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Factors affecting the efficiency of hybrid chiral mesoporous silicas used as heterogeneous inorganic–organic catalysts in the enantioselective alkylation of benzaldehyde

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Abstract

Chiral hybrid organic–inorganic materials were prepared by anchoring optically active β-aminoalcohols such as (−)-ephedrine on MCM-41 type silica as a member of micelle-templated silicas (MTS). Silylation of the surface was performed with halogenopropyltrimethoxysilane. Then, (−)-ephedrine was anchored through halogen substitution. These materials were used as chiral auxiliaries in the heterogeneous enantioselective catalysis of the alkylation of benzaldehyde by diethylzinc. This work deals with the study of the various factors such as accessibility to the catalytic sites and coverage of the inorganic surface, which affect their efficiency (activity, selectivity and enantioselectivity).

1. Introduction

Enantioselective catalysis allows the synthesis of pure enantiomers from prochiral reactants using small amounts of appropriate chiral catalysts. In this domain, heterogeneous catalysis providing supplementary advantages in the easy separation and re-use of the catalysts needs to be developed. Interest in the heterogenization of homogeneous catalysts by covalent linkage to mineral supports has been growing in the recent years.[1,2] The stability of the modified material is improved if covalent links are used in the immobilization process. Mineral supports generally possess higher mechanical resistance than organic polymers and are quite insoluble in almost all solvents. Moreover, porous metal oxides feature higher accessible surface areas than polymeric fibers. Hence, we have developed the synthesis of hybrid organic–inorganic materials based on the functionalization of the new mesoporous templated silicas (MTS). These MTS, which are characterized by a regular mesoporosity are efficient in base

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catalysis[3,4] or in monoglyceride synthesis,[5] when modified by covalent grafting of basic functions. They can be used for immobilization of transition-metal complexes.[6] Nevertheless, studies are scarce in the domain of enantioselective catalysis.[7,8]

In the domain of carbon–carbon bond forming reactions, the model reaction we have chosen is the enantioselective alkylation of benzaldehyde by diethylzinc. This well-known reaction in homogeneous catalysis is catalyzed by chiral β-aminoalcohols such as (−)-ephedrine. Heterogeneous chiral auxiliaries obtained by grafting (−)-ephedrine on MTS surface characterized by an initial pore diameter of 36 Å present an interesting efficiency.[8] However, they demonstrate lower activity and lower enantioselectivity than (−)-ephedrine in homogeneous catalysis. Results may be compared with those obtained by Soaï et al.[9–11] whose work dealt with hybrid chiral auxiliaries synthesized from silica gel as support. Similar trends as in homogeneous catalysis (amount of chiral auxiliary, diethylzinc and benzaldehyde concentrations) were observed.[8] Therefore, the lower rates, selectivities and enantioselectivities obtained in heterogeneous rather than in homogeneous catalysis may result from either a restricted accessibility to the catalytic sites or from the participation of the uncovered surface to the racemic alkyl transfer in heterogeneous catalysis.

The aim of this work was to analyze the main factors that govern the efficiency of these new chiral inorganic–organic auxiliaries. In this respect we investigated the effect of the mesopore size and of the density of the chelating aminoalcohol moieties on the activity and enantioselectivity. On the other hand, the modification of the chemical nature of the surface was performed in order to highlight the role of the intrinsic nature of the support.

2. Results

2.1. Synthesis and characterization of chiral inorganic–organic MTS auxiliaries

2.1.1. Inorganic supports

Two MTS samples (MTS-1 and MTS-2), possessing different textural characteristics, were used as supports in order to synthesize heterogeneous chiral auxiliaries. MTS-1 features a pore diameter of 36 Å estimated from the ratio 4V/S (V=mesoporous volume, S=surface area). The pore size of this material is similar to that of the MTS support used in a previous work[8] but the wall thickness is slightly higher (12 and 10 Å, respectively). MTS-2 is characterized by a larger mesoporosity (52 Å) with a 10 Å wall thickness. The textural characteristics of the two samples are reported in Table 1.

2.1.2. Synthesis of the hybrid materials

Covalent immobilization of ephedrine over mesoporous MTS surfaces was carried out in two steps (Scheme 1). The first step involved the covalent grafting of a coupling halogeno function by silylation. In a second step the substitution of the halogen by (−)-ephedrine was performed.

Conventional grafting of 3-halogenopropyltrialkoxysilane (XPAS, X=Cl, I) on the supports led to the hybrid materials MTS-1-Cl, MTS-1-I, MTS-2-Cl. After reaction with (−)-ephedrine, the heterogeneous chiral auxiliaries, MTS-1-Cl-E, MTS-1-I-E, MTS-2-Cl-E, were obtained (Scheme 1). Excess ephedrine or ephedrine chlorohydrate were removed by washing with methanol.

