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Chiral mesoporous templated silicas as heterogeneous inorganic–organic catalysts in the enantioselective alkylation of benzaldehyde

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Abstract

New mesoporous templated silicas of the MCM-41 family covalently linked to chiral ephedrine are used as heterogeneous chiral auxiliaries in the enantioselective alkylation of benzaldehyde by diethylzinc. Promising results are obtained with these inorganic–organic catalysts. Various factors which may affect the activity, selectivity and enantioselectivity are studied. Comparison with homogeneous catalysis is carried out. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

In the domain of asymmetric carbon–carbon bond forming reactions, the enantioselective addition of organometallic reagents to aldehydes has attracted much attention owing to its application in the synthesis of chiral secondary alcohols.[1–4] Among the various organometallic compounds, diorganozincs act as ideal alkyl donors for catalytic asymmetric alkylation. β-Aminoalcohols are the chiral auxiliaries most commonly used in the catalytic process. Although the mechanism of the reaction has been elucidated in homogeneous catalysis, studies are still in progress in order to generalize the applicability of a chiral auxiliary in the reaction with carbonyl compounds of various reactivities.

Taking into account environmental and economical considerations, the handling of immobilized chiral auxiliaries presents many advantages such as easier separation and recovery from the reaction mixture and thus enhanced recycling possibilities, which are now well established in fine organic synthesis. Some studies deal with the heterogenization of chiral auxiliaries on different polymer supports.[5–7] Beside organic polymers, inorganic materials are a new class of support for the heterogenization of

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homogeneous catalysts.[8] These inorganic supports have many advantages over most polymers because of their superior mechanical and thermal stability.[9] However, no report has appeared to our knowledge since the pioneering work of Soai et al. concerning the immobilization of β-aminoalcohols on alumina and silica gel and their use in the enantioselective addition of dialkylzinc to aldehydes, leading to moderate activities and ees.[10]

The increasing interest focused on supported catalysts led us to study the new mesoporous micelle templated silicas (MTS) as supports. These silicas are different from amorphous silicas due to their regular porosity, consisting of uniformly sized channels with pore diameters within a mesoporous range of 2 to 10 nm.[11] Taking into account their characteristic structure, the insertion and grafting of functional molecules was investigated in our laboratory,[12,13] with the aim of enhancing the turnover frequency through better accessibility to the catalytic sites.

The present work is concerned with the synthesis and characterization of new supported chiral auxiliaries prepared by immobilization of a chiral β-aminoalcohol, the (−)-(1*R*,2*S*)- or (+)-(1*S*,2*R*)-ephedrine, on MTS surfaces and their use in the enantioselective addition of diethylzinc to benzaldehyde. The latter study deals with the influence of the ligand amount, diethylzinc and benzaldehyde concentrations, which are known to affect both the reaction rate and the enantioselectivity, and with the effect of the stirring rate and of the density of chiral modifier at the mineral surface, which are characteristic of heterogeneous catalysis. The results thus obtained using heterogeneous catalysis are compared with those described under homogeneous conditions.

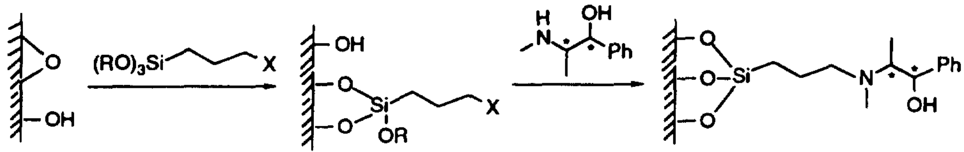
2. Results and discussion

The synthesis and the characterization of the solid chiral auxiliaries containing MTS and the results concerning asymmetric alkylation of benzaldehyde with these solids are described below.

2.1. *Immobilization of ephedrine over MTS: synthesis and characterization of the chiral materials*

2.1.1. *Synthesis of the chiral inorganic–organic materials*

The immobilization of ephedrine over mesoporous MTS type silicas **1** was carried out in two steps (Scheme 1).



