

Proline and benzylpenicillin derivatives grafted into mesoporous MCM-41: Novel organic–inorganic hybrid catalysts for direct aldol reaction[†]

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Abstract. New organic–inorganic hybrid catalysts were synthesized by covalent grafting of proline and benzylpenicillin derivatives into mesoporous MCM-41. These catalysts were extensively characterized using FT-IR, ¹³C CP MAS solid state NMR, XRD and TEM techniques. These were used as catalysts for direct, asymmetric aldol reaction between acetone and activated aromatic aldehydes. In the reaction of 4-nitro and 4-fluoro benzaldehyde, the aldol products were obtained in 36% and 59% *ee* respectively. The catalysts were reusable with neither significant drop in enantioselectivity nor loss of mesostructure. An attempt was made to substantiate the proposed ‘enamine’ mechanism for direct aldol reaction by trapping the intermediate between proline-MCM-41 and acetone.

Keywords. Proline; MCM-41; hybrid catalysts; grafting; aldol reaction; enamine.

1. Introduction

The catalytic asymmetric aldol reaction is a fundamental C–C bond forming reaction in chemistry and biology. In 1970’s, an asymmetric intramolecular aldol reaction catalysed by proline was reported by Wiechert¹ and Hajos² which gave very high enantiomeric excesses for the synthesis of the so-called Hajos–Parrish ketone. Since then, there have been several approaches for asymmetric aldol reaction mostly involving preformed enolate equivalents in combination with a chiral catalyst.^{3–5} Recently, Shibasaki *et al*^{6,7} reported a small molecule catalysed direct aldol reaction using lanthanum complexes mimicking the natural class 2 aldolase enzyme.⁸ However, List^{9,10} demonstrated that a simple molecule like proline could catalyse the direct asymmetric aldol reaction mimicking class 1 aldolase enzyme which follows an enamine mechanism.¹¹

Recent years have seen a lot of interest in heterogeneous catalysis because of simpler product purification and catalyst recycling.¹² The catalyst support could range from soluble polymers such as polyethylene glycol (PEG) to highly porous and rigid MCM-41.¹³ Recently, proline supported on PEG monomethyl ether was shown to be an efficient catalyst for enantioselective aldol reaction.¹⁴ Choudary *et al*¹⁵ reported that ethylene diamine anchored on MCM-41 was an efficient catalyst for aldol and Knoevenagel

[†]Dedicated to Professor C N R Rao on his 70th birthday

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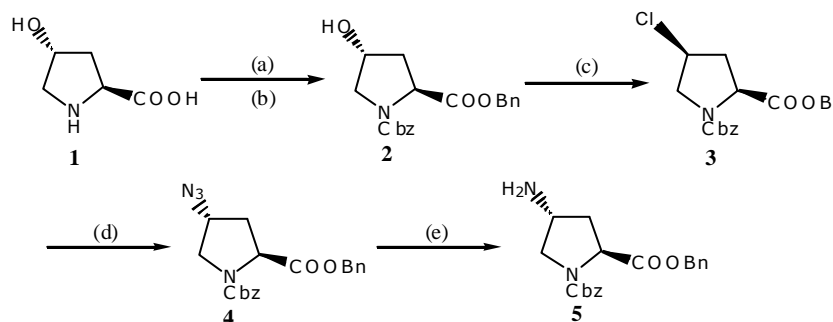
reactions. Proline catalysed asymmetric aldol reaction has also been carried out successfully in room temperature ionic liquids with efficient catalyst recovery.¹⁶

The synthesis of organic-inorganic hybrid materials is now a rapidly growing field.^{17,18} Among various other applications, their use as enantioselective catalysts is particularly noteworthy.¹⁹ Most frequently, they have been synthesized by covalent grafting of mono trialkoxy silylated organic molecules into amorphous, mesoporous and microporous inorganic supports.¹⁹ Herein, we report the use of proline and benzyl penicillin derivatives covalently anchored to mesoporous MCM-41 with a suitable organic spacer as catalysts for aldol reactions. The catalysts **8** & **11** have good mechanical and thermal stability and do not require swelling as in the case of organic polymers. Moreover, the catalysts do not involve any metal; hence the problem of leaching encountered with many metallic catalysts does not arise.

