaporation of all surface water. The temperature was increased to 500 °C at 10 °C min^{-1} under nitrogen to estimate the concentration of organic groups attached to the silica surface. Nitrogen and chlorine levels in the catalysts were determined by elemental analysis (MEDAC Ltd.). Infrared spectra of catalysts were recorded using attenuated total reflectance on a Nicolet 380 FTIR spectrometer over 400-4000 cm^{-1}.

Catalyst synthesis

Chloropropyl-functionalized silica gels (SiO_2-Cl)

These catalysts, as shown in Scheme 1, were synthesized using a modification of a published procedure.[22] The two amorphous silica gels were used. Silica gel (1.0 g) was added to toluene (40 mL). The mixture was heated to 110 °C and stirred for 1 h under nitrogen. (3-chloropropyl)trimethoxysilane (2.0 mmol, 0.4 mL) was added under stirring at the same temperature under nitrogen. After 12 h the solid was filtered, washed with toluene and then dried in an oven at 120 °C in air for 12 h. The material prepared from silica gel with low surface area was labelled SiO_2-Cl (L) and the material with high surface area SiO_2-Cl (H).

Proline-functionalized silica gel (SiO_2-Pr) by the direct route

SiO_2-Cl (1.0 g) was suspended in xylene (20 mL) at 140 °C under nitrogen and stirred for 1 h. Trans-4-hydroxy-L-proline (2 mmol, 0.26 g) was added under stirring at the same temperature under nitrogen. After 12 h, the solid catalyst was filtered, washed with water and ethanol, and dried in an oven at 120 °C in air for 12 h to give SiO_2-Pr. The two catalysts using the low and the high surface area silica gel supports were labelled SiO_2-Pr (L) and SiO_2-Pr (H).

Proline-functionalized silica gel by the amine protecting/deprotecting route

SiO_2-Cl (L) (1.0 g) was suspended in xylene (20 mL) at 140 °C under nitrogen and stirred for 1 h. Boc-trans-4-hydroxy-L-proline (2 mmol, 0.46 g) was added under stirring at the same temperature under nitrogen. After 12 h the reaction mixture was filtered. The solid was washed with water and ethanol, and dried as before to give SiO_2-Pr-Boc. To remove the Boc group, SiO_2-Pr-Boc (0.5 g) was suspended in CH_2Cl_2 (5.0 mL) for 10 min, then trifluoroacetic acid (99%) (10 mL) was added to the solution.[23] The mixture was left for 12 h at room temperature. The solid was filtered, washed with water and then ethanol, and dried at 120 °C to give SiO_2-Pr $(Boc)_{deprotected}$.

Proline-functionalized silica gel by the amine and carboxylic acid protecting/deprotecting route

SiO_2-Cl (L) (1.0 g) was suspended in xylene (20 mL) at 140 °C under nitrogen and stirred for 1 h. Then N-Boc-trans-4-hydroxyproline methyl ester (2 mmol, 0.5 g) was added under stirring at the same temperature under nitrogen. After 12 h, the proline catalyst was filtered, washed with water and ethanol, and then dried at 120 °C to give SiO_2-Pr-Boc-Me. For deprotection, SiO_2-Pr-Boc-Me (0.5 g) was suspended in 30% HBr in acetic acid (10 mL).[24] The mixture was left for 12 h at room temperature then the solid was filtered, washed with water and ethanol and then dried in an oven at 120 °C in air for 12 h to give SiO_2-Pr $(Boc, Me)_{deprotected}$.

Proline-functionalized MCM-41 silica by the direct route (MCM-41-Pr)

Mesoporous silica (MCM-41) was synthesized according to a literature procedure using cetyltrimethylammonium bromide as template.[25] For a typical synthesis, 65% NH_4OH (69 mL) was mixed with water (525 mL). CTAB (0.125 g) was added with stirring at 80 °C. When the solution became homogenous, TEOS (1.0 g) was added. After 2 h, the resulting product was filtered, washed with water, dried at ambient temperature, and calcined in air at 540 °C for 4 h to obtain MCM-41. Covalent grafting of the proline derivative onto MCM-41 was carried out as outlined for the amorphous silica by grafting (3-chloropropyl)trimethoxysilane in toluene at 110 °C for 12 h, followed by direct reaction with trans-4-hydroxy-L-proline in xylene at 140 °C for 12 h. The solid was filtered, washed and dried as before to give MCM-41-Pr.