1

2a-e

a: R = Me, X = Cl
b: R = Et, X = Cl
c: R = Me, X = I
d: R = Me, X = Cl
e: R = Et, X = Cl

3a-e: (-)-ephedrine
3a': (+)-ephedrine

Scheme 1. Immobilization of (−)- or (+)-ephedrine over mesoporous MTS type silicas

The first step involved the grafting of 3-chloro- or 3-iodopropyltrialkoxysilane (XPAS) onto the surface through Si–O–Si bonds, leading to the solids **2a–c**. Solids **2d** and **2e** were obtained by a basic treatment performed after the grafting of the halogeno functions in order to increase the number of links between the entering silicon atom and the inorganic surface.[14] In the second step, nucleophilic substitution of the

Table 1
Characterization of the chiral inorganic–organic MTS silicas

Grafted XPAS				Grafted chiral ephedrine					
Solids	N_X x 10^3	S (m^2 g^{-1})	V_{mp} (mL g^{-1})	Solids	N_X x 10^3	N_E x 10^3	N_T x 10^3	S (m^2 g^{-1})	V_{mp} (mL g^{-1})
1		801	0.74						
2a	1.4	774	0.41	**3a**	0.6	0.8	1.4	649	0.28
				3a'[a]	0.5	0.8	1.3	650	0.28
2b	1.3	789	0.42	**3b**	0.3	0.9	1.2	631	0.29
2c	1.6	608	0.27	**3c**	0.5	1.1	1.6	311	0.13
2d	1.5	689	0.40	**3d**	0.7	0.7	1.7	618	0.31
2e	1.3	698	0.41	**3e**	0.6	0.9	1.5	570	0.28

[a] (+)-ephedrine

halogen by the basic amino group of (−)- or (+)-ephedrine led to the catalysts **3a–e** or **3a'**, respectively. The excess ephedrine or ephedrine chlorohydrate was removed by accurate washing with methanol.

2.1.2. Characterization of the solid chiral auxiliaries

The solids thus obtained have been characterized by FTIR spectroscopy, thermogravimetry and elemental analyses.[14]

The infrared spectra of solids **3** show aromatic CH stretching vibrations characteristic of immobilized ephedrine.

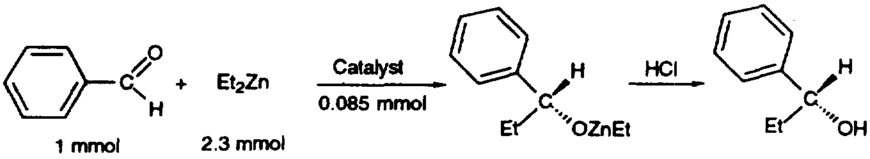
Loadings (mol g^{-1}) of grafted moieties, N_X or N_E, for solids bearing either a halogeno (solids **2a–e**) or an ephedrine function (solids **3a–e** and **3a'**) were calculated from elemental and thermogravimetric data. Both results are in good agreement; the average number obtained is given in Table 1, together with the specific area and mesoporous volume values. Whatever the solid, the substitution of the halogen atom by ephedrine is never quantitative; indeed, halogen moieties remain on the final chiral supported catalysts (Table 1). It is worth noting that conservation of the total number of grafted species is generally observed. Therefore, after modification by ephedrine, the sum of the number of grafted ephedrine N_E and of remaining halogeno moieties N_X is nearly equal to the initial number of grafted coupling halogeno functions. Taking into account this result, we can assume that ephedrine substitutes the halogen atom.

The textural characteristics of these new inorganic MTS supports were determined by nitrogen volumetry; typical adsorption and desorption isotherms (type IV) are obtained.[15] After grafting of the organic functions on the surface, the conservation of the same type of isotherms indicates that the structure of the inorganic surface was maintained after the modification. However, surface areas S (m^2 g^{-1}) and mesoporous volume V_{mp} (mL g^{-1}) decrease with the grafting of halogeno functions as shown by the comparison between the naked support (solid **1**) and any of the inorganic–organic XPAS materials (Table 1). Moreover, the substitution of the halogen by (−)- or (+)-ephedrine leads to another decrease of both surface areas and available mesoporous volumes, particularly for **3c** synthesized by iodine substitution.

2.2. Enantioselective addition of diethylzinc to benzaldehyde

2.2.1. General features

Enantioselective alkylation of benzaldehyde by diethylzinc (Scheme 2) performed using (−)- and (+)-ephedrine and their supported MTS analogues as chiral auxiliaries yields (*R*)- or (*S*)-1-phenylpropan-1-ol via their alcoholates.