Taking into account the possibility of formation of dimers between two catalytic sites,[8] the density of anchored (−)-ephedrine was decreased by the competitive grafting on MTS-1 and MTS-2 of the coupling XPAS agent with an unfunctionalized ethyl trialkoxysilane, $CH_3CH_2Si(OR)_3$, used as diluent. Solids

Table 1
Effect of the support on the loading of grafted functions and on the texture of the hybrid materials before and after treatment with (−)-ephedrine

Inorganic MTS supports

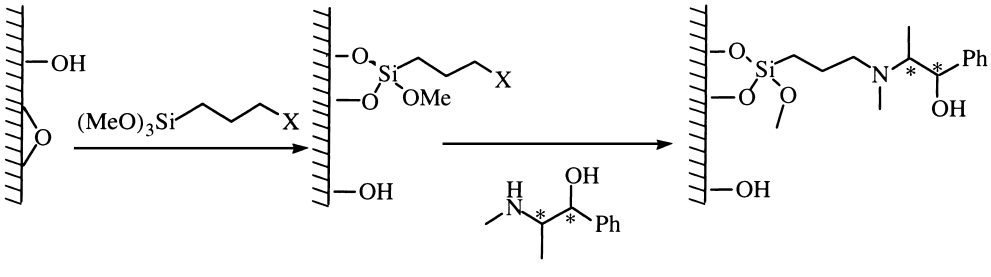
Solids	S ($m^2\ g^{-1}$)	Vmp ($mL\ g^{-1}$)	4V / S (Å)
MTS-1	626	0.56	36
MTS-2	853	1.1	52

Hybrid MTS with halogeno moieties

Entry	Solids	N_X x10^3 (mol g^{-1})	d_X x 10^6 (mol m^{-2})	S ($m^2\ g^{-1}$)	Vmp ($mL\ g^{-1}$)
1	MTS-1-Cl	1.0	1.6	623	0.34
2	MTS-1-I	1.0	1.6	578	0.24
3	MTS-2-Cl	1.3	1.5	680	0.66

Hybrid MTS after nucleophilic substitution by (–)-ephedrine

Entry	Solids	N_X x10^3 (mol g^{-1})	N_E x10^3 (mol g^{-1})	N_T x10^3 (mol g^{-1})	d_E x 10^6 (mol m^{-2})	S ($m^2\ g^{-1}$)	Vmp ($mL\ g^{-1}$)
4	MTS-1-Cl-E	0.4	0.6	1.0	1.0	556	0.27
5	MTS-1-I-E	0.1	0.9	1.0	1.4	393	0.16
6	MTS-2-Cl-E	0.5	0.8	1.3	0.9	600	0.53