2. Experimental

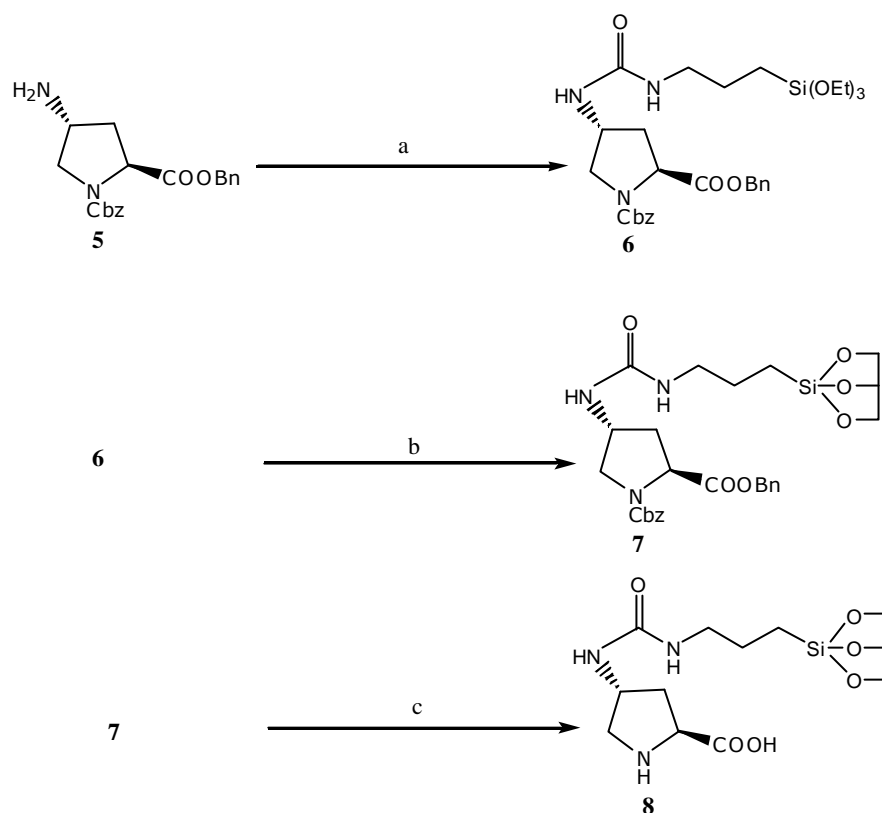
2.1 Synthesis and characterisation of organic-inorganic hybrid catalysts – Proline derivative-MCM-41, **8** and benzylpenicillin derivative-MCM-41, **11**.

Mesoporous silica (MCM-41) was synthesized according to the original literature procedure using cetyl trimethylammonium bromide as a template.¹³ Covalent grafting of the chiral proline derivative onto MCM-41 was carried as outlined in schemes 1 and 2. Trans-4-hydroxy L-proline **1** was protected as the benzyl carbamate and the benzyl ester to give **2**. The hydroxy compound **2** was converted into chloride **3** and subsequently to azide **4** according to literature procedure.²⁰ Reduction of the azide to the amine **5** was carried out using the Staudinger reaction.²¹ The resulting amine **5** was treated with 3-isocyanatopropyl triethoxysilane in pyridine to provide a suitable linker for covalent anchoring to the siliceous support (scheme 3). The modified proline derivative **6** had the following spectral characteristics: IR (thin film): $\nu = 3354, 2975, 2884, 1748, 1714, 1636, 1567, 1416, 1355, 1165, 1078, 956, 769, 698 \text{ cm}^{-1}$; ¹H NMR (CDCl₃, 300 MHz): δ 7.27–7.33 (*m*, 10H), 5.15 (*m*, 2H), 5.0 (*d*, 2H, *J* = 6.3), 4.69 (*m*, 1H), 4.44 (*m*, 1H), 3.8 (*q*, 6H), 3.4 (*m*, 1H), 3.15 (*m*, 3H), 2.17–2.27 (*m*, 2H), 1.58 (*m*, 2H), 1.21 (*t*, 9H), 0.6 (*m*, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ 172.0, 157.6, 155.0, 136.0, 135.2, 128.4, 128.3, 128.2, 127.7, 67.3, 66.9, 57.7, 52.6, 48.9, 42.7, 37.5, 36.2, 23.6, 18.2, 7.5.