Scheme 2. Enantioselective addition of diethylzinc to benzaldehyde

The mechanism (Scheme 3) of this reaction in homogeneous conditions has been established by Noyori et al. according to the results obtained with (−)-3-exo-(dimethylamino)isoborneol (DAIB) as the chiral auxiliary.[3,16] This mechanism generalized to other chiral auxiliaries[17,18] implies the addition of dialkylzinc to the chiral auxiliary which leads to the coordinatively unsaturated catalyst **1**. This complex is in equilibrium with the corresponding dimer. An intramolecular alkyl transfer is proposed to occur via a 4/4-bicyclic transition structure **2** from another Et_2Zn molecule complexed on the Lewis base to benzaldehyde activated by the tricoordinate zinc atom of **1**. The coordination geometry of the zinc atom in the coordinated Et_2Zn molecule serves to increase the nucleophilicity of the alkyl group. The obtained enantiomeric phenylpropanol zinc alcoholates afford, after hydrolysis, the enantiomeric alcohols together with the regenerated catalyst.

This mechanism is in fair agreement with the one proposed by Frechet et al. using DAIB immobilized on polymeric supports as the chiral auxiliary.[19]

Table 2 shows our results using (−)- or (+)-ephedrine immobilized on inorganic MTS. Under standard conditions (8.5 mol%), (*R*)- or (*S*)-1-phenylpropan-1-ol (entry 6 or 7) is obtained with an enantioselectivity equal to 35 or 26%, respectively. Enantioselectivities are moderate but these supported ligands control the sense of the asymmetric induction, (−)-ephedrine leading to (*R*)-phenylpropanol (entry 6) and (+)-ephedrine to the (*S*)-enantiomer (entry 7). Such an effect was previously described in homogeneous catalysis, the configuration of the six-center transition state **2** (Scheme 3) depending on the configuration of the α and β substituents of the chiral auxiliary.[2] The α *S* and β *R* configuration of the chiral auxiliary led to the (*S*)-enantiomer whereas the (*R*)-enantiomer was obtained from the α *R* and β *S* configuration.

A typical reaction obtained with supported (−)-ephedrine is shown in Fig. 1.

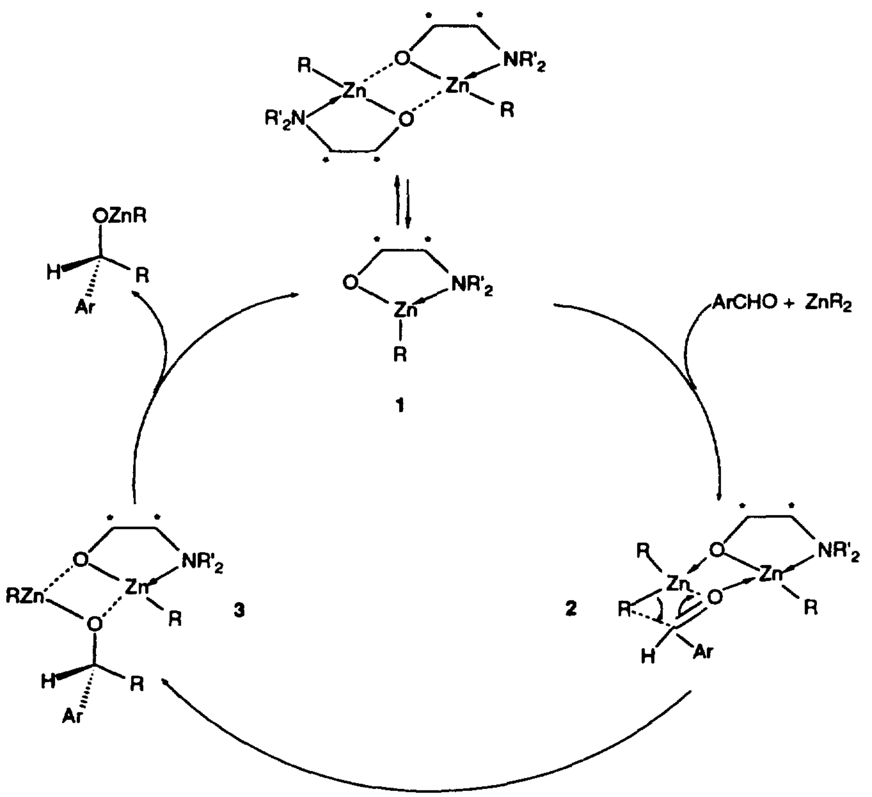
Disappearance of benzaldehyde (BA) leads to the formation of the enantiomeric alcohols together with benzylalcohol ($PhCH_2OH$) as a by-product, as in homogeneous conditions. The initial rate of benzaldehyde disappearance agrees with a competitive mechanism, according to:

$$-\frac{d[BA]}{dt} = \frac{d([R]+[S])}{dt} + \frac{d[PhCH_2OH]}{dt}$$

The initial rate (r_0, Table 2) depicts the rate of formation of the enantiomeric alcohols in each experiment: $r_0 = d([R]+[S])/dt$.

In most cases, the selectivity in enantiomeric alcohols, expressed as:

$$\%\ \text{selectivity} = 100 \times \frac{[R]+[S]}{[R]+[S]+[PhCH_2OH]}$$



Scheme 3. Mechanism of the asymmetric alkylation of aldehydes by diethylzinc in homogeneous conditions

Table 2
Effect of the immobilization of (+)- or (−)-ephedrine on the reaction and sense of the asymmetric induction

Entry	Catalyst	$r_0 \times 10^3$ (mol L^{-1} h^{-1})	Conversion[a] (%)	Selectivity (%)	Configuration	ee[b] (%)
1	without[c]	0.6	28	45	–	0
2	without[d]	1.4	46	51	–	0
3	(-)-ephedrine[d]	180	98	97	R	67
4	MTS[c]	1.7	64	70	–	0
5	**3a**[c]	5.5	89	84	R	37
6	**3a**[d]	11	99	89	R	35
7	**3a'**[d]	15	99	87	S	26

[a] % conversion = $100\ ([BA]_0 - [BA]_t) / [BA]_0$; [b] % ee = $100\ ([R] - [S]) / [R] + [S]$

[c] toluene as solvent; [d] hexane as solvent

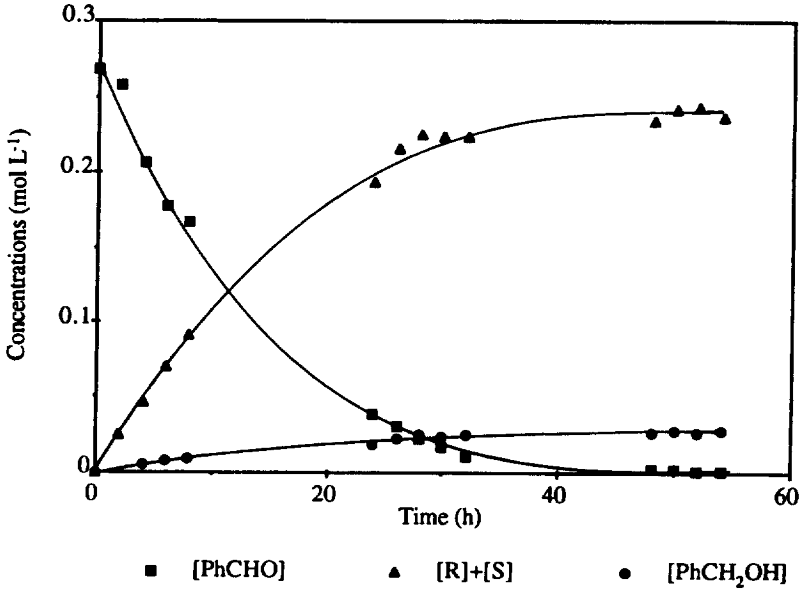
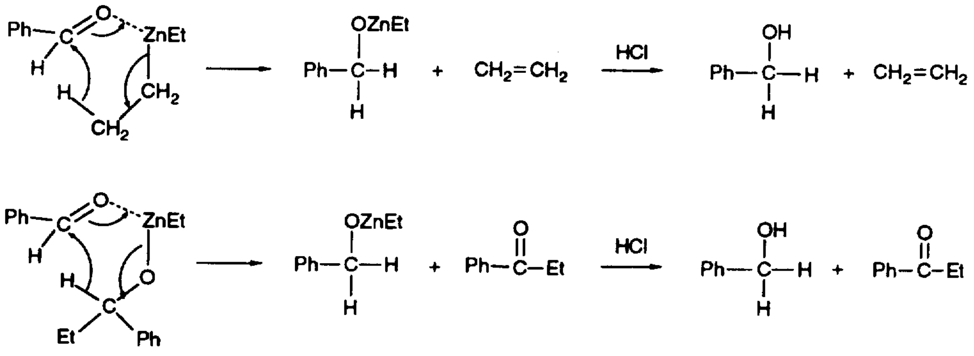