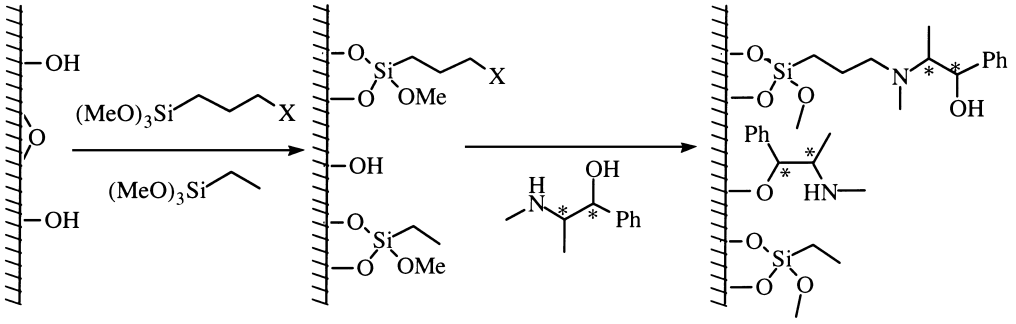


MTS-1 **MTS-1-Cl** (X = Cl) **MTS-1-Cl-E**
MTS-1-I (X = I) **MTS-1-I-E**

MTS-2 **MTS-2-Cl** (X = Cl) **MTS-2-Cl-E**

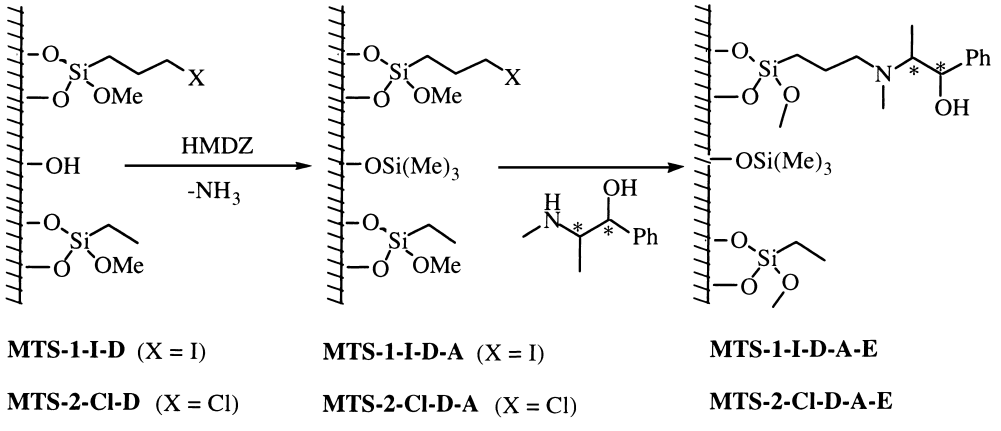
Scheme 1. Covalent grafting of (−)-ephedrine on the surface of various MTS

MTS-1-I-D and MTS-2-Cl-D were obtained; D stands for diluent. These solids were then reacted with (−)-ephedrine to give MTS-1-I-D-E and MTS-2-Cl-D-E (Scheme 2).



Scheme 2. Dilution of the chiral aminoalcohol moieties by competitive grafting

End-capping of MTS-1-I-D and MTS-2-Cl-D was performed with hexamethyldisilazane (HMDZ) before halogen substitution by (−)-ephedrine according to Scheme 3. The solids thus obtained (MTS-1-I-D-A and MTS-2-Cl-D-A where A stands for HMDZ) were treated with (−)-ephedrine to give MTS-1-I-D-A-E and MTS-2-Cl-D-A-E (Scheme 3).



Scheme 3. Surface passivation by HMDZ treatment

2.1.3. Characterization of the hybrid materials

The loadings of grafted moieties versus gram of dried solid, N_X and N_E (mol g^{-1}), corresponding either to an halogeno or to an ephedrine function, were determined by elemental and thermogravimetric analyses. Results are in fairly good agreement and average values were done. The density of functions, d_X or d_E (mol m^{-2}), was expressed by the ratio of their loading (mol g^{-1}) to the surface area (m^2 g^{-1}) of the parent MTS. Porous texture was controlled by nitrogen volumetry; results are summarized in Tables 1 and 2.

The loading in halogenopropylsilane varies between 0.9–1.0 and 1.3×10^{-3} mol g^{-1} (Table 1) depending on the support, MTS-1 (entries 1 and 2), or MTS-2 (entry 3). This difference results mainly from the

surface area value of the corresponding parent MTS because densities are nearly the same ($1.5–1.6\times10^{-6}$ mol m^{-2}).

When silylation is performed with XPAS alone, the sum after substitution by (−)-ephedrine ($N_T=N_E+N_X$) of the loadings of grafted ephedrine (N_E) and of remaining halogeno moieties (N_X) is nearly equal to the initial number of grafted coupling halogeno functions, whatever the surface. On the contrary, when diluents are present on the support (Table 2), the total loading, N_T, is higher than the initial loading in halogenopropyl chains, N_X (compare entries 1 and 5 or entries 3 and 7, Table 2). The excess of (−)-ephedrine can be calculated (Table 3) considering that the difference between the loadings in halogeno functions before and after reaction with (−)-ephedrine corresponds to ephedrine loading performed through halogen substitution (N_{EN}). Then, we assume that the difference (N_E-N_{EN}) between the total number of amino functions (N_E) as indicated by analyses and N_{EN} gives the ephedrine loading performed by direct anchorage on the silica surface (N_{EO}).

Table 2
Characterization of the hybrid materials obtained after dilution of the chiral aminoalcohols and after passivation of the mineral surface

Hybrid MTS with halogeno moieties

Entry	Solids	N_X x 10^3 (mol g^{-1})	d_X x 10^6 (mol m^{-2})	S (m^2 g^{-1})	Vmp (mL g^{-1})
1	MTS-1-I-D	0.5	0.8	565	0.30
2	MTS-1-I-D-A	0.4	0.6	507	0.24
3	MTS-2-Cl-D	0.4	0.5	652	0.69
4	MTS-2-Cl-D-A	0.4	0.5	549	0.55

Hybrid MTS after nucleophilic substitution by (–)-ephedrine

Entry	Solids	N_X x 10^3 (mol g^{-1})	N_E x 10^3 (mol g^{-1})	N_T x 10^3 (mol g^{-1})	d_E x 10^6 (mol m^{-2})	S (m^2 g^{-1})	Vmp (mL g^{-1})
5	MTS-1-I-D-E	0.1	0.6	0.7	1.0	533	0.27
6	MTS-1-I-D-A-E	0.1	0.3	0.4	0.5	511	0.25
7	MTS-2-Cl-D-E	0.3	0.4	0.7	0.5	571	0.59
8	MTS-2-Cl-D-A-E	0.3	0.2	0.5	0.2	546	0.55

End-capping of the MTS-1-I-D surface by HMDZ totally prevents the direct anchorage of (−)-ephedrine. This treatment only reduces such a reaction on the MTS-2-Cl-D surface (Table 3).