General procedure for asymmetric aldol reaction

The catalyst (0.05 g), 4-nitrobenzaldehyde (151 mg, 1 mmol), acetone (10 mL) and benzyl alcohol (0.10 mL) as internal standard were placed in a 50 mL round-bottomed flask and stirred

at 50 °C for 3 h under nitrogen. When testing trans-4-hydroxy-L-proline in homogeneous solution, 0.19 mmol were used. This corresponds to three to five times the amount of proline that was present on the 0.05 g of supported catalyst. Samples (100 μL) were removed at regular intervals, and the % conversion of nitrobenzaldehyde and aldol product yield were estimated by analysis on a Shimadzu HPLC instrument using a C18 column (water/xylene = 70/30) with 254 nm UV detection. The identity of reaction products were confirmed with NMR (see supplementary information). The enantiomeric excess (%) of the aldol product was determined by HPLC analysis using a Lux Cellulose-3 column (0.1% formic acid in hexane/isopropanol = 90/10) with 254 nm UV detection after re-dissolving the product in isopropanol. All kinetic experiments were run at least twice and usually three or more times, and 95 % confidence limits for conversions, yields and enantiomeric excesses were estimated from the replicate data.

Catalytic tests were also performed using benzaldehyde, 4-chlorobenzaldehyde and 4-isopropylbenzaldehyde in place of 4-nitrobenzaldehyde. Experiments with 4-nitrobenzaldehyde were also performed using 2.0 mL acetone and 8.0 mL dimethylsulfoxide (DMSO) in place of 10.0 mL acetone, at the lower reaction temperature of 25 ^{o}C, for 20 h.

To assay the retained catalytic activity of the silica-supported proline organocatalysts, two methods were used. In the first, the catalyst was separated from the reaction mixture after reaction, washed with acetone, and dried. It was re-introduced to the reaction vessel. Fresh starting materials were added and the reaction was run again. In the second method, the leaching of proline was tested by stirring the catalyst in acetone at 50 °C for 12 h. The catalyst was then removed by filtration and the filtrate solution was tested for catalytic activity in the aldol reaction.

Results and Discussion

The powder XRD patterns for MCM-41, MCM-41-Cl and MCM-41-Pr are presented in Figure 2. They show characteristic reflections that can be indexed on a hexagonal unit cell to (100), (110) and (200) by analogy with literature reports.[26] This data confirms the preservation of the ordered structure throughout the grafting and proline modification procedures.

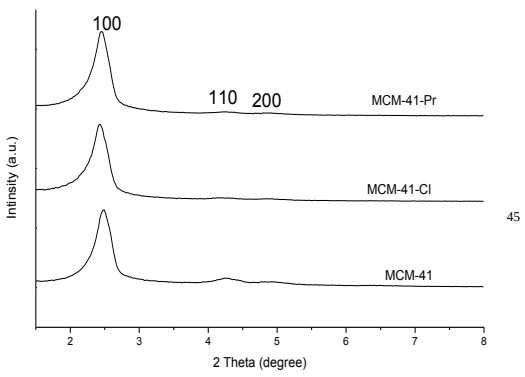


Fig. 2 Powder X-ray diffraction patterns of MCM-41, MCM-41-Cl and MCM-41-Pr.

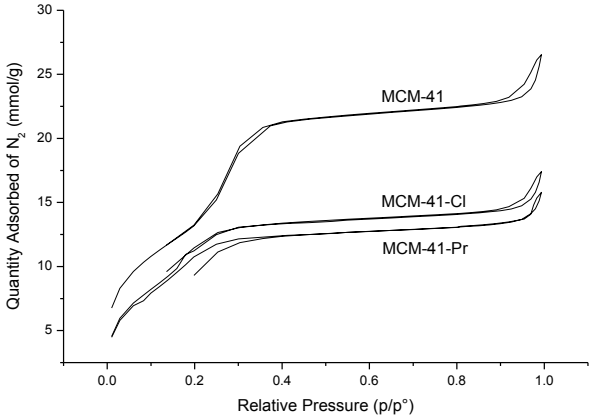


Fig. 3 N_2 adsorption–desorption isotherms at 77 K for MCM-41, MCM-41-Cl and MCM-41-Pr.