Fig. 1. Evolution of the alkylation of benzaldehyde with time using solid chiral auxiliaries

does not depend on the conversion. This result is explained, as suggested by the rate law, by the formation of benzylalcohol in a competitive way from benzaldehyde reduction by Et_2Zn (Scheme 4).



Scheme 4. Mechanisms of the formation of benzylalcohol

The formation of benzylalcohol in a consecutive way (Meerwein–Pondorf–Verley reduction[20]) would result in a decrease of selectivity with conversion, especially at high conversions (*vide infra* results concerning the effects of the stirring rate and of Et_2Zn concentration) accompanied by the appearance of 1-phenylpropan-1-one (Scheme 4).

At the same time, enantioselectivities are considered as constant all along the reaction. Toluene or hexane have been used as solvents. As previously reported,[21] higher rates and selectivities are obtained in hexane (Table 2, entries 1 and 2 or 5 and 6). Nevertheless, ees are slightly higher in toluene (entries 5 and 6).

Without catalyst and whatever the solvent, the reaction is characterized by low rates r_0 and selectivities (entries 1 and 2). Addition of 8.5 mol% of supported chiral auxiliary (entries 5 and 6) serves to increase the rates and selectivities which indicate that alkyl transfer is favored. However, rates and ees are notably lower than under homogeneous conditions (entry 3). On the other hand, it can be noted that the naked surface (entry 4) enhances the racemic alkyl transfer.

Table 3
Effect of the stirring rate on the reaction

Entry	Stirring rate (rpm)	$r_0 \times 10^3$ (mol L^{-1} h^{-1})	Conversion (%)	Selectivity (%)	ee (%)
1	400	5.5	83	93	40
2	750	5.0	86	87	37
3	1000	4.8	87	76	37

Table 4
Effect of the amount of chiral auxiliary on the reaction

Entry	Weight (g)	n_E (mol %)	$r_0 \times 10^3$ (mol L^{-1} h^{-1})	Conversion (%)	Selectivity (%)	ee (%)
0	0	0	0.6	28	45	0
1	0.111	2.1	1.8	72	53	25
2	0.222	4.2	3.5	70	58	28
3	0.503	9.6	7.5	87	83	38
4	0.889	17.0	13	98	91	41

In order to understand the reasons which affect the catalyst activity, various parameters have been studied affecting both the kinetic and the mechanism of the reaction. They include the effect of the stirring rate, of the amount of chiral auxiliary, of the alkylzinc and benzaldehyde concentrations and of the density of the chiral modifier at the surface of the inorganic support. Results are compared to those described using homogeneous catalysis. Reactions are carried out in toluene as the solvent.

2.2.2. *Effect of the stirring rate*

The effect of the stirring rate has been studied to ensure the absence of external diffusional limitations.[22] The heterogeneous medium was thus stirred at 400, 750 and 1000 rpm, under the standard conditions using solid **3e** as the chiral auxiliary.

The results (Table 3) show that the stirring rate has no effect either on r_0 or on the enantiomeric excess. Thus, in the enantioselective alkylation of BA by Et_2Zn, external diffusion of reactants to the external surface of the solid chiral auxiliary does not seem to be the limiting factor. The decrease of the selectivity observed for the reaction stirred at 1000 rpm can be accounted for by a decrease of Et_2Zn concentration due to the fast stirring rate under a nitrogen flow. Effectively, appearance of phenylpropanone is noticed indicating that formation of benzylalcohol occurs, in this case, in a consecutive way (Scheme 4). Hence, catalytic experiments were performed at a stirring rate of 750 rpm.

