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Asymmetric Aldol Reaction Catalyzed by a Heterogenized Proline on a Mesoporous Support. The Role of the Nature of Solvents

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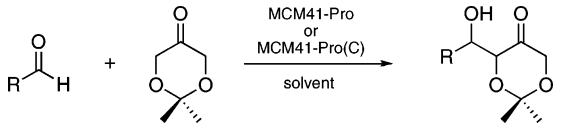

A heterogenized (*S*)-proline on mesoporous support MCM-41 catalyzes the asymmetric aldol reaction in a wide range of solvents. The progress of the reaction is dependent on the nature of the solvent. Reactions proceed more efficiently in hydrophilic polar solvents; however, the addition of a small amount of water has a positive effect on the rate and the stereoselectivity of the reaction performed in hydrophobic toluene. The reaction under heterogeneous conditions has also been performed on chiral aldehydes, furnishing useful intermediates for the synthesis of azasugars.

There is a growing interest in asymmetric organocatalysis,[1] particularly in the use of the amino acid proline[2] and its derivatives[3] as catalysts for asymmetric aldol additions. The main advantages of proline-catalyzed reactions are that this amino acid is *innocuous* and nonexpensive and both enantiomers are available. In addition, the reaction can be performed in a stereoselective manner, under mild conditions, and without the need of any metal. However, due to the solubility of proline the reactions are normally carried out in polar solvents, such as DMSO or DMF. In this context, we have recently described[4] that a proline derivative heterogenized on amorphous silica and structured mesoporous material MCM-41 (MCM41-Pro, Figure 1) can catalyze the aldol reaction between different aldehydes and hydroxyacetone. MCM-41 was the most convenient support to be functionalized since its high surface area allows us to bind more moles of catalysts per surface unit, consequently decreasing the risk of nonlinear effect usually found in other heterogeneous catalysis.[5] We also showed that reactions in the presence of MCM41-Pro can be performed in DMSO and in hydrophobic toluene, giving aldol products with stereoselectivities in some cases complementary to those obtained by homogeneous catalysis. Due to the potential effect that the solvent may have on the progress of the aldol addition, we were interested in evaluating the role of the solvent for this reaction.

Herein we present the results of the reaction of *p*-nitrobenzaldehyde (**1**) with 2,2-dimethyl-1,3-dioxan-5-one (**2**) that we have selected as a standard model, in the presence of MCM41-Pro (Scheme 1). The influence of the solvent, the presence of water in the reaction medium, and the change of the linker moiety used for the attachment of proline to the support have been evaluated. In addition, the reactions were performed on chiral aldehydes that furnished useful intermediates for the synthesis of azasugars. The present work offers new insights

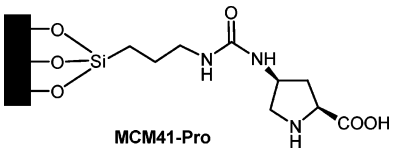

FIGURE 1. Proline derivative grafted into mesoporous MCM-41.

TABLE 1. Solvent Screen for the Aldol Reaction between *p*-Nitrobenzaldehyde 1 and Dioxanone 2 in the Presence of MCM41-Pro

entry	solvent (log *P*)[a]	time (h)	conv.[b] (%)	*anti*:*syn*[b]	ee[b] (%)
1	formamide (−1.65)	13	96	2:1	67
2	formamide (−1.65)[c]	13	93	2:1	65
3	DMF (−1.00)	61	80	5:1	82
4	DMF (−1.00)[d]	48	82	2:1	63
5	MeOH (−0.76)	61	46	3:1	76
6	MeCN (−0.33)	96	20	2:1	63
7	THF (0.49)	96	23	2:1	50
8	*t*-BuOMe (0.94)	96	<5	n.d.	n.d.
9	CH_2Cl_2 (1.25)	96	20	2:1	65
10	Toluene (2.50)	96	14	2:1	64

[a] Log *P* is the partition coefficient of the solvent in octanol/water. [b] Determined by HPLC analysis. n.d. = not determined. [c] Recycled MCM41-Pro was used as catalyst. [d] (*S*)-Proline was used as catalyst in homogeneous media.