Reagents and conditions: (a) Cbz-Cl, NaOH, dioxan/H₂O; (b) PhCH₂Br, K₂CO₃, DMF, rt; (c) Ph₃P, CCl₄, THF, rt; (d) NaN₃, DMF, 70°C, 64 h; (e) Ph₃P, THF, rt, then H₂O reflux

Scheme 1.



Reagents and conditions: (a) $(\text{EtO})_3\text{Si}(\text{CH}_2)_3\text{NCO}$, Pyridine, cat. DMAP, rt, 12 h; (b) MCM-41, toluene, reflux, 12 h; (c) 30% HBr in AcOH, 4d, NaOAc, pH 7

Scheme 2.

Modified proline **6** was tethered to the channels of MCM-41 by refluxing in toluene to form the organic–inorganic hybrid material **7**. The hybrid material **7** was characterised by FT-IR and ^{13}C CP MAS NMR spectroscopy (CP MAS = cross polarisation magic-angle spinning). FT-IR (KBr): $\nu = 2939, 1742, 1703, 1567, 1431, 1360, 1015, 770, 698\text{ cm}^{-1}$; ^{13}C CP MAS NMR (75 MHz): δ 175.4, 162.6, 158.9, 139.0, 131.1, 70.6, 61.4, 52.9, 45.9, 39.1, 25.9, 12.4; elemental analysis: C 22.73%, H 2.78%, N 2.85%; BET surface area: $579\text{ m}^2/\text{g}$; pore volume: $0.432\text{ cm}^3/\text{g}$.

Removal of the protecting groups in **7** was achieved by stirring with 30% HBr in acetic acid for 2 days. Deprotection of benzyl carbamate was indicated by disappearance of the peak at 1700 cm^{-1} in the FT-IR spectrum and disappearance of signals at 159, 139, 131, and 71 ppm, characteristic of the protecting groups, in the ^{13}C CP MAS spectrum (figure 1). Deprotection resulted in the formation of hybrid catalyst **8** which had the following spectral characteristics: FT-IR (KBr): $\nu = 2944, 1738, 1571, 1433, 1360, 1008, 770, 698\text{ cm}^{-1}$; ^{13}C CP MAS NMR (75 MHz): δ 175.9, 162.1, 62.6, 53.5, 45.2, 37.5, 25.8, 11.9; elemental analysis: C 10.20%, H 2.19%, N 3.51%; BET surface area: $448\text{ m}^2/\text{g}$, pore volume: $0.2567\text{ cm}^3/\text{g}$.

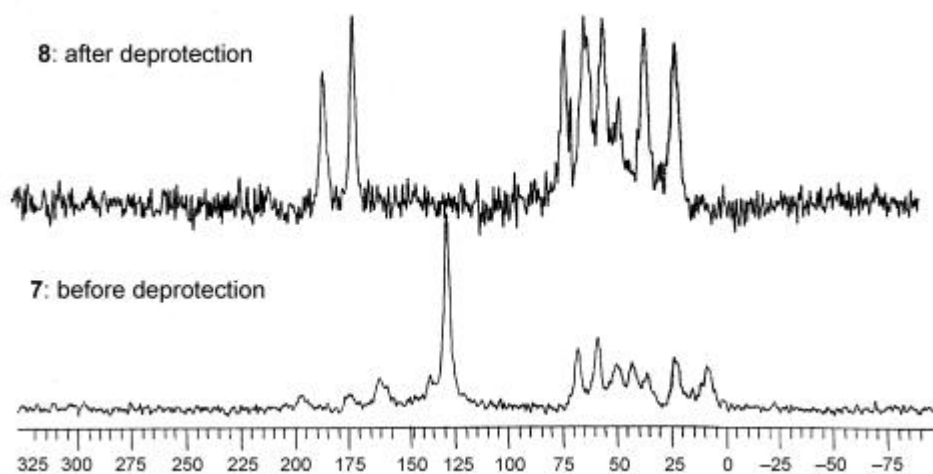


Figure 1. ^{13}C CP MAS NMR (75 MHz) spectra of organic-inorganic hybrid material **7** (before deprotection) and **8** (after deprotection).

