



# Design of mesoporous aluminosilicates supported (1*R*,2*S*)-(–)-ephedrine: evidence for the main factors influencing catalytic activity in the enantioselective alkylation of benzaldehyde with diethylzinc

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**Abstract**—(–)-Ephedrine, used as a model  $\beta$ -amino alcohol, was covalently anchored on mesoporous micelle templated aluminosilicates (Al-MTS) through nucleophilic substitution of halogenoalkyl(aryl)silane chains previously grafted on the surface. The covalent grafting was performed either by silylation (method **a**) or by surface sol–gel (method **b**). The latter method provided higher loading. However, the higher loading lowers the resulting mesoporous volume. The coupling alkyl halide moiety was then substituted with (1*R*,2*S*)-(–)-ephedrine. Used as chiral auxiliaries in the heterogeneous enantioselective catalysis of the alkylation of benzaldehyde by diethylzinc, these materials showed properties which depend mainly on the grafting method. The best results (activity, enantioselectivity) were obtained with catalysts prepared from supports featuring high initial pore diameter. The effect of the regular porosity on the efficiency and enantioselectivity was shown. Dilution of catalytic sites by alkyl groups and rigidification of the linker were also studied. © 2002 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

Increasing interest is focused on heterogeneous enantioselective catalysis owing to the possibility of the easy recovery and reuse of the catalyst. In the domain of carbon–carbon bond forming reactions, the homogeneous enantioselective alkylation of aldehydes with dialkylzinc reagent has been largely studied since the work of Oguni and Omi<sup>1</sup> who showed that addition of a catalytic amount of a homochiral  $\beta$ -amino alcohol catalyses the formation of the corresponding enantiomerically enriched secondary alcohols. This field was further developed by Noyori et al.<sup>2</sup> who demonstrated that constrained  $\beta$ -dialkylamino alcohols, (–)-3-*exo*-(dimethylamino)isoborneol (DAIB), not only direct the absolute stereochemical outcome (enantioselectivity), but accelerate the alkylation reaction (catalyst efficiency). Thus, enantioselectivity does not depend on the amount of chiral auxiliary, it being high with low catalyst loadings (2 mol% relative to carbonyl compound), while the efficiency is linearly correlated with

the amount of catalyst used.<sup>3</sup> Until now other chiral ligands have been reported including  $\beta$ -amino alcohols (proline derivatives,<sup>4–6</sup> camphor derivatives,<sup>7,8</sup> ephedrine derivatives<sup>9–13</sup>), amino thiols, diols and diamines and research into the synthesis and study of new ligands and catalysts is still being actively carried out.<sup>14</sup>

In the zinc-catalyzed reaction with a chiral  $\beta$ -amino alcohol ligand, the catalytic site obtained by reaction with dialkylzinc reagents was described by Noyori et al. as a monomeric alkylzinc aminoalkoxide.<sup>15–18</sup> Under standard conditions, homochiral and heterochiral dimers dissociate into the monomer prior to reacting with the dialkylzinc and the aldehyde.<sup>18</sup> In the titanium-catalyzed reaction, the catalytic site is formed by addition of an organotitanium compound to a diol such as TADDOL ( $\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-1,3-dioxolane-4,5-dimethanol)<sup>14</sup> or BINOL (1,1'-bi-2-naphthol).<sup>14</sup> Whatever the metal included in the catalytic system, the choice of the auxiliary is of prime importance due to the role it plays not only on enantioselectivities but also on activities. Additives such as *n*-BuLi also improve e.e.s in certain systems.

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Heterogeneous catalysis is mostly carried out using chiral auxiliaries immobilized onto supports. The aim of the use of supported chiral catalysts, irrespective of the nature of the support (polymeric or mineral), is to provide at least the same activities and enantioselectivities as those obtained in homogeneous catalysis. In a few cases, it has even been claimed that the support could enhance both activity and enantioselectivity via a confinement effect.<sup>19</sup>

The model reaction most usually investigated is the enantioselective alkylation of benzaldehyde with diethylzinc which leads to (*R*)- or (*S*)-1-phenylpropan-1-ol depending on the chirality of the auxiliary used. These studies have mainly focused on the data in regard to enantioselectivities and few of them reported the catalytic activities. However, the products of the reaction operating without chiral auxiliary are racemic alcohols and benzylalcohol as a by-product. Hence, when the chiral auxiliary is not efficient enough to provide a strong ligand accelerated effect, the non-ligand promoted reaction can compete with the enantioselective reaction and lower both chemoselectivity and enantioselectivity.