Nitrogen adsorption–desorption isotherms for the MCM-41 support, and for MCM-41-Cl and MCM-41-Pr are shown in Figure 3, illustrating the effect of functionalisation on surface properties. All three materials display type IV isotherms, indicating the presence of mesopores.[27] With the introduction of organic functional groups, the surface areas and pore volumes progressively decrease, implying successful grafting of these groups in the pores of the support. Table 1 summarises the data derived from the nitrogen adsorption-desorption experiments for the prepared materials.

Table 1 Textural properties of catalysts and catalyst precursors.

Sample	Surface area /m^2 g^{-1}	Pore volume /cm^3 g^{-1}	Average pore diameter /nm
SiO_2 (L)	313	1.1	11.1
SiO_2-Cl (L)	278	0.9	9.9
SiO_2-Pr (L)	265	0.8	9.6
SiO_2-Pr-Boc (L)	260	0.8	8.9
SiO_2-Pr-Boc,Me (L)	257	0.8	8.8
SiO_2 (H)	517	0.8	4.6
SiO_2-Cl (H)	361	0.5	3.9
SiO_2-Pr (H)	357	0.4	3.9
MCM-41	1100	1.0	2.9
MCM-41-Cl	998	0.5	2.6
MCM-41-Pr	959	0.4	2.1

The thermogravimetric curve for SiO_2-Cl (H) is given in Figure 4. This example is shown to illustrate how TGA data has been used to characterise the extent of functionalisation of the catalysts. There are two weight loss steps, at 20–200 °C and 200–500 °C. The first is related to the drying of silica. The second, which is the more important, is attributed to the decomposition of the organic groups grafted on the surface (after correction for weight loss over the same temperature range for the parent silica support). Elemental analysis data for nitrogen and for chlorine (Table 2) are taken as indicators of the molar concentrations of the supported proline and the unreacted chloropropyl groups on the silica surface. These values are checked for their consistency with TGA data. Using the ratio of the concentrations of the supported proline and the unreacted chloropropyl tether, a weighted average of the molecular weights of the two functional groups on each catalyst is determined, and this average molecular

weight is then used to convert the measured weight loss (by TGA) from each sample over 200–500 °C to an effective molar concentration of organic groups on the catalyst surface.

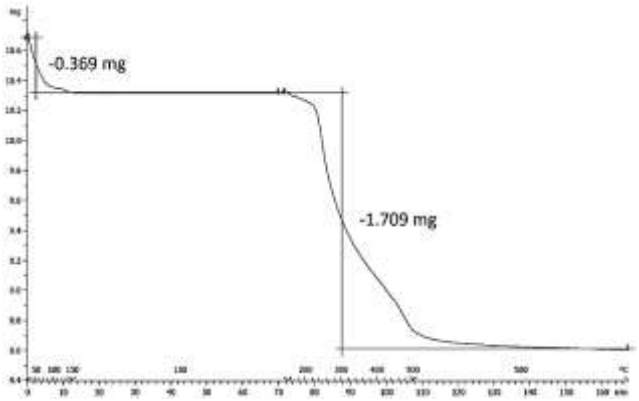


Fig. 4 TGA-curve for SiO_2-Cl (H).

These values appear as the "organic content" in Table 2. These values can be compared with the sum of the molar concentrations of N and Cl from elemental analysis. On this basis, it can be seen that the overall concentrations of surface functional groups from elemental analysis (N plus Cl concentrations) agree very well with the overall concentrations based on TGA.

Table 2 TGA and elemental analytical for the synthesized materials.

Sample	Organic content[a] /mmol g^{-1}	N content[b] /mmol g^{-1}	Cl content[b] /mmol g^{-1}
SiO_2-Cl (L)	0.62	-	0.64
SiO_2-Pr (L)	0.61	0.43	0.20
SiO_2-Pr-Boc	0.63	0.42	0.21
SiO_2-Pr-Boc,Me	0.61	0.39	0.22
SiO_2-Pr $(Boc)_{deprotected}$	0.58	0.41	0.19
SiO_2-Pr $(Boc,Me)_{deprotected}$	0.33	0.17	0.14
SiO_2-Cl (H)	1.31	-	1.32
SiO_2-Pr (H)	1.30	1.30	-
MCM-41-Cl	1.12	-	1.05
MCM-41-Pr	1.10	0.71	0.29

[a] thermogravimetric data. [b] elemental analysis data.