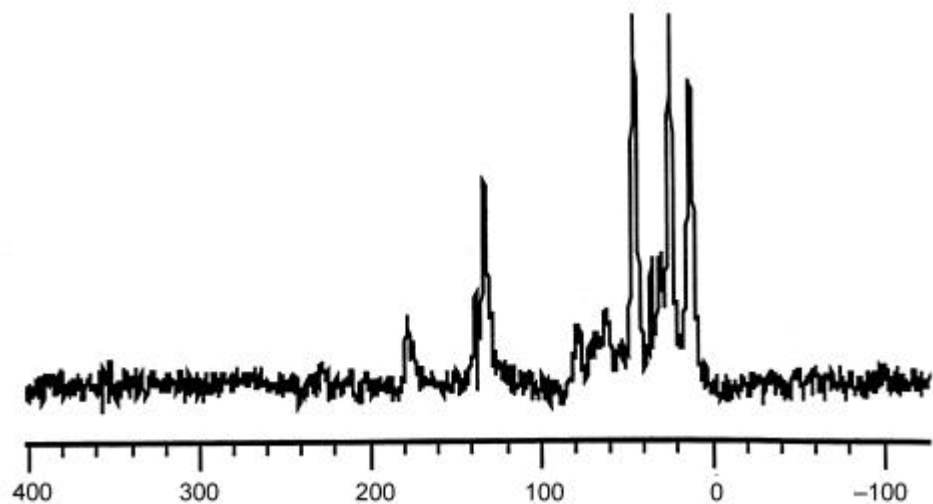
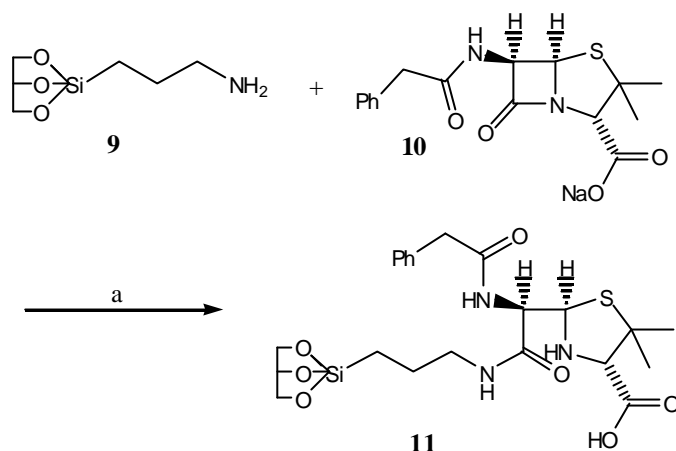


Figure 2. ^{13}C CP MAS NMR (75 MHz) spectrum of catalyst **11** (benzyl penicillin derivative anchored to MCM-41).

The structural integrity of MCM-41 was preserved during anchoring and deprotection as indicated by small angle XRD and TEM.

Aminopropyl MCM-41 **9** was prepared by refluxing pure silica MCM-41 with 3-aminopropyl triethoxysilane in toluene for 12 h. The highly electrophilic β -lactam ring of benzylpenicillin **10** was used to acylate aminopropyl modified MCM-41 by reaction of commercially available Penicillin G sodium salt to give the hybrid catalyst **11** (scheme 3). The grafting of benzylpenicillin derivative onto the solid support was confirmed by FT-IR and ^{13}C CP MAS NMR spectroscopy (figure 2).



Reagents and conditions: (a) cat. DMAP, MeOH, 6 h, then AcOH

Scheme 3.