In the literature, polymers have been used more extensively than mineral supports. In the pioneering work, Fréchet et al.<sup>20</sup> immobilized various  $\beta$ -amino alcohols, (–)-ephedrine, (–)-3-*exo*-methylaminoisoborneol on 1–2% crosslinked partially chloromethylated polystyrene via nucleophilic substitution of halide by the secondary amine moiety. Hence, the anchored  $\beta$ -amino alcohols bore the hydroxyl group free for zinc alcoholate formation. It is noteworthy that the stereoselectivity depends on the amino alcohol structure. On the other hand, with low amounts of chiral auxiliary (5 mol%), good enantioselectivities were obtained though higher reaction times than in homogeneous conditions were necessary for high conversions. In a subsequent work,<sup>21</sup> the authors have already mentioned that slower rates were observed when chiral polymers were substituted for their low-molecular weight analogues and that toluene which is a better swelling solvent than hexane afforded higher e.e.s. Such results were corroborated by Soai et al.<sup>22,23</sup> using polymer-bound *N*-alkylnorephedrine with a similar polymeric support. Later, more enantioselective catalysts were obtained by using a six-methylene spacer for immobilization of chiral auxiliaries.<sup>24</sup> Recently, comparison of soluble linear polymers of ephedrine and camphor derivatives with the corresponding crosslinked ones showed that the most important factor was a favorable interaction of the polymer matrix with the reaction solvent so that the polymer will dissolve or swell in order to allow the reactants easy access to the catalytic sites.<sup>25,26</sup> Moreover, taking into account that activity and enantioselectivity of both polymer-supported (1*R*,2*S*)-*N*-benzylephedrine<sup>25</sup> and polymer-supported *N*-alkyl- $\alpha,\alpha$ -diphenyl-L-prolinol<sup>27</sup> do not increase with loading, the authors suggested that at higher loading and higher percentages of crosslinking a significant fraction of catalytic sites becomes inaccessible. However, the reaction required 24 h at 20°C using the best linear polymer-supported ephedrine (5 mol%,

e.e. = 83–88%). Higher e.e. was obtained (98%) by changing polymer-supported (1*R*,2*S*)-*N*-benzylephedrine for a more efficient auxiliary (polymer-supported DAIB analogue, 5 mol%) without notable increase of activity. The main difference between homogeneous and heterogeneous catalysis results from the lower activity of supported catalysts together with a small decrease of e.e.s.<sup>27</sup> Such a result does not depend on the mode of anchorage. Thus, the use of amino-diols ligands (5 mol%) grafted on polystyrene resins by one of the hydroxyl moieties led to good enantioselectivities if steric hindrance around the hydroxyl moiety was increased (Barlos resin), but conversions higher than 90% were only achieved for reaction times of 24 h at room temperature. Moreover, the polymer needed to be stirred for 24 h in the appropriate solvent to swell properly prior to use.<sup>28</sup> The use of polymer-supported *N*-tritylaziridinyl(diphenyl)methanol as chiral auxiliary led to high enantioselectivities in the alkylation of aromatic and aliphatic aldehydes.<sup>29</sup> In order to obtain high yields and enantioselectivities, the reaction was performed at room temperature overnight with 10 mol% of chiral auxiliary and a swelling effect of the solvent was observed.

Direct polymerization of the chiral auxiliary bearing a polymerizable unit (*N*-(4-ethynylbenzyl) ephedrine,<sup>30</sup> chiral binaphthyl monomer<sup>31–33</sup>) led to main chain chiral polymers. In the former case, results are poorer than those obtained with the corresponding monomer. In the latter case, the binaphthyl-based rigid chiral polymers, which have a well-defined microenvironment around the catalytic centers, present the other advantage of being soluble in the reaction solvent. 100% conversion were achieved in 12 h at 0°C in the presence of 5 mol% catalyst based on the binaphthyl unit but the monomer had greater enantioselectivity as well as catalytic activity than the polymer.<sup>34</sup>

Chiral TADDOL derivatives<sup>35–39</sup> grafted on polymeric supports are known to be excellent ligands for the alkylation of aldehydes catalyzed by titanium catalysts. TADDOLs with dendritic arms embedded as crosslinkers in polystyrene provided a material which led to enantioselectivities and rates similar to those obtained in homogeneous conditions. However, the reaction, performed at –20°C, requires the use of 20 mol% of chiral auxiliary and 1.5 equiv. of organotitanium compound relative to the carbonyl compound. Functionalized BINOL<sup>40–42</sup> attached to aminomethylated polystyrene by linkage at the 3 and 3'-positions used in the better conditions, with 20 mol% of ligand in dichloromethane, was in most cases more enantioselective than the monomer analogue.<sup>42</sup> A profound solvent effect was observed and reported reaction times were high. Curiously, the monomeric analogue induced a faster reaction but lower enantioselectivity.

