MCM-41 heterogenized chiral amines as base catalysts for enantioselective Michael reaction

A. Corma [a,*], S. Iborra [a], I. Rodríguez [a], M. Iglesias [b], and F. Sánchez [b]

[a] Instituto de Tecnología Química, UPV-CSIC, Universidad Politécnica de Valencia, Avda. de los Naranjos s/n, 46022 Valencia, Spain
[b] Instituto de Química Orgánica, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain

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Cinchonidine and cinchonine have been grafted onto pure silica MCM-41. It has been shown that both supported alkaloids are active catalysts for the Michael addition of ethyl 2-oxocyclopentanecarboxylate and methyl vinyl ketone, anchored cinchonidine being more active and enantioselective than anchored cinchonine. The study of the influence of the polarity of the solvent and reaction temperature on the optical induction shows that there is not a direct correlation between solvent polarity and enantioselectivity, and the maximum optical yield was obtained between 278 and 273 K.

KEY WORDS: enantioselective Michael reaction; MCM-41 heterogenized cinchonine; heterogenized cinchonidine; solid chiral base catalyst; enantioselective catalysts.

1. Introduction

The preparation of optically pure compounds is of great interest in the areas of pharmaceuticals [1] and agrochemicals [2], and in the near future the preparation of enantiomerically pure flavors and fragrances [3] and chiral polymers and chiral materials with non-linear optical characteristics [4] will be of increasing importance.

Enantioselective processes transform prochiral starting materials into chiral products under the effect of a chiral auxiliary. This auxiliary can be attached to the substrate molecule, to a stoichiometric reagent (diastereoselective synthesis) or to a catalyst (enantioselective catalysis) [5]. The most convenient and challenging way to produce enantiomerically pure products is by chiral catalysis [6]. From a technical and environmental point of view, immobilized soluble catalysts (heterogeneous catalysts) are often preferable to homogeneous catalysts because of the easy separation of the products from the reaction medium, along with the possibility of recovery and reuse of the catalyst. In fact, nowadays the design of chiral solids able to perform enantioselective catalysis constitutes an important target in chemical synthesis [7]. Two main approaches have been undertaken in order to obtain heterogenized catalysts: polymer-supported [8] and inorganic oxide heterogenized catalysts. Concerning heterogenization on inorganic supports, encapsulation of transition metal complexes inside zeolitic materials [9] and the grafting of ligands onto the silicic wall surface of zeolites [10–12], silica, [13,14] and micelle-templated silicas (MTS) [15,16] have been the preferential ways used in order to produce chiral catalyst for enantioselective reactions such as hydrogenation of prochiral alkenes [10,13], epoxidation reactions [12,15] or asymmetric alkylation of aldehydes with dialkylzincs [14,16–18]. However, if one looks into the field of base catalysis, the number of enantioselective base-catalyzed reactions are scarce. More specifically, Michael additions can be achieved by the use of chiral catalysts and allow the formation of C–C bonds with the potential formation of one or two new chiral centers, producing in such cases one or two pairs of enantiomers. Langstrom and Bergson [19] reported the first example of chiral catalysis for Michael reactions, and following this different chiral catalysts have been investigated in recent years [20,21]. For example, an alanthanum–sodium–BINOL complex has been used in homogeneous phase for catalytic asymmetric Michael reaction of various enones with malonate to give Michael adducts in up to 92% enantiomeric excess (ee) [22]. Chiral crown ethers incorporating a D-glucose unit afforded, in the presence of a base, Michael addition of 2-nitropropane to a chalcone under solid–liquid phase transfer conditions from 65% ee [23] to 90% ee [24].