2.2.3. *Effect of the amount of chiral auxiliary*

The absence of external diffusional constraints is corroborated by studying the effect of the weight of solid **3d** on r_0 (Table 4). In this case, the amount of chiral auxiliary (percentage n_E) is directly related to the weight of solid.

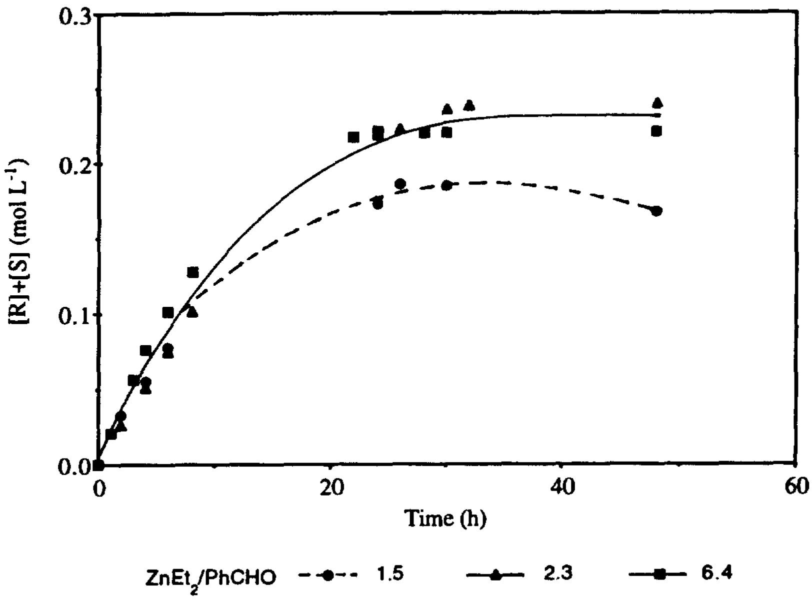


Fig. 2. Effect of the initial concentration of diethylzinc on r_0

Effectively, r_0 increases linearly with the weight of solid and, therefore, with the amount of chiral auxiliary as in homogeneous catalysis.[23] With regards to the selectivity or to the enantioselectivity, it is worth noting that increasing the amount of ephedrine leads to better selectivities and enantiomeric excesses (Table 4). For low weights, the participation of the uncatalyzed reaction is not negligible and selectivities are close to that obtained without catalyst. The latter increase with the ratio of the observed rate to the uncatalyzed rate. Selectivities of the same order of magnitude as in homogeneous conditions are obtained using 17.0 mol% of chiral auxiliary. Under standard catalytic homogeneous conditions,[3,23] the rate of the reaction was shown to be first order in chiral auxiliary concentration (2–25 mmol L^{-1}) using $[BA]_0$=0.3–1.3 mol L^{-1} and $[Et_2Zn]_0$=0.3–1.3 mol L^{-1} in toluene at 0°C. However, an increase in the concentration of the catalyst enhanced the rate but the enantioselectivity remained virtually constant.[2]

2.2.4. *Effect of the concentration of diethylzinc*

While keeping the initial BA concentration constant ($[BA]_0$=0.33 mol L^{-1}) and using the same amount (8.5 mol%) of the grafted auxiliary, the initial Et_2Zn concentration was varied leading to $[Et_2Zn]_0/[BA]_0$ ratios between 1.5 and 6.4 (Fig. 2). Under the conditions used, r_0 does not vary with $[Et_2Zn]_0$, which is characteristic of a zero order.

Fitting of our results with the general first order Eq. 1:

$$-\frac{d[BA]}{dt} = k_{obs}[BA]$$

$$[BA] = [BA]_0 e^{-k_{obs}t} \qquad (1)$$

leads to good correlations between BA concentration and time of reaction indicating global first order kinetics. Taking into account the observed zero order with initial Et_2Zn concentration, we can assume a first order with aldehyde concentration.