The immobilization of chiral auxiliaries on mineral surfaces has attracted little attention since the work of Soai et al.<sup>43</sup> who used ephedrine supported on silica gel and alumina. It is worth noting that with small

amounts of silica- (5–7 mol%) or alumina- (2 mol%) supported auxiliary (hexane, 0°C), the enantioselectivities and rates were lower than with polymer-bound ephedrine (10 mol%, hexane, room temperature).<sup>22</sup> Anchorage of commercially available (–)-ephedrine onto mesoporous templated silicas (MTS) or aluminosilicates (Al-MTS) was performed using supports of various mean initial diameter and composition. E.e.s<sup>44</sup> with MTS of 3.6 nm initial pore diameter as supports were near to those obtained with silica.<sup>43</sup> Rates were around ten times lower than in the analogous homogeneous catalysis whatever the solvent, toluene or hexane. Kinetic results were in good agreement with homogeneous catalysis.<sup>3</sup> Increasing the pore diameter of the support from 3.6 to 5.2 nm led to a two-fold increase in the rates without any effect on the enantioselectivities.<sup>45</sup> Dilution of the catalytic sites to prevent the formation of inactive dimers<sup>16</sup> led to a better accessibility to the mineral surface. Therefore, direct interaction of (–)-ephedrine with the surface<sup>46</sup> was demonstrated. The major role of this surface, which catalyzes the non-enantioselective alkylation of benzaldehyde was shown. Similar results were obtained with Al-MTS supports.<sup>47</sup> The activity depended on the composition of the support, and is higher for Al-MTS than for pure silica MTS but four times lower than in homogeneous conditions. (–)-Ephedrine seemed to have no effect on the rate<sup>45,46</sup> and e.e.s were close whatever the support composition. Attempts to improve e.e.s by the use of a more efficient proline derivative supported on MCM-41 or SBA silicas were especially positive when *n*-BuLi was added to the reaction medium.<sup>48</sup> Heterogeneous Ti-catalysis by immobilization of TADDOL on controlled pore glasses (20 nm pore size) and passivation to render the surface hydrophobic led to the same enantioselectivities as in homogeneous phase catalysis.<sup>49</sup> However, activities remained lower. In general, heterogeneous catalysts may be reused in suitable conditions whatever the support.

Thus, in the area of enantioselective addition of dialkylzinc reagents to aldehydes catalyzed by chiral auxiliaries supported on mineral surfaces, progress is needed for a better understanding of the solid catalysts, the role of site accessibility, site–site interaction and site proximity within the support. Taking into account the negative role played by the mineral surface support, the aim of this work was first of all to increase the surface covering by changing the grafting method and to study the effect of such a surface modification on the catalytic activity and enantioselectivity in the model reaction. All of the preceding hybrids were prepared by covalent grafting of 3-halopropyltrimethoxysilane (XPTMS) under anhydrous conditions and substitution of halogen by the amine moiety of (–)-ephedrine. Higher loadings were performed by a surface sol–gel method on MTS surface. Preliminary results were reported recently.<sup>50,51</sup> On the other hand, we show in this work the effect of (i) the accessibility to the catalytic sites by comparison of Al-MTS supports of 3.6 and 8.3 nm of mean initial pore diameter and (ii) of the regularity of the surface mesoporosity on the efficiency of the chiral auxiliary (diffusion limitations). Dilution of catalytic

sites and rigidification of the anchoring arms were also studied in order to determine the role of site–site and site–surface interactions.

## 2. Results

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

**2.1.1. Inorganic supports.** Three Al-MTS supports, Al-MTS **1**, Al-MTS **2** and Al-MTS **3** had the same composition (Si/Al=27), but various porosities were used. Their textural characteristics are described in Table 1. Mean pore diameters are estimated from the  $4V_{mp}/S_{BET}$  ratio. The use of Al-MTS **1** as support was previously reported.<sup>46,47</sup> Synthesis of Al-MTS of high regular pore diameter was previously described.<sup>52,53</sup> Al-MTS **2** and Al-MTS **3** were obtained using the same conditions except their drying temperatures (115 and 80°C, respectively). Nitrogen volumetry at 77 K shows a hysteresis loop for each solid with a *p/p*0 narrow domain (<0.1) for Al-MTS **2** and a large one for Al-MTS **3** ( $0.4 < p/p0 < 1$ ) indicating either a narrow or large distribution of pore diameters.