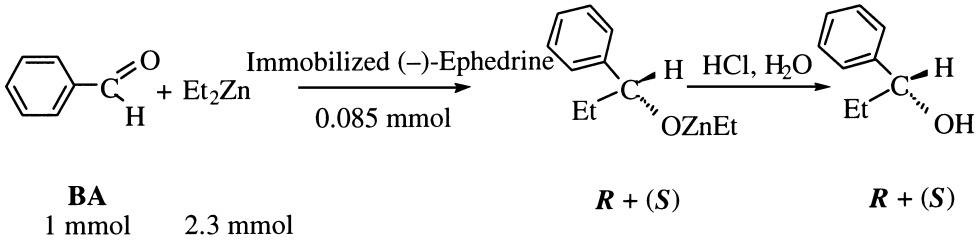
Nitrogen adsorption isotherms of the MTS samples, either naked supports or after silylation and reaction with (−)-ephedrine, feature type IV isotherms according to the IUPAC classification, characteristic of these mesoporous silicas. The functionalized MTS show significant decrease of both surface areas, S (m^2 g^{-1}) and mesoporous volume, V_{mp} (mL g^{-1}) compared to those of the parent MTS (Tables 1 and 2). It should be noted that substitution of the halogen by (−)-ephedrine leads to another decline of both surface areas and available mesoporous volumes. As expected, residual volumes accessible to nitrogen molecules are higher for hybrid materials obtained from MTS-2 than from MTS-1 supports.

Table 3
Direct immobilization of (−)-ephedrine on the MTS supports

Entry	Solids	N_{EN} x 10^3 (mol g^{-1})	d_{EN} x 10^6 (mol m^{-2})	N_{EO} x10^3 (mol g^{-1})	d_{EO} x 10^6 (mol m^{-2})	Excess of ephedrine %
1	MTS-1-I-D-E	0.4	0.6	0.2	0.3	33
2	MTS-1-I-D-A-E	0.3	0.5	0.0	0.0	0
3	MTS-2-Cl-D-E	0.1	0.1	0.3	0.4	75
4	MTS-2-Cl-D-A-E	0.1	0.1	0.1	0.1	50

2.2. Enantioselective addition of diethylzinc to benzaldehyde

Enantioselective alkylation of benzaldehyde (BA) with diethylzinc is usually carried out in apolar solvents; in this work hexane was used. BA (0.0038 mol) was reacted with an excess of diethylzinc ([Et_2Zn]/[BA]=2.3) in a total volume of 11.4 mL (Scheme 4). Reactions were always performed with the same amount of solid chiral auxiliary (8.5 mol%, relative to BA) whatever the hybrid material used.



Scheme 4. Enantioselective addition of diethylzinc to benzaldehyde

Results previously reported showed that heterogeneous chiral auxiliaries synthesized from a support analogous to MTS-1 are efficient in the enantioselective alkyl transfer.[8] Disappearance of benzaldehyde leads to the formation of the enantiomeric alcohols together with benzylalcohol ($PhCH_2OH$) as a by-product, as in homogeneous catalysis (Scheme 4). The initial rate of benzaldehyde disappearance (r_0) agrees with a competitive mechanism,[8] according to Eq. 1.

$$r_0 = -\frac{d\,[BA]}{dt} = \frac{d\,([R] + [S])}{dt} + \frac{d\,[PhCH_2OH]}{dt} \quad (1)$$

The initial rate of formation of the enantiomeric alcohols is given by Eq. 2.

$$\frac{d\,([R] + [S])}{dt} = r_0 \times \%\ \text{selectivity} \quad (2)$$

Taking into account that the mass of solid chiral auxiliary was adjusted in order to keep its concentration constant (8.5 mol%), the activity of the catalyst was expressed by the initial rate of BA disappearence per gram of solid (r_0/m). As shown previously, under our standard conditions, external diffusion limitation was avoided.

In order to highlight the respective effects of the immobilized chiral auxiliary and of the surrounding achiral chains and achiral surface, we have investigated the catalytic behavior of the halogenopropyl hybrid or naked materials. In this case, average weight of solids was used. Results are summarized in Table 4.