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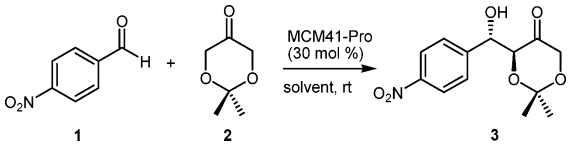
SCHEME 1



into the effect of the nature of the solvent on proline-catalyzed reactions under heterogeneous conditions.

The results of the aldol addition between **1** and **2** in the presence of MCM41-Pro[6] at room temperature[7] in a variety of solvents are summarized in Table 1. For comparative purposes the results using (*S*)-proline in DMF are also included (entry 4). It could be observed that the catalytic efficiency of MCM41-Pro decreased as the solvent hydrophobicity increased. Thus, the aldol reaction proceeded with high conversion in formamide and DMF (96 and 80%) and with moderate conversion in MeOH (46%). On the contrary, the reaction in toluene furnished **3** in low conversion (14%) after 96 h, and in *tert*-butylmethyl ether only trace amounts of **3** were observed. In most of the solvents the diastereoselectivity was low, and the enantioselectivity, moderate, except for the reaction performed in DMF that led to the *anti* isomer with good diastereoselectivity and high ee value. Moreover, the stereoselectivity obtained in DMF was even better than that of (*S*)-proline under homogeneous conditions (entry 3 versus entry 4). After filtering and washing,[8] the catalyst could be reused in a new reaction that proceeded without significant differences regarding conversion and stereoselectivity (entry 2).

On the other hand, it has been reported that small amounts of water are sometimes beneficial in proline-catalyzed aldol reactions.[9] Considering the proposed mechanism, which is consistent with an enamine intermediate and the consequent formation of a molecule of water,[10] once the acceptor aldehyde reacts with the enamine a new C−C bond is formed, and the resulting iminium intermediate is attacked by a molecule of water to regenerate the catalyst. Under our heterogeneous reaction conditions, the water present in the reaction medium will partition between the organic solvent and the solid surface; the partition ratio will depend on the hydrophobicity of the solvent used. In the most hydrophobic solvent, the molecules of water will tend to remain attached to silanols on the support and, therefore, the loss of H_2O will inhibit proline turnover. This situation would account for the poor catalytic efficiency observed when the reactions were carried out in hydrophobic solvents. On the basis of this assumption,[11] we next examined the effect of addition of water to the reaction of **1** with **2** in two solvents of distinct hydrophobicity, MeCN and toluene, whose reactions furnished aldol products in low yields (Table 2). While in hydrophilic MeCN the addition of small amounts of water did not affect the production of the aldols (entries 1−4), in hydrophobic toluene there was an appreciable increase in conversion when 2 and 5 equiv of water were added.

Interestingly, the reactions in toluene exhibited a progressive increase of stereoselectivity as water was added up to 5 equiv (entries 5−7), reaching a diastereoselectivity ratio of 10:1. However, when 10 and 20 equiv of water were added to toluene, the yield dropped drastically and only traces of aldol products were observed (entries 8 and 9). This result could be rationalized assuming that the added water molecules (up to 5 equiv) gather together around the interphase solid solution, very close to the catalytic site, favoring the catalytic cycle. However, with an excess of water (10 and 20 equiv), the formation of a biphasic system could be responsible for the drastic drop of reactivity.

The nature of the linker moiety used for attachment of proline to MCM-41 could also influence the progress of the reactions. It could be the case that the urea moiety in MCM41-Pro interacts with the carbonyl group of the substrates in a solvent-dependent manner, thus affecting the reaction rate and yield. Considering this possibility, we synthesized a new catalyst MCM41-Pro(C) in which the urea group was replaced by a carbamate group

TABLE 2. Effect of Water on MCM41-Pro-Catalyzed Aldol Reactions of 1 and 2

entry	solvent	H_2O (equiv)	conv.[a] (%)	*anti*:*syn*[a]	ee[a] (%)
1	MeCN	0	20	2:1	63
2	MeCN	2	20	3:1	73
3	MeCN	5	21	3:1	62
4	MeCN	10	22	3:1	66
5	toluene	0	14	2:1	64
6	toluene	2	33	6:1	65
7	toluene	5	47	10:1	78
8	toluene	10	<5	n.d.	n.d.
9	toluene	20	<5	n.d.	n.d.