2.2 A typical procedure for aldol reaction using chiral hybrid catalyst **8**

To a stirred suspension of the chiral hybrid catalyst **8** (0.2 g, 0.94 mmol/g. loading, 9.4 mol%), previously dried under vacuum at 100°C for 4 h in dry DMSO (8 ml) and acetone (2 ml) was added 4-nitrobenzaldehyde **12** (0.302 g, 2 mmol) in one portion. The reaction mixture was stirred at room temperature for 24 h. The solid catalyst was filtered, washed thoroughly with water and toluene and dried under vacuum for further use. The filtrate was washed with water and extracted with ether. The aldol product **14** was purified by column chromatography on silica gel using ethyl acetate/hexane mixture. Yield (0.188 g, 45%). $^1\text{H NMR}$ (300 MHz): δ 8.2 (d, 2H, $J = 8.4$ Hz), 7.6 (d, 2H, $J = 8.4$ Hz), 5.2 (m, 1H), 3.6 (br s, OH), 2.9 (m, 2H), 2.2 (s, 3H); $[\alpha]_D^{25} = 50$ ($c = 0.2$, CHCl_3). Enantiomeric excess (*ee*) of 36% as determined by HPLC using Chiralpak AD-H column.

3. Results and discussion

3.1 Direct aldol reaction of acetone with activated aromatic aldehydes using organic–inorganic hybrid catalysts **8** and **11**

The chiral hybrid materials **8** and **11** were tested for their catalytic activity in the aldol reaction between acetone and 4-nitro benzaldehyde **12** (scheme 4). When proline derivative on MCM-41 **8** was used as a catalyst, aldol product **14** was isolated in a chemical yield of 45% and an enantiomeric excess of 36% (table 1, entry 1).

Interestingly, the hybrid catalyst **8** can be recovered by simple filtration and reused several times without significant loss in activity. The chiral hybrid catalyst **11** was also found to be catalytically active in the direct aldol reaction between acetone and 4-nitro benzaldehyde. However, the aldol product **14** was obtained in <5% *ee* (table 1, entry 3).

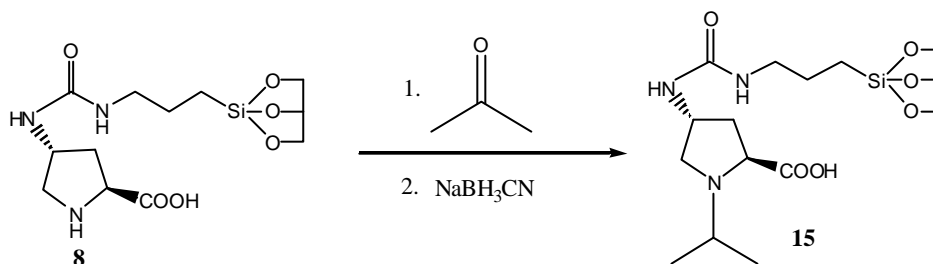
Proline and benzylpenicillin derivatives grafted on to amorphous silica gel did not improve the chemical yield or the enantiomeric excess of the aldol **14** (table 1, entries 2 and 4). The chiral hybrid catalyst **8** was therefore chosen for further studies.

little effect on the enantioselectivity, giving an *ee* of 34.5% for the aldol **14**, compared with the previous value of 36% before the modification.

3.2 Mechanism of direct aldol reaction catalysed by Proline derivative-MCM-41 **8**

It was originally proposed by List *et al*⁹ that proline catalysed direct asymmetric aldol reaction follows the same pathway as that followed by class 1 aldolase enzyme. It was suggested that proline gets converted to a nucleophilic enamine catalyst due to the presence of secondary amine and the carboxylic acid acts as a general Bronsted catalytic site.¹⁰ It is further known that proline can be reductively alkylated with unactivated ketones.²² In the light of this a separate experiment was carried out where the proline derivative-MCM-41 catalyst **8** was stirred with acetone at RT for 4 h followed by slow addition of NaBH₃CN to get **15** (scheme 5).

The catalyst **15** was filtered, washed with water and ethanol and dried under vacuum. ¹³C CP MAS NMR confirmed that proline derivative-MCM-41 was reductively alkylated (figure 3) to give **15**. However, the catalyst **15** was not active in the aldol reaction between acetone and 4-nitro benzaldehyde providing indirect evidence for enamine catalysis.



Scheme 5.