There are some trends seen in the data in Table 2. Comparison between SiO_2-Pr (L) and SiO_2-Pr (H) suggests there may be a link between the surface area of the support and the level of functionalisation. The fact that the much higher surface area of MCM-41 does not correspond to a proportionally higher level of functionalisation may reflect a less accessible surface in the deep pores in this material, or it may be a consequence of a less reactive surface arising from high temperature calcination and a relatively low concentration of reactive surface silanol groups.

The extent to which chloropropyl groups are reacted with the proline derivatives is also significant. This is quantitative for SiO_2-Cl (H) but only about 70% conversion occurs for SiO_2-Cl (L) and MCM-41-Cl. It is possible that this is related to the facility with which 4-hydroxyproline can access the surface chloropropyl groups, although there is no obvious link with average pore diameter.

The data in Table 2 for the functionalised silicas prepared by the protection/deprotection routes show that the act of protecting and then de-protecting results in significant losses of functional group concentrations, especially through the esterification of the carboxylic acid group and its subsequent hydrolysis.

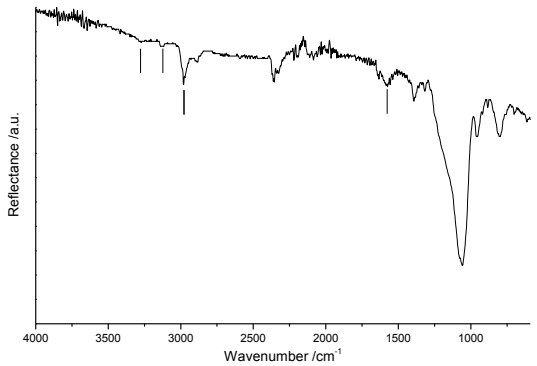


Fig. 5 FTIR spectrum of SiO_2-Pr (L).

The FTIR spectrum of SiO_2-Pr (L) is shown in Figure 5, as an example of a catalyst prepared without the use of protecting groups. The band at 2970 cm^{-1} is characteristic of CH_2 stretch of the propyl chain. The vibrations at 1058 cm^{-1} (Si-O-Si asymmetric stretching), 799 cm^{-1} (symmetric stretching), 452 cm^{-1} (bending) and 957 cm^{-1} (Si-OH) are characteristic of the silica support. The very weak bands at 3273, 3145 and 1570 cm^{-1} can be assigned to N-H stretching, hydrogen-bonded N−H stretching and the carbonyl group (carboxylic acid) respectively.[28-30] These three weak vibrational bands are characteristic of the secondary amine and carboxylic acid functional groups on proline. Their low intensity is a consequence of the relatively low concentration of proline on the silica, but their presence confirms that the proline functional groups have been largely unaffected through reaction with surface tethers.

Catalytic data

The catalytic data for the supported organocatalysts in the aldol reaction are summarised in Table 3.

Table 3 Catalytic data for the aldol condensation reaction between 4-nitrobenzaldehyde and acetone using proline catalysts.

	Catalyst	Conversion[a] of 1 /%	TOF /h^{-1}	Yield[a] of 2 /%	ee[b] /%
1	MCM-41	0	0	0	-
2	MCM-41-Cl	0	0	0	-
3	MCM-41-Pr	44	2.3	41	27
4	SiO_2-Pr (H)	42	1.9	40	63
5	SiO_2-Pr (L)	23	1.4	22	51
6	SiO_2-Pr $(Boc)_{deprotected}$ (L)	35	3.4	34	37
7	SiO_2-Pr $(Boc,Me)_{deprotected}$ (L)	17	3.5	12	2
8	Hydroxyproline (dissolved)[c]	35	0.3	35	37
9	Hydroxyproline-Boc $_{protected}$	0	0	0	-
10	SiO_2-Pr (H)[d]	41	1.4	38	65

Reaction conditions: 4-nitrobenzaldehyde (151 mg, 1.0 mmol), acetone (10 mL), solid catalyst (0.05 g), 50 °C for 6 h. [a] 95 % confidence limit = ±3 %. [b] enantiomeric excess 95 % confidence limit = ±2 %. [c] 0.19 mmol of hydroxyproline. [d] re-used three times: activity on fourth cycle.