Under homogeneous conditions, Noyori et al.[23] reported that when using (−)-DAIB as the chiral auxiliary, the reaction was zero order with aldehyde concentration, in default of Et_2Zn ($[Et_2Zn]_0$=cte=0.33 mol

Table 5
Effect on the reaction of the organic loading on the silica surface

Solid	Density x10^6 (mol m^{-2})	Weight (g)	r_0 x 10^3 (mol L^{-1} h^{-1})	Conversion (%)	Selectivity (%)	ee (%)
3a	1.0	0.385	5.5	84	84	37
3b	1.1	0.364	5.6	87	87	37
3c	1.4	0.262	2.9	61	61	23
3d	0.9	0.445	6.7	87	83	38
3e	1.1	0.374	5.0	86	87	37

L^{-1} and $[BA]_0>0.33$ mol L^{-1}). Nevertheless, a first order was obtained when the reaction was performed in an excess of Et_2Zn ($[Et_2Zn]_0$=cte=0.33 mol L^{-1} and $[BA]_0<0.33$ mol L^{-1}). Concerning the effect of the initial Et_2Zn concentration, the initial rate did not depend on $[Et_2Zn]_0$, in excess of alkylzinc and became first order in default.

Hence, kinetic results for heterogeneous alkyl transfer catalyzed by immobilized ephedrine are in good agreement with those of Noyori et al. showing a first or zero order versus aldehyde or alkylzinc concentration respectively, when excess of Et_2Zn is used.

Decreasing of the $[Et_2Zn]_0/[BA]_0$ ratio leads to a decrease of selectivity at high conversions. When the diethylzinc concentration diminishes, as noticed above at high stirring rate, the formation of benzylalcohol and of phenylpropanone in a consecutive way lowers the phenylpropanol concentration and the selectivity (Fig. 2). Similarly, in homogeneous catalysis, benzylalcohol was observed as the major by-product whose yield increases with a decreasing alkylzinc/benzaldehyde ratio.[2]

The variation of the $[Et_2Zn]_0/[BA]_0$ ratio results in no change in the enantiomeric excess (ee=31±3%) in agreement with results reported in homogeneous media.[2] However, an increase of the enantioselectivity was simultaneously mentioned.[24]

Our results related to kinetics and mechanism are in good agreement with those obtained in homogeneous catalysis. Nevertheless, rates and enantiomeric excesses remain moderate whatever the conditions used. A key point in the comprehensive study of enantioselective heterogeneous catalysis may be the understanding of the role of the various parameters linked to heterogenization of the chiral auxiliaries. With this in mind, it is important to consider the accessibility of the reactants to the chiral molecules grafted on the internal surface of the support.

2.2.5. *Effect of the density of organic ligands on the inorganic surface*

Results obtained with the various chiral inorganic–organic auxiliaries (Table 1) are summarized in Table 5.

The density of grafted ligands on the mineral surface can be expressed by the ratio of their number (mol g^{-1}) to the surface area (m^2 g^{-1}) of the parent MTS (N_E/S mol m^{-2}). Table 5 shows that densities are included between 0.9 and 1.4 mol m^{-2}. A regular decrease of r_0 with such a density is observed. For example, the more loaded solid **3c** presents the lower activity and enantioselectivity; in this case, r_0 is only five times higher than the rate of the reaction without catalyst. Such a solid is characterized by the lowest available mesoporous volume (Table 1). It can then be concluded that the functionalization of the same support leads to heterogeneous chiral auxiliaries whose activity may be related to the accessibility of the catalytic sites.

With regard to the enantioselectivity, except for **3c**, enantiomeric excess does not seem to be correlated with r_0. In heterogeneous enantioselective hydrogenation[25] as in homogeneous asymmetric dihydroxylation,[26] a ligand-accelerated catalysis was noticed; for example, rate accelerations by a factor of 10–100 were observed. In these cases, the ligand efficiency affected both initial rate and enantiomeric purity. In our case, such a lack of correlation can be explained taking into account that the enantioselective alkylation seems to be limited by the accessibility to the chiral catalytic sites. Another assumption could be the participation of the mineral surface to the racemic alkyl transfer. On the one hand, internal diffusion limitation may reduce the accessibility to the catalytic sites; moreover, the proximity of these sites may be responsible for the formation of dimers (Scheme 3) which are relatively stable in homogeneous catalysis.[16] On the other hand, the activity of the inorganic surface can not be discarded compared to the activities of the chiral solids (Table 2). However, the reactions were performed with similar weights of catalysts and therefore, the participation of the uncovered surface would be of the same order of magnitude for all the catalysts. Consequently, the effect of the accessibility and of the proximity of the catalytic sites appears to be of prime importance.