Table 4
Heterogeneous alkylation of benzaldehyde by diethylzinc

Entry	Solid	Activity x 10^4 (mol $h^{-1}g^{-1}$)	Selectivity[a] %	Enantioselectivity[b] %	d_E x 10^6 (mol m^{-2})
1	MTS-1	14.5	88	0	
2	MTS-1-Cl	9.6	82	0	
3	MTS-1-Cl-E	6.5	86	28	1.0
4	MTS-1-I-E	3.8	84	33	1.4
5	MTS-1-I-D-E	5.4	85	26	1.0
6	MTS-1-I-D-A-E	4.3	89	33	0.5
7	MTS-2-Cl	21	77	0	
8	MTS-2-Cl-E	12	93	28	0.9
9	MTS-2-Cl-D-E	10.2	91	14	0.5
10	MTS-2-Cl-D-A-E	6.7	89	14	0.2

[a] % selectivity = 100 ([*R*] + [*S*]) / ([*R*] + [*S*] + [$PhCH_2OH$]),

[b] % ee = 100 ([*R*] - [*S*]) / [*R*] + [*S*]

Under the same conditions, MTS-1, MTS-1-Cl (Table 4, entries 1 and 2) and MTS-2-Cl (entry 7) are more active than MTS-1-Cl-E and MTS-2-Cl-E, respectively (entries 3 and 8). Moreover, the naked MTS-1 surface presents a higher activity than MTS-1-Cl. Whatever the initial pore diameter, the activity decreases with the substitution of chlorine by ephedrine (compare entries 2 and 3 for MTS-1 and 7 and 8 for MTS-2). Activities of the heterogeneous chiral auxiliaries are shown on Fig. 1.

Enantiomeric excesses are of the same order of magnitude (28%, Table 4, entries 3 and 8) for the higher degree of functionalization of the surface from chlorine substitution, whatever the support MTS-1 or MTS-2. Dilution of the catalytic sites by competitive grafting with unfunctionalized chains leads to a decrease of ees from 33 to 26% (MTS-1-I-E and MTS-1-I-D-E, Table 4, entries 4 and 5) and from 28 to 14% (MTS-2-Cl-E and MTS-2-Cl-D-E, Table 4, entries 8 and 9). Passivation of MTS-1 or MTS-2 surfaces by HMDZ results in a slight increase in the former case from 26 to 33% (entry 6) and in no effect in the latter (14%, entry 10).

3. Discussion

(−)-Ephedrine covalently grafted on MTS possessing pores of 36 Å diameter revealed enantioselective activity as heterogeneous chiral auxiliaries in the asymmetric transfer of the ethyl group from diethylzinc to benzaldehyde.[8] Kinetic results were in good agreement with those established in homogeneous catalysis.[12] However, enantiomeric excesses were moderate and rates much lower than in homogeneous catalysis. In many of modified materials, only fractions of the surface-bound ligands were found to interact with targeted metal ions. In the case of silica gels, despite their high surface area, their small and irregular pore structure limits access to the grafted ligands.[13] The drawbacks associated with the irregular

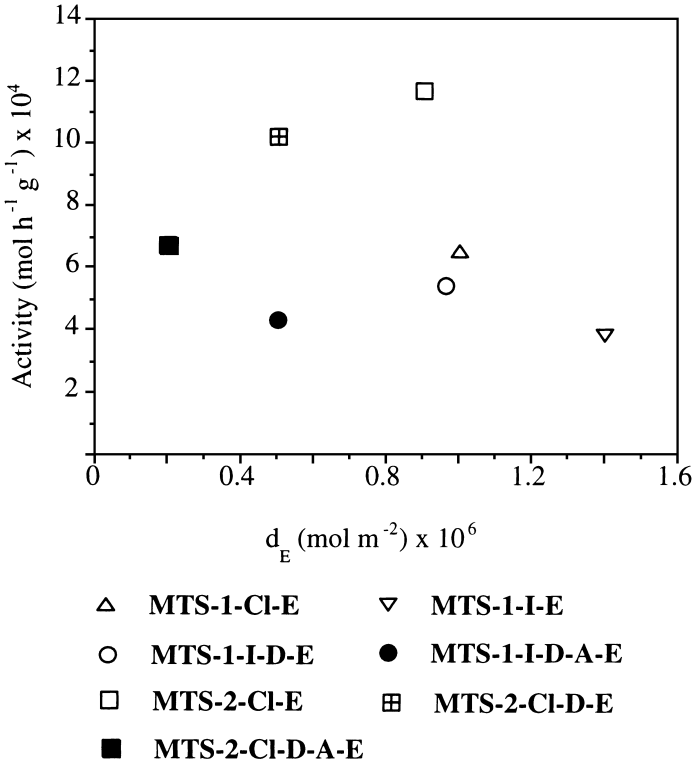


Figure 1. Activity as a function of the density of the chiral aminoalcohol auxiliary

texture and heterogeneous chemical nature of silica gel can be overcome by the use of MTS as supports. Indeed, the major interest of MTS materials concerns their monodisperse pore size depending on the synthesis conditions. Varying the initial pore diameter from 36 Å (MTS-1) to 52 Å (MTS-2) gave access to the effect of internal diffusion. The proximity of catalytic sites was controlled by competitive grafting of an alkyl function on MTS-1 and MTS-2. The effect of the uncovered mineral surface on activities and enantioselectivities was investigated through its modification by end-capping with hexamethyldisilazane.