[a] Determined by HPLC.

TABLE 3. Aldol Reaction between 1 and 2 in the Presence of MCM41-Pro(C)

solvent	time (h)	conv.[a] (%)	*anti*:*syn*[a]	ee[a] (%)
formamide	48	88	2:1	46
DMF	84	67	2:1	40
toluene[b]	84	79	3:1	34

[a] Determined by HPLC. [b] Reaction performed with 5 equiv of water.

TABLE 4. Aldol Reaction between 7 and 8 with 2 in the Presence of MCM41-Pro and MCM41-Pro(C)

entry	aldehyde	catalyst	solvent	yield[a] (%)	*anti*:*syn*[b]
1	**7**	MCM41-Pro	formamide	62	5:1
2	**7**	MCM41-Pro	toluene[c]	30	3:1
3	**7**	MCM41-Pro(C)	formamide	56	2:1
4	**7**	MCM41-Pro(C)	toluene[c]	64	3:1
5	**8**	MCM41-Pro	formamide	52	3:1
6	**8**	MCM41-Pro	toluene[c]	10	n.d.
7	**8**	MCM41-Pro(C)	formamide	57	3:1
8	**8**	MCM41-Pro(C)	toluene[c]	44	2:1

[a] Isolated yield. [b] Determined by ^{1}H NMR. n.d. = not determined. [c] Reaction performed with 5 equiv of water.

(6) The loading (0.7 mmol/g) of the MCM41-Pro catalyst was calculated by elemental analysis based on nitrogen. Anal. Found: C, 13.87; H, 2.53; N, 2.95 %.

(7) No reaction was observed when the aldol addition was carried out at 4 °C in two distinct solvents, DMF and toluene, during 72 h.

(8) The catalyst was filtered and thoroughly washed with methanol, ethyl acetate, dichloromethane, hexane, and diethyl ether (two times each).

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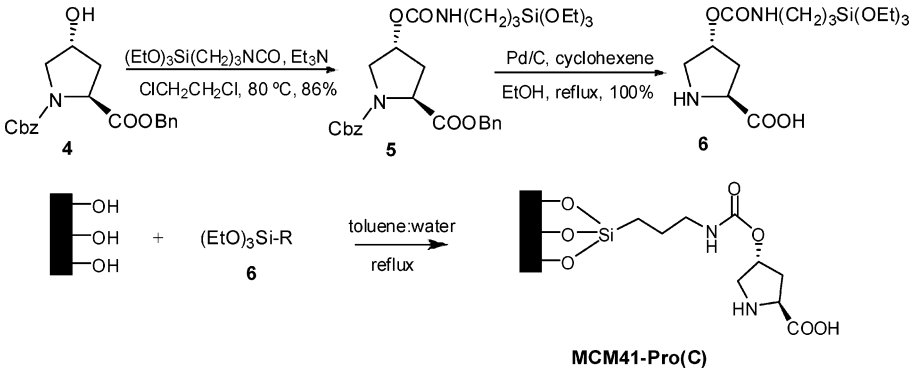
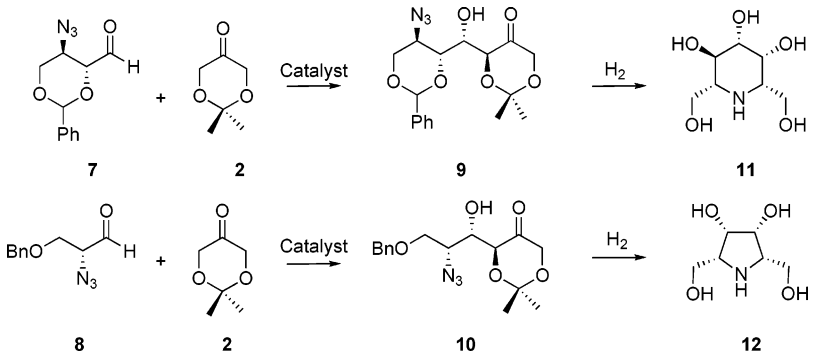
SCHEME 2. Synthesis of MCM41-Pro(C)



SCHEME 3



(Scheme 2). The synthesis of MCM41-Pro(C) was achieved in a few steps from protected hydroxy-(*S*)-proline as described in Scheme 2.