When chiral monoaza-crown ethers are used, the adduct can reach an ee up to 90% [25]. High turnover numbers have been obtained with chiral crowns complexed with potassium bases for the Michael addition of a β-ketoester to methyl vinyl ketone and of two phenylacetic esters to methyl acrylate, with an optical purity of 60–99% [26]. Cinchona alkaloids have also been used as chiral homogeneous catalysts for the Michael reaction [27], showing that this can be an interesting system. As far as we know, only one attempt has been reported for supported cinchona as catalyst for

* To whom correspondence should be addressed.
E-mail: acorma@itq.upv.es

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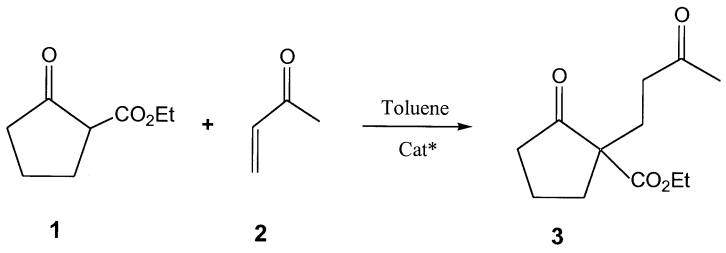


Scheme 1.

the Michael addition of alkyl and aryl mercaptanes to racemic 5-methoxy-2 (5H)-furanone [28]. Unfortunately, the diastereoisomeric excess obtained in this case was moderate (up to 35%).

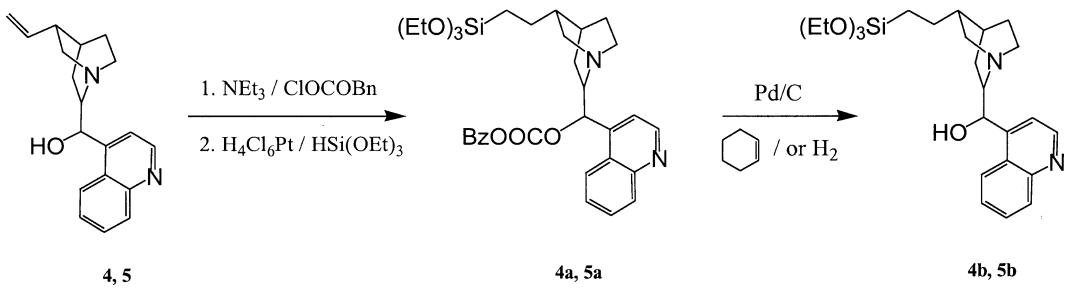
In the present work we report a methodology for the heterogenization of cinchonine and cinchonidine on MCM-41 and their use for the enantioselective Michael addition of ethyl 2-oxocyclopentanecarboxylate (**1**) and methyl vinyl ketone (**2**) (Scheme 1). The influence of the reaction temperature and the amount of catalysts on the optical yield, as well as the comparison of the activity under homogeneous catalysis, will be presented.

2. Experimental

The preparation of heterogenized cinchonine and cinchonidine was carried out according to the following method: $(EtO)_3Si$-intermediates **4b** and **5b** were prepared from cinchonine (**4**) and cinchonidine (**5**) in a three-step sequence as shown in Scheme 2: first, the protection of hydroxyl group of alkaloids as their carbobenzoxy derivative was carried out by reaction with benzyl chloroformate at 273 K in the presence of triethylamine. In the second step, the hydrosilylation of the 10–11 double bond by treatment with an excess of triethoxysilane using a hexachloroplatinic acid–isopropanol complex (0.1 mol%) as catalysts at 433 K for 24 h (yielding **4a** and **5a**) was performed. Finally in the third step the protector group was removed by hydrogenolysis using hydrogen atmosphere or cyclohexene as hydrogen source, in the presence of Pd/C, to give the triethoxysilyl amines **4b** and **5b** (Scheme 2).

A solution of triethoxysilyl amine (**4b**, **5b**) (2×10^{-3} mol) in dry toluene (2 ml) was added to a well-stirred suspension of MCM-41 (1 g) in toluene (50 ml). The mixture was maintained for 24 h at room temperature and refluxed for an additional 6 h or alternatively ultrasound irradiated for 6 h at 333 K. The solid was then filtered, washed successively with toluene and dichloromethane and Soxhlet-extracted with dichloromethane-ethyl ether (1:2) for 16–24 h to remove the remaining non-bonded product. The heterogenized catalysts were thoroughly dried in vacuum and the organic content was determined by elemental C, H, N analysis based on the nitrogen percentages. The samples named as MCM41-4b ((+)cinchonine derivative) and MCM41-5b ((−)cinchonidine derivative) had anchored alkaloid contents of 0.39 mmol/g and 0.43 mmol/g respectively.