Detailed kinetic data is given in the supplementary information. In all cases, the aldol reactions were found to follow pseudo-first order kinetics (first order in nitrobenzaldehyde) up to and beyond the 6 h period. Turnover frequencies (TOFs) are based on nitrobenzaldehyde conversion and first order plots, assuming that the supported proline concentration is given by the nitrogen content (Table 2). In most cases a small amount of the aldol dehydration product, 4-(4-nitrophenyl)but-3-en-2-one ("C" in supplementary information), was also detected.

Data for MCM-41 and MCM-41-Cl (entries 1 and 2) show that the support materials exhibit no activity. Data is shown for the supported proline catalysts prepared without using the protection/deprotection routes (entries 3, 4 and 5), and using the protecting groups (entries 6 and 7). Data for 4-hydroxy-L-proline in homogeneous solution (at elevated concentration) (entry 8) is shown, and data for the same homogeneous 4-hydroxy-proline catalyst with protection of the amine, N-Boc-trans-4-hydroxy-L-proline (entry 9), is also given.

Entry 10 shows that SiO_2-Pr (H) is readily recycled and loses negligible activity and negligible enantioselectivity over four reaction cycles. Leaching tests were also performed as described above and no evidence for catalyst leaching to the reaction mixture was found.

MCM-41-Pr, SiO_2-Pr (H) and SiO_2-Pr (L) catalyse this transformation effectively (Entries 3, 4 and 5). Overall activities are higher than, or comparable with, those of the catalysts prepared by the protection/deprotection routes. Turnover frequencies (based on nitrogen content) are lower however. Enantiomeric excesses are recorded with all three, although they are not consistent. A possible explanation for the wide differences might be linked to the involvement of surface silanol groups on the catalysts. The enantioselectivity of proline is believed to arise from a relatively rigid transition state involving coordination of a proline-derived enamine and the aldehyde via hydrogen bonding to the carboxylic acid group. It is possible that acidic silanol groups on the silica surface interfere, competing with the carboxylic acid groups for the localisation of the aldehyde, and the extent of this competition might reasonably be expected to differ between supports.

The catalysts prepared by the protection/deprotection routes (entries 6 and 7) show moderate activity, in line with other reports[17] but with higher TOFs than for those prepared by the simpler route. It is significant that turnover frequencies are the same for the catalyst prepared by protection of both amine and carboxylic acid groups (entry 7) and the catalyst where only the amine is protected (entry 6). The former catalyst shows very low enantioselectivity which possibly suggests that the ester group used to protect the carboxylic acid is difficult to remove since, as discussed above, enantioselectivity is thought to be controlled by an intermediate involving the free acid group.

Remarkably, 4-hydroxy-L-proline used as a homogeneous catalyst (entry 8) shows significantly lower activity than the supported proline catalysts (the conversion data corresponds to the use of much more 4-hydroxy-L-proline in homogeneous solution than was used on the supported catalysts). The use of 4-hydroxy-L-proline as a homogeneous analogue to the supported proline catalysts, rather than L-proline itself, is justified on the basis that it has been shown by others to be a more active catalyst than L-proline in typical aldol reactions.[11] We can therefore be sure that homogeneous L-proline would also be very much less active than the supported proline catalysts. The higher activities of supported proline suggest that the silica support enhances the activity of tethered proline, possibly through interaction between the carboxylic acid group on the proline and nearby silanol groups, as mentioned briefly above.[31]

The protected homogeneous catalyst N-Boc-trans-4-hydroxy-L-proline (entry 9) shows no significant activity, confirming that the secondary amine is required to catalyse the aldol reaction. This observation is in agreement with reported work.[7, 11, 18]

In conclusion, it seems that it is possible to prepare an effective supported chiral proline catalyst without having to protect the amine and carboxylic acid groups through the tethering process. The catalytic and characterisation data suggest that the hydroxyproline reacts with the chloropropyl tether via the hydroxy group (thereby leaving free the secondary amine and carboxylic acid functionalities), Higher levels of proline functionalisation are achieved when the protection/deprotection steps are avoided, resulting in higher overall activities. However, the lower nominal TOFs observed for these catalysts may mean that not all the supported proline is in an active form, and is possibly bound to the surface in some way other than through reaction between the hydroxy and chloropropyl groups.