The new catalyst was tested for the reaction of **1** and **2** in toluene with 5 equiv of water, as well as in formamide and DMF (Table 3). With this catalyst the reaction in toluene proceeded more efficiently, giving the aldol products in a conversion comparable to that obtained in formamide. In the three solvents, however, the diastereoselectivities and the ee values were lower than those obtained with MCM41-Pro, which could be attributed to the configuration change at C-4 of the proline ring.

We are interested in efficient preparation of iminocyclitols,[12] also called azasugars as the ring oxygen of a carbohydrate is replaced by nitrogen, due to their ability to act as potent inhibitors of enzymes involved in carbohydrate processing, such as glycosidases and glycosyltransferases.[13] We have recently reported[14] a new route to synthesize compounds of this family through a proline-catalyzed aldol reaction on aldehydes derived from diethyltartrate. The main point of this synthetic approach relies on the possibility of obtaining a variety of azasugars combining the use of both enantiomers of diethyltartrate as starting material and (*R*)- or (*S*)-proline as catalyst. In connection with this work we have now evaluated MCM41-Pro and MCM41-Pro(C) for their ability to catalyze the reaction of dioxanone **2** with two chiral aldehydes **7** and **8** derived from tartaric acid (Scheme 2). The results of the reaction of **2** with **7** and **8** in the presence of MCM41-Pro and MCM41-Pro(C) in formamide and toluene with 5 equiv of water are shown in Table 4. With MCM41-Pro the reactions in formamide furnished **9** and **10** in 62 and 52% yield, respectively, while in toluene a significant decrease in yield was obtained (30 and 10%, respectively). However, the catalyst MCM41-Pro(C) bearing a carbamate moiety furnished **9** and **10** in comparable yields in both solvents. Concerning stereoselectivity, the reactions furnished exclusively the *S*-configured carbon at position C-3, with (4*R*,3*S*)/(4*S*,3*S*) ratios varying from 2:1 to 5:1. The major aldol products *anti*-**9** and *anti*-**10** were transformed into six- and five-membered iminocyclitols by hydrogenation (compounds **11** and **12**, Scheme 3).

In summary, we have shown that a heterogeneized (*S*)-proline on mesoporous support MCM-41 can catalyze the asymmetric aldol reaction in solvents of different polarity. This fact leads to enlarge the application of a fundamental variable, the solvent, to the study of proline-catalyzed reactions. Under heterogeneous conditions we have obtained precursors of azasugars from an aldol addition performed in toluene, a solvent where the use of (*S*)-proline is hampered by insolubility problems.

Experimental Section

General Procedure for the Catalytic Asymmetric Aldol Reaction of *p*-Nitrobenzaldehyde (1) and Ketone 2 Using MCM41-Pro. To a suspension of ketone **2** (16.9 mg, 0.13 mmol) and MCM41-Pro (30% mol; 27.8 mg, loading: 0.7 mmol/g) in the corresponding solvent (0.21 mL), aldehyde **1** was added (10 mg, 0.065 mmol). The mixture was stirred at rt for the time indicated in Table 1. Then, the catalyst was separated by centrifugation, and the filtrate was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (3 × 1 mL). The

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combined organic layers were concentrated under vacuum. Yields and diastereoselectivities are reported in Table 1.

General Procedure for the Catalytic Asymmetric Aldol Reaction of 7 and Ketone 2 Using MCM41-Pro or MCM41-Pro(C). To a solution of **7** (0.5 mmol) in the solvent (1.6 mL), ketone **2** (260 mg, 2 mmol) and the catalyst (30% mol; 214 mg for MCM41-Pro and 163 mg for MCM41-Pro(C)) were added. The mixture was stirred at rt for 24−72 h. Then, the catalyst was separated by centrifugation, and the filtrate was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (3 × 1 mL). The combined organic layers were concentrated under vacuum. Yields and diastereoselectivities are reported in Table 4.

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Supporting Information Available: General information, experimental procedures, copies of the NMR spectra of compounds **5**, **6**, **8**, and **10**, and copies of solid ^{13}C NMR and IR of MCM41-Pro(C). This material is available free of charge via the Internet at http://pubs.acs.org.

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