3.1. Synthesis and characterization of chiral inorganic–organic MTS auxiliaries

Functionalization of MTS supports with 3-halogenopropylsiloxanes was achieved according to a silylation process. The mechanism of such a process, performed in an aprotic and anhydrous solvent, was previously established by different ways using ^{13}C and ^{29}Si MAS NMR, microcalorimetric and polarity measurements.[14–16] These different studies agree with a grafting taking place mainly on the hydrophobic portion of the MTS surface. Hence, the uncovered surface features hydrophilic properties. The presence of such an uncovered surface can affect the selectivity of the halogen substitution by (−)-ephedrine.

3.1.1. Nature and number of organic moieties

Tables 1 and 2 show that, whatever the solid, the substitution of the halogen atom by (−)-ephedrine is never quantitative. Some halogen moieties remain on the final materials. The densities of halogeno or amino functions (mol m^{-2}) are of the same order of magnitude for the various supports (Table 1). When a high degree of functionalization is performed (Table 1), conservation of the total number of organic moieties after reaction with (−)-ephedrine leads to the assumption that (−)-ephedrine substitutes the

halogen atom. The dispersion of grafted aminoalcohols favors the direct immobilization of (−)-ephedrine (Scheme 2). Therefore, when diluents are present on the support, the protection of the inorganic surface seems to be less effective due to the shorter organic ethyl chain or due to the absence of the halogen atom which can generate some interactions with the surface.[17]

3.1.2. Texture of the inorganic–organic materials

The textural characteristics of these new supported MTS catalysts, determined by nitrogen volumetry,[18] show that the structure of the inorganic surface was maintained after grafting of the organic functions on the surface and after passivation. A regular mesoporosity is preserved.

3.2. Enantioselective addition of diethylzinc to benzaldehyde

The mechanism of the alkylation implies the complexation of diethylzinc by the chiral auxiliary which leads to the catalyst with elimination of ethane.[8] Then, ethyl transfer is proposed to take place between another molecule of diethylzinc and benzaldehyde which are activated by adsorption on the nitrogen or zinc atoms of the catalyst, respectively. Our results show that the enhancement of the initial rate with the available mesoporous volume is not accompanied by an increase of the enantiomeric excess (Table 4). Therefore, the effect of the internal diffusion of the reactants to the catalytic sites, which would defavor the enantioselective catalysis, may be questioned.

3.2.1. Activities and selectivities

It is noteworthy that solids possessing immobilized (−)-ephedrine are always less active than the parent halogeno hybrid materials and more less active than the pure silicic MTS surface (Table 4). That demonstrates the efficiency of the unfunctionalized surface in the racemic alkyl transfer. The formation of benzylalcohol as a by-product proceeds in a competitive way and selectivities increase with activities certainly by a lower participation of the uncatalyzed reaction.[8] Thus, activity does not appear to be correlated with the amount of chiral auxiliary and an expected ligand-accelerated catalysis[8] is not evidenced. The uncovered surface of the hybrid MTS-2 solid appears to be more active than the corresponding MTS-1 one (entries 2 and 7, Table 4).

This higher efficiency would explain the generally highest activity of the MTS-2 series compared to the MTS-1 series, whatever the density of catalytic sites (Fig. 1). For the same support, substitution of chlorine by (−)-ephedrine is accompanied by a decrease in the activity and it can be noticed that the ratio ($6.5\times10^{-4}/9.6\times10^{-4}$ and $12\times10^{-4}/21\times10^{-4}$) of the overall activity of the solid (MTS-1-Cl-E or MTS-2-Cl-E) to the activity of the corresponding surface before modification by (−)-ephedrine (MTS-1-Cl or MTS-2-Cl) is of the same order of magnitude, 0.7 and 0.6, respectively. Moreover, a spacing of the sites by competitive grafting of an alkyl function, which can reduce the formation of dimers, leads to comparable activities than for the solids without spacing, either slightly higher (MTS-1-I-D-E) or slightly lower (MTS-2-Cl-E).