We admit that it is at first surprising that the tethering process works through reaction between the chloropropyl group on the silica surface and the hydroxy group on proline, and not the secondary amine. We suggest that this may be because the mildly acidic silanol groups on the silica surface protonate the amine, effectively protecting it during reaction (the pKa of silanol groups can be as low as 3).[32] The protonated amine group would also serve as protection against any racemisation at the α-carbon atom, a major concern in amino acid chemistry.[29]

The supported proline is clearly more active towards aldol condensation than dissolved 4-hydroxy-L-proline and, by extension, proline itself.[11] There appears to be some cooperative catalytic mechanism through which the support enhances activity. This could be because the catalytic amine group is activated by hydrogen-bonding to adjacent surface silanol groups, or perhaps these same silanol groups could play a role in activating the reactant ketone or aldehyde, or the intermediate enamine. Finally, it may be that the silanol groups simply act to concentrate the reactants by surface adsorption.

Supported proline catalysts in dimethyl sulfoxide (DMSO)

Proline-catalyzed aldol reactions are typically carried out in organic solvents such as dimethyl sulfoxide (DMSO), dimethylformamide (DMF) or chloroform. Dimethyl sulfoxide has been identified as the solvent of choice in many cases.[24] In the work reported above, the reactant acetone was also the solvent. We also carried out catalytic experiments in DMSO/acetone (4/1 v/v) mixtures at 25 ^{o}C . Kinetic data and enantiomeric excesses for these reactions are shown in Table 4. Bearing in mind the much lower reaction temperature, it is clear that activities are higher in this solvent system than in acetone. This is consistent with DFT calculations[33] which have shown that the energy barrier to complexation between acetone and proline is 171.4 kJ mol^{-1}, but this is reduced to 40.7 kJ mol^{-1} in the presence of excess DMSO. The supported proline catalysts are more

active than hydroxyproline in homogeneous solution, as in acetone. Enantioselectivities are also higher, but this may be simply a consequence of the lower reaction temperature.

Table 4 Conversion and yield data in the aldol condensation between 4-nitrobenzaldehyde and acetone in DMSO at 25 °C for 20 h.

Catalyst	Conversion of 1 /%	TOF /h^{-1}	Yield of 2 /%	ee /%
MCM-41-Pr	74	1.8	72	77
SiO_2-Pr (H)	90	1.7	87	75
SiO_2-Pr (L)	54	1.8	51	59
Hydroxyproline	67	0.3	85	78

Supported proline catalysts with other aromatic aldehydes

To examine the generality of the reaction, a variety of aromatic aldehydes were also used in the reaction. As shown in Table 5, aromatic aldehydes bearing electron-withdrawing groups, such as chloro- and nitro- groups, undergo aldol condensation smoothly in the presence of MCM-41-Pr in DMSO/acetone (v/v: 4/1). The reactions generate the corresponding aldols in good yields (59–74%) and high enantioselectivities (73–77% ee).

Table 5 Conversion and yield data in the aldol condensation between acetone and a range of aldehydes in DMSO at 25 °C for 20 h, using MCM-41-Pr catalyst .

Catalyst	Conversion of 1 /%	Yield of 2 /%	ee /%
4-nitrobenzaldehyde	74	72	77
4-isopropylbenzaldehyde	47	43	70
benzaldehyde	69	69	82
4-chlorobenzaldehyde	59	56	73

Conclusions

L-proline-functionalized mesoporous silica has been successfully synthesized by a relatively simple route. The effect of protecting the amine and the carboxylic acid groups through the synthesis of the supported proline on the ultimate activity and enantiomeric selectivity of the catalyst has been investigated. The results show that the most active and selective catalysts are prepared without protecting the two functional groups on the proline. This new route could be an economical and green step towards chiral catalysts in general and solid-supported proline catalysts in particular.

Furthermore, there seems to be a relationship between the nature of the silica support and the ultimate activity and enantioselectivity of the supported proline. It seems that a high surface area for the support is beneficial and it is possible that pore size is also important in terms of imparting enantioselectivity to the catalyst. Current research is directed at ordered mesoporous silica supports with a range of pore sizes, in an effort to identify the relationship between the porosity of the support material and the activity and selectivity of supported proline catalysts.

Notes and references

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