The results we obtained, using a support which is characterized by a regular mesoporosity, are comparable to those previously reported with silica gel as a support.[10] Work is in progress to provide a better internal diffusion of the reactants inside the pores and to study the effect of the inorganic surface on the rates, selectivities and enantioselectivities of the alkylation by diethylzinc.

3. Conclusion

Immobilization of chiral auxiliaries on inorganic mesoporous templated silicas was carried out. New solid auxiliaries were prepared and used in the enantioselective alkylation of benzaldehyde by diethylzinc; as in homogeneous catalysis, the configuration of the chiral auxiliary controls the configuration of the product. In order to increase the efficiency of these new solid auxiliaries and to compare heterogeneous with homogeneous catalysis, various parameters were studied. They include the effect of the stirring rate, of the amount of chiral auxiliary, of diethylzinc and benzaldehyde concentrations and of the density of catalytic sites at the surface. Comparison with homogeneous catalysis shows that various effects are identical (amount of chiral auxiliary, concentrations). The lower rates, selectivities and enantioselectivities obtained in heterogeneous than in homogeneous catalysis are explained either by the participation of the uncovered surface to the racemic alkyl transfer or by a restricted accessibility to the catalytic sites in heterogeneous catalysis, the latter being certainly the most important.

4. Experimental

4.1. Immobilization of ephedrine over MTS

4.1.1. Grafting of XPAS

MTS **1**, prepared following a previously described procedure,[11] was first calcined at 550°C and then activated at 140°C for 16 h. Then, a suspension of freshly activated MTS **1** (1 g) in toluene (10 mL) was refluxed and stirred for 2 h with XPAS (4.2 mmol) under dry nitrogen. After distillation in a Dean–Stark collector of a fraction of toluene containing methanol (or ethanol), the mixture was again heated at toluene refluxing temperature for 2 h and the distillation sequence was repeated. The modified solid was filtered, extracted in a Soxhlet apparatus for 24 h with methanol, then dried at 100°C (solids **2a–e**).

Elemental analysis: **2a**: C 6.75, Cl 5.23%; **2b**: C 7.58, Cl 4.78%; **2c**: C 6.66, I 19.93%; **2d**: C 6.74, Cl 5.45%; **2e**: C 6.22, Cl 4.57%.

4.1.2. Modification of the halogeno function by ephedrine

A suspension of the freshly activated modified solid (solids **2a–e**) (1 g) in xylene (10 mL) was refluxed and stirred with an excess of (−)- or (+)-ephedrine (9.6 mmol) for 6 h. The functionalized solid was filtered, extracted according to the previous procedure, then dried at 100°C (solids **3a–e** or **3a′**).

Elemental analysis: **3a**: C 14.93, Cl 2.43, N 1.15%; **3a′**: C 14.06, Cl 1.96, N 1.06%; **3b**: C 12.98, Cl 0.92, N 1.21%; **3c**: C 17.76, I 4.64, N 1.55%; **3d**: C 13.91, Cl 2.68, N 0.99%; **3e**: C 14.37, Cl 2.06, N 1.16%.

4.2. General procedure for the enantioselective addition of diethylzinc to benzaldehyde by using these supported catalysts

The catalyst (8.5 mol%) was activated at 130°C under vacuum for 16 h. Then, 8 mL of 1.1 M solution of diethylzinc in toluene (or 8.8 mL of 1 M solution of diethylzinc in hexane (2.3 mmol) was added under a nitrogen atmosphere. The resulting mixture was stirred at 0°C for 15 min. Benzaldehyde (1 mmol) was added dropwise in 2 mL of toluene. The reaction mixture was stirred at 0°C. The progress of the reaction was monitored by periodically withdrawing samples which were analyzed by gas chromatography on a chiral capillary column (LIPODEX E) after acidic treatment (HCl 0.5 M, CH_2Cl_2). The final product was analyzed after the same acidic treatment.

In order to study the effect of the diethylzinc concentration, the 1 M solution of diethylzinc in hexane was used. This solution was first diluted and then concentrated by distillation of hexane under a nitrogen atmosphere.

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