The larger the uncovered surface, the higher the activity of the corresponding solid. Hence, these results are totally in agreement with the competitive participation of the silicic surface to the overall catalytic activity. This assumption is consistent with the preservation of the hydrophilic portion of the MTS surface during the silylation process in anhydrous conditions. The passivation of the remaining mineral surface by trimethylsilylation[19–21] may result in the modification of its hydrophilicity, which governs the adsorption of polar molecules, and which depends on the concentration of surface silanol groups.[19] The HMDZ treatment of the surface leads to a subsequent decrease of the activity. This decrease with the progressive covering of the surface is again consistent with the direct involvement of the uncovered surface in the

activity. The effect of end-capping is higher for the MTS-2 (entries 9 and 10) than for the MTS-1 solid (entries 5 and 6), probably because the intrinsic activity of the silicic surface of MTS-2 is higher than that of MTS-1. In fact, passivation of silanols of MTS by HMDZ is never complete as shown by quantitative measurement of $\%Q_3$ species type silicon.[16]

3.2.2. Enantioselectivities

The same enantioselectivities are obtained using MTS-1-Cl-E or MTS-2-Cl-E whose overall activity is very different (Table 4, entries 3 and 8) but for which the participation of the surface to the overall activity is of the same order of magnitude (0.7 and 0.6, respectively, vide supra). Thus, the values of ees when chiral auxiliaries are supported on a mineral surface reflect the role of the uncovered surface in the catalysis of the racemic alkyl transfer. Similar effects are obtained by the progressive covering of the surface by organics when a same support is used. For example, for MTS-1, the easier substitution of iodine than chlorine by (−)-ephedrine leads to a higher density of (−)-ephedrine in the former case than in the latter, 1.4 versus 1.0 mol m^{-2}, respectively, which is accompanied by a decrease of the enantiomeric excess from 33 to 28% (Table 4, entries 4 and 3). In the same manner, the presence of unfunctionalized alkyl chains and the concomitant decrease of the density of grafted (−)-ephedrine from 1.4 to 1.0 mol m^{-2} results in a decrease of the enantiomeric excess from 33 to 26% for MTS-I-E and MTS-I-D-E, respectively (Table 4, entries 4 and 5). A similar result is obtained with the MTS-2 support. Decrease of the density of (−)-ephedrine from 0.9 to 0.5 mol m^{-2}, without and with dilution of the catalytic sites, respectively, leads to a decrease of ee from 28 to 14% (Table 4, entries 8 and 9). Thus, we assume that the increase of ees with the density of (−)-ephedrine results from a lower effect of the surface. Hence, the effect of the passivation by HMDZ treatment (Table 4, entries 5 and 6) and the grafting of trimethylsilyl groups (Scheme 3) results in an increase of ee from 26 to 33%. However, considering the MTS-2-Cl-D-E and MTS-2-Cl-D-A-E chiral auxiliaries (Table 4, entries 9 and 10), passivation which leads to a diminution of the catalyst activity does not allow us to obtain a better enantioselectivity.

In this case as for the MTS-1 support, we showed that an excess of ephedrine is observed when dilution is performed, explained by a grafting of ephedrine directly on the surface (Table 3). Taking into account that in homogeneous conditions, the catalytic site is formed via a zinc alcoholate obtained by reaction of the hydroxyl group of (−)-ephedrine with diethylzinc, the role of the hydroxyl function is of prime importance[12] in the obtention of good ees. If this function is involved in the link with the support, the amount of efficient (−)-ephedrine decreases strongly leading to lower ees. MTS-2-Cl-D-E and MTS-Cl-D-A-E, for which the excess of (−)-ephedrine amounts to 75 and 50%, respectively (Table 3), conduce to low ees (14%). Therefore, we suggest that ephedrine reacts with the surface leading to (−)-ephedrine bound by the hydroxyl function (Scheme 2).

Thus, ees are determined both by the effect of the mineral surface and by the amount of efficient (−)-ephedrine,[8] the former being of prime importance.

4. Conclusion

Heterogeneous chiral auxiliaries were prepared by covalent immobilization of (−)-ephedrine on MTS surfaces. They were used in the enantioselective alkylation of benzaldehyde with diethylzinc which was chosen as the model reaction of carbon–carbon bond formation. The characteristics of these new auxiliaries were modulated either by changing the support (pore diameter, passivation with hexamethyldisilazane) or by dilution of the catalytic sites. Whatever the auxiliary, the enantioselectivities do not appear to depend on the activities and remain moderate. These results are explained by the activity

of the naked surface towards the formation of racemic alcohols. They show that the accessibility to the surface was increased when dilution was performed, leading to the grafting of (−)-ephedrine directly on the surface and that passivation by trimethylsilylation was insufficient to prevent the formation of racemic alcohols. Work is in progress to understand the role of the naked surface.

5. Experimental

5.1. General

Benzaldehyde was purchased from Aldrich and maintained on basic alumina under an argon atmosphere in order to eliminate traces of benzoic acid. Diethylzinc was supplied by Aldrich and used without further purification. Elemental analyses were performed at the Service Central d'Analyses du CNRS in Solaize. Thermogravimetric measurements were carried out on a Seratam SF 85 balance under air flow (20 mg samples heated up to 1123 K at 5 K min^{-1}). Textural properties have been determined by N_2 sorption at 77 K in a Micromeritics ASAP 2000 apparatus.