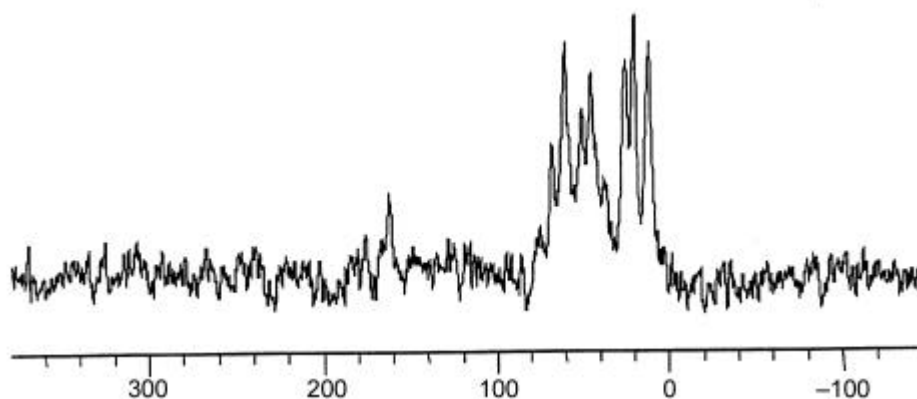


Figure 3. ¹³C CP MAS NMR spectrum (75 MHz) of **15** (Proline derivative-MCM-41 after reductive alkylation).

4. Conclusion

Novel organic–inorganic hybrid catalysts were synthesized by covalent anchoring of proline and benzylpenicillin derivatives into MCM-41. These were tested as catalysts for direct aldol reaction between acetone and activated aromatic aldehydes. The so called ‘enamine’ intermediate involved in the direct aldol reaction was ‘trapped’ using proline derivative-MCM-41 **8** and was characterized by solid state NMR.

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References

1. Eder U, Sauer G and Wiechert R 1971 *Angew. Chem., Int. Ed. Engl.* **10** 496
2. Hajos Z G and Parrish D R 1974 *J. Org. Chem.* **39** 1615
3. Nelson S G 1998 *Tetrahedron Asym.* **9** 357
4. Groger H, Vogl E M and Shibasaki M 1998 *Chem. Eur. J.* **4** 1137
5. Bach T 1994 *Angew. Chem., Int. Ed. Engl.* **33** 417
6. Yoshikawa N, Yamada Y M A, Das J, Sasai H and Shibasaki M 1999 *J. Am. Chem. Soc.* **121** 4168
7. Yamada Y M A and Shibasaki M 1998 *Tetrahedron Lett.* **39** 5561
8. Fessner W D, Shneider A, Held H, Sinerius G, Walter C, Hixon M and Schloss J D 1996 *Angew. Chem., Int. Ed. Engl.* **35** 2219
9. List B, Lerner R A and Barbas C F (III) 2000 *J. Am. Chem. Soc.* **122** 2395
10. Noltz W and List B 2000 *J. Am. Chem. Soc.* **122** 7386; List B 2001 *Synlett* **11** 1675
11. March J J and Lebherz H G 1992 *Trends Biochem. Sci.* **17** 110
12. Vankelecom I F J and Jacobs P A 2000 *Chiral catalyst immobilisation and recycling* (eds) DE de Vos, I F J Vankelecom and P A Jacobs (Weinheim: Wiley-VCH) ch. 2
13. Kresgge C T, Leonowitz M E, Roth W J, Vartuli J C and Beck J S 1992 *Nature (London)* **359** 710
14. Benaglia M, Celentano G and Cozzi F 2001 *Adv. Synth. Catal.* **343** 171
15. Choudary B M, Kantam M L, Sreekanth P, Bandopadhyay T, Figueras F and Tuel A 1999 *J. Mol. Cat.* **A142** 361
16. Kotrusz P, Mentova I, Gotov B, Toma S and Solcaniova E 2002 *Chem. Commun.* 2510
17. Asefa T, Maclachlan M J, Crooms N and Ozin G A 1999 *Nature (London)* **402** 867
18. Inagaki S, Guan S, Fukushima Y, Ohsuna T and Terasaki O 1999 *J. Am. Chem. Soc.* **121** 9611
19. Wight A P and Davis M E 2002 *Chem. Rev.* **102** 3589
20. Webb T R and Eigenbrot C 1991 *J. Org. Chem.* **56** 3009
21. Vaultier M, Knouzi N and Carrie R 1983 *Tetrahedron Lett.* **24** 763
22. Toth G, Kovacs A, Tarnai T and Tungler A 1993 *Tetrahedron Asym.* **4** 331