In a typical experiment, the Michael reaction between **1** (0.5 mmol/ml) and **2** (1 mmol/ml) was performed in the presence of MCM41-4b (50 mg, equivalent to 2 mol% of anchored cinchonine) with respect to reactant **1** and MCM-41-5b (30 mg, equivalent to 1.3 mol% of anchored cinchonidine) with respect to **1** at 273 K, in a batch reactor using toluene (2 ml) as solvent. The results obtained for the evolution of the reaction with time were monitored by GLC using a 25 m capillary column of cross-linked 5% phenylmethylsilicone, whereas the enantiomeric excess was estimated by GLC using a 30 m γ-cyclodextrin trifluoroacetyl capillary column.



Scheme 2.

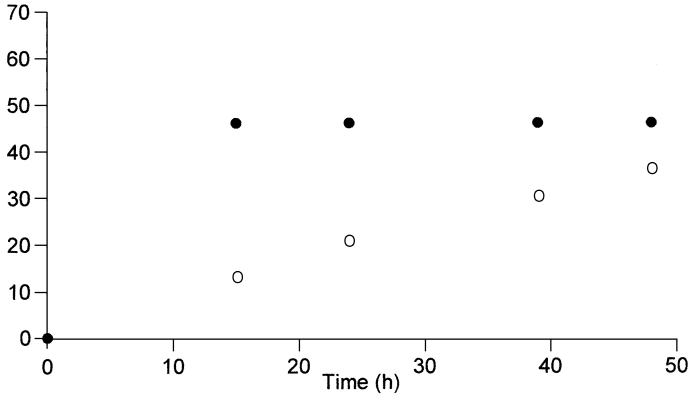


Figure 1. Michael condensation between **1** and **2** using anchored cinchonidine (MCM41-5b)) 1.2%, in toluene as solvent at 273 K. (○) Yield (%) of the Michael adduct (**3**); (●) ee (%).

3. Results and discussion

The reaction between 2-oxocyclopentane carboxylate (**1**) and methyl vinyl ketone (**2**) was performed in the presence of MCM41-4b and MCM41-5b as catalysts in toluene as solvent at 273 K. Results of yields and the enantiomeric excess of the Michael adduct obtained for both catalysts are displayed in figures 1 and 2. As can be seen, the Michael addition promoted by heterogenized cinchonidine (MCM41-5b) (figure 1) took place at a remarkably higher rate than with the grafted cinchonine (MCM41-4b) (figure 2). In fact, the reaction rate per mmol of grafted alkaloid is three times higher for heterogenized cinchonidine, their optical induction (ee = 47%) being sixfold higher than that of MCM41-4b catalyst (ee = 8%). For both catalysts, the ee appears to be independent of the conversion level and remains unchanged with the reaction time, indicating that no racemization of the Michael adduct occurs.

In order to study the effect of the solvent on the optical induction of the catalyst, the reaction between methyl vinyl ketone (**2**) and **1** was carried out in the presence of anchored cinchonidine using solvents with different polarities. The results (table 1) show that higher polarity of the solvent enhances the reaction rate. However, a direct correlation between enantioselectivity and solvent polarity was not observed, achieving the best results when the reaction was performed in the presence of toluene.

For comparison purposes, the reaction between **1** and **2** was carried out in homogeneous phase using cinchonidine and cinchonine as catalysts. The reaction was carried out with 2.4% of alkaloid with respect to reactant **1**, at 273 K using toluene as solvent (2 ml). After 20 h of reaction time the conversion of **1** in the presence of cinchonidine was 98% with ee = 65%, while for cinchonine the conversion was 78% with ee = 28%. These results are comparable with those reported by Brunner and Krumey [27d] in the addition of ethyl 2-oxocyclohexanecarboxylate to acrolein with the same alkaloids. Moreover, these authors found that when additional $Zn(acac)_2$ or $Co(acac)_2$ are used as metal component, the optical induction drops appreciably for cinchonidine but increases slightly for cinchonine [27d,29]. We have observed here that the heterogenization of the bases produces a decrease of conversion and enantioselectivity, which could be due to the existence of interactions between the silanol groups of the support and the alkaloid. Indeed, the IR spectra of the grafted cinchonine and cinchonidine on MCM-41 showed that the typical

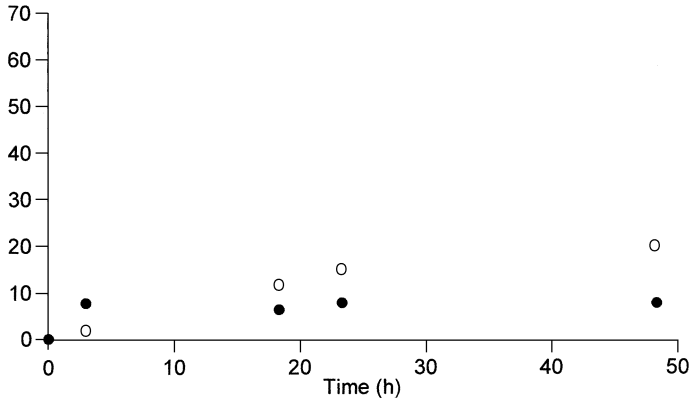


Figure 2. Michael condensation between **1** and **2** using anchored cinchonine (MCM41-4b) 2%, in toluene as solvent at 273 K. (○) Yield (%) of the Michael adduct (**3**); (●) ee (%).

Table 1
Influence of the solvent on the activity and optical induction of the catalyst

Solvent (polarity index)	Reaction time (h)	Chemical yield (%)	Enantioselectivity (% ee)
Hexane (0)	48	72	5
CH_2Cl_2 (3.4)	48	50	17
Toluene (2.3)	48	80	47
MeOH (6.6)	21	96	10

Note: Reaction conditions: ethyl 2-oxocyclopentanecarboxylate (**1**): 1 mmol; methyl vinyl ketone; (**2**): 2 mmol; Catalyst: MCM-41-5b (2.4%); solvent: 2 mL. Reaction temperature: 273 K.

narrow absorption band corresponding to silanol groups (at 3740 cm^{-1}) appears in the final catalysts as a broad band, shifted toward lower wave numbers. This can support the existence of interactions between the Si–OH groups and the grafted organic.

Moreover, the reaction between **1** and **2** was performed in the presence of MCM-41 and free cinchonidine. The experiment was carried out using 2.4% of cinchonidine with respect to **1** and the necessary amount of MCM-41 in order to achieve 0.43 mmol of alkaloid per gram of the inorganic material. Toluene was used as a solvent and the reaction temperature was 273 K. In this case we observed 97% conversion of **1** after 20 h reaction time, *i.e.*, the same result in conversion as that working in the homogeneous phase. However, only ee = 20% was achieved (instead of ee = 65% in the homogeneous reaction in the absence of MCM-41). In an additional experiment we found that under these reaction conditions, 88 wt% of cinchonidine was adsorbed on the MCM-41 surface and only 12 wt% remains as homogeneous in the solvent. The high catalytic activity observed in this case suggests that the interaction of the silanol groups of the MCM-41 should not be through the catalytic site (the tertiary nitrogen of the cinchonidine), while the poor enantiomeric excess obtained suggests that other types of interaction, probably through the free OH group of the cinchonidine, has a negative impact on the enantioselectivity.

Taking into account these results we can assume that when the cinchonidine is grafted onto MCM-41 it is possible that both types of interactions with the Si–OH groups exist, one of them with the active site, and the other with the free OH group of the alkaloid, decreasing the catalytic activity and enantioselectivity with respect to cinchonidine in the homogeneous phase.

When the influence of the amount of supported catalyst on conversion and enantiomeric excess was studied using MCM41-5b as catalyst, we found (figure 3(a)) that when the molar ratio MCM41-5b/**1** is increased from 1.2 to 2.4 the chemical yield increases by a factor of two, while the enantiomeric excess remains practically the same (figure 3(b)). This result, along with those presented above, allows us to conclude that the decrease of turnover observed when heterogenizing cinchonine and cinchonidine on the MCM-41 support is not due to diffusional problems, but should be caused by interaction of the amino group with the surface silanols of the MCM-41 support. Meanwhile, the interaction through the free OH group of the alkaloid should be responsible for the negative effect on enantioselectivity observed with the heterogenized catalysts. These results suggest that the free OH group can interact with the reagents in the transition state, favoring preferentially the formation of one of the two enantiomers.

The MCM41-5b in a molar ratio MCM41-5b/**1** of 2.4 was used to study the effect of the reaction temperature on the chemical and optical yields. We can observe in table 2 that the chemical yield increases with temperature, whereas the enantioselectivity increases when temperature decreases from 288 to 273 K, achieving the maximum optical yield at 278 (48%) and 273 K (47%). This nonlinear behavior of the enantioselectivity with the temperature has been reported previously in other reactions [30].

The influence of the hydroxyl group of the alkaloid molecule on the Michael reaction has been investigated. For this purpose, the heterogenization of the protected precursor **5a** (carbobenzoxy derivative of cinchonidine) has been performed according to the same methodology as previously described (Scheme 2). The organic content of the heterogenized catalytic material (MCM41-5a) determined by elemental analysis was 0.4 mmol g^{-1}.

In order to compare the catalytic behavior of MCM41-5b and MCM41-5a, the reaction between **1** and **2** was carried out under the optimal conditions previously found for the MCM41-5b catalyst (**1**: 1 mmol; **2**: 2 mmol; toluene: 2 ml; molar ratio of catalyst: 2.4; *T*: 273 K). As we can see in table 3, while the reaction rate increases upon protecting the OH group (MCM41-5a), the enantioselectivity decreases with respect to the unprotected catalyst (MCM41-5b), being the opposite enantiomer produced preferentially.

To explain why the reaction rate and conversion increase when protecting the OH group, we have calculated the stability of the different conformations of the cinchonidine and protected cinchonidine using a semiempirical method. [Calculations were performed with the Cerius 2 Visualizer Program, Version 3.8. Molecular Simulations Inc., San Diego, 1999.] The results showed that the most stable conformation of cinchonidine corresponds to the conformation which possesses the tertiary nitrogen of the molecule (the catalytic site), most sterically hindered, while the opposite occurs in the case of the protected cinchonidine, *i.e.*, the most stable conformation possesses a less steric hindrance. These results could explain the difference in catalytic activity for both samples.

On the other hand, the fact that the unprotected cinchonidine exhibits higher enantioselectivity than the protected one strongly supports the hypothesis presented above on the existence of interactions between the free OH group of the alkaloid and the reagents in the

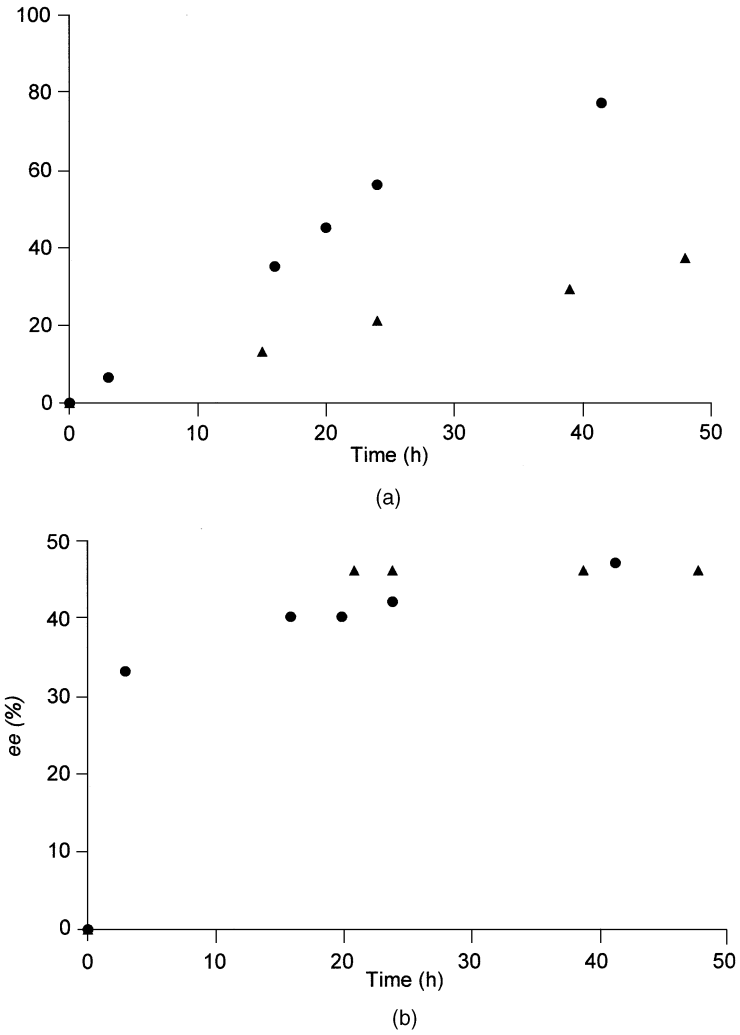


Figure 3. (a) Influence of the MCM-41-5b/**1** molar ratio on the chemical yield of **3** in toluene as solvent at 273 K. (●) MCM41-5b/**1** molar ratio of 2.4; (▲) MCM41-5b/**1** molar ratio of 1.2. (b) Influence of the MCM-41-5b/**1** molar ratio on the enantiomeric excess in toluene as solvent at 273 K. (●) MCM41-5b/**1** molar ratio of 2.4; (▲) MCM41-5b/**1** molar ratio of 1.2.

transition state, which favors preferentially the formation of one of the two enantiomers.

In a similar way as was observed with the unprotected catalyst (MCM41-5b), we have observed that when the hydroxyl groups of cinchonidine are protected, the reaction rate increases with the molar ratio MCM41-5a/**1** but the ee remains unchanged. However, a decrease of temperature leads to a small increase of the enantioselectivity.

Table 2
Influence of the reaction temperature

T (K)	Reaction time (h)	Chemical yield (%)	Enantioselectivity (% ee)
288	30	95	38
278	48	80	48
273	48	80	47
268	48	70	35

Note: Reaction conditions: ethyl 2-oxocyclopentanecarboxylate (**1**): 1 mmol; methyl vinyl ketone (**2**): 2 mmol; catalyst: MCM-41-5b (2.4%); toluene: 2 mL.

In conclusion, cinchonidine has been successfully grafted onto the surface of MCM-41, forming stable basic catalysts that are highly active for the Michael addition of ethyl 2-oxocyclopentanecarboxylate to methyl vinyl ketone. A moderate enantiomeric excess of ~50% has been found. Cinchonine was not only less active for the Michael reaction, but also gave a much lower enantiomeric excess. When protecting the

Table 3
Results obtained with the anchored protected precursor (carboxybenzoxy derivative of cinchonidine) for the Michael addition

Molar ratio MCM41-5a/1	Reaction time and temperature	Chemical yield (%)	Enantioselectivity (% ee)
2.4	25 h at 237 K	99	25
4.8	4 h at 237 K	99	26
4.8	24 h at 263 K	99	33
4.8	24 h at 253 K	99	35

Note: Reaction conditions: ethyl 2-oxocyclopentanecarboxylate (**1**): 1 mmol; methyl vinyl ketone (**2**): 2 mmol; toluene: 2 mL.

hydroxyl group of the heterogenized cinchonidine the catalytic activity increases. However, the enantioselectivity decreases with respect to the unprotected catalyst, while the opposite enantiomer is formed preferentially.

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