5.2. Preparation of MTS

5.2.1. Synthesis of MTS-1

MTS-1 was prepared following a procedure derived from Mobil's original method.[22–24] Zeosil 175 MP (70 g, 1.13 mol) of precipitated silica (Rhône–Poulenc) was added to a stirred (at 343 K) solution of cetyltrimethylammonium bromide (Aldrich) (17.5 g, 0.048 mol) and sodium hydroxide (4.9 g, 0.1225 mol) in deionized water (238 g). The mixture was then heated in a mechanically stirred autoclave at 393 K under autogeneous pressure for 16 h. The solid phase was then filtered, washed with deionized water (until pH 7) and then with ethanol. The solid was then dried at 353 K in air. Calcination at 853 K in flowing air for 8 h allowed the elimination of the organic template.

5.2.2. Synthesis of MTS-2

MTS-2 was prepared following a previously described procedure[25] by addition of sulfuric acid (0.3 M) to a stirred solution of Zeosil 175 MP precipitated silica (Rhône–Poulenc, 0.17 weight% Al) (10.5 g, 0.17 mol) and sodium hydroxide (3.3 g, 0.08 mol) in deionized water (24 mL). The resulting mixture was stirred at room temperature for 10 min. Then, a solution of cetyltrimethylammonium bromide (33.7 g, 0.092 mol) in deionized water (112 mL) was added and stirring was performed for 30 min. After an addition of mesitylene (Aldrich) (0.139 mol, 16.7 g) and deionized water (40 mL) the mixture was stirred at room temperature during 18 h and then heated in a autoclave at 388 K for 6 days. After filtration and washing with deionized water to pH 7 and then with ethanol, the solid phase was dried at 353 K. The occluded organic template was decomposed by calcination at 853 K in flowing air for 8 h.

5.3. Functionalization of MTS

5.3.1. Grafting of XPAS

MTS was activated under vacuum at 413 K for 16 h. Then, a suspension of freshly activated MTS (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 alcohol, the mixture was heated at the refluxing temperature of toluene 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. Elemental analysis: MTS-1-Cl: C% 5.35, Cl% 3.32; MTS-1-I: C% 4.83, I% 10.93; MTS-2-Cl: C% 5.43, Cl% 4.51.

5.3.2. Competitive grafting of XPAS and ethyltrimethoxysilane

MTS-1-I-D and MTS-2-Cl-D were obtained by grafting XPAS (1.4 mmol) and ethyltrimethoxysilane (2.8 mmol), in toluene (10 mL), on MTS-1 or MTS-2 (1 g) according to the same silylation procedure as described above. Elemental analysis: MTS-1-I-D: C% 5.05, I% 5.42; MTS-2-Cl-D: C% 4.05, Cl% 1.48.

5.4. Passivation of the surface with hexamethyldisilazane

The passivation procedure was a controlled vapor deposition method using dynamic vacuum.[26] The samples MTS-1-I-D and MTS-2-Cl-D (2 g) were laid in a glass scinter inside a vertical glass tube heated with an electric furnace. The solids were activated at 453 K for 2 h under reduced pressure (6 mm Hg). The organic vapor of HMDZ was then admitted through the heated solid under dynamic vacuum by means of a heated connection with the reservoir containing the liquid silylating agent (7 mL) heated at 308 K. After all the silazane compound was consumed (4 h), the solid was reevacuated for 1 h. Elemental analysis: MTS-1-I-D-A: C% 7.42, I% 5.24; MTS-2-Cl-D-A: C% 8.47, Cl% 1.47.

5.5. Substitution of halogen by (−)-ephedrine

Freshly activated solids (1 g) were stirred with an excess of (−)-ephedrine (9.6 mmol) for 6 h, under reflux of xylene (10 mL). Modified solids were filtered, extracted according to the previous procedure and dried at 100°C. Elemental analysis: MTS-1-Cl-E: C% 10.58, Cl% 1.32, N% 0.80; MTS-1-I-E: C% 13.53, I% 0.74, N% 1.21; MTS-2-Cl-E: C% 14.64, Cl% 1.74, N% 1.16; MTS-1-I-D-E: C% 9.94, I% 0.47, N% 0.77; MTS-2-Cl-D-E: C% 9.20, Cl% 0.90, N% 0.60; MTS-1-I-D-A-E: C% 9.01, I% 1.02, N% 0.45; MTS-2-Cl-D-A-E: C% 9.29, Cl% 1.14, N% 0.31.

5.6. General procedure for the enantioselective addition of diethylzinc to benzaldehyde using solid chiral auxiliaries

The solid auxiliary (8.5 mol%) was activated at 130°C under vacuum during 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 with 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 analysed by gas chromatography on chiral capillary column (lipodex E) after classical acidic treatment (HCl 0.5 M, CH_2Cl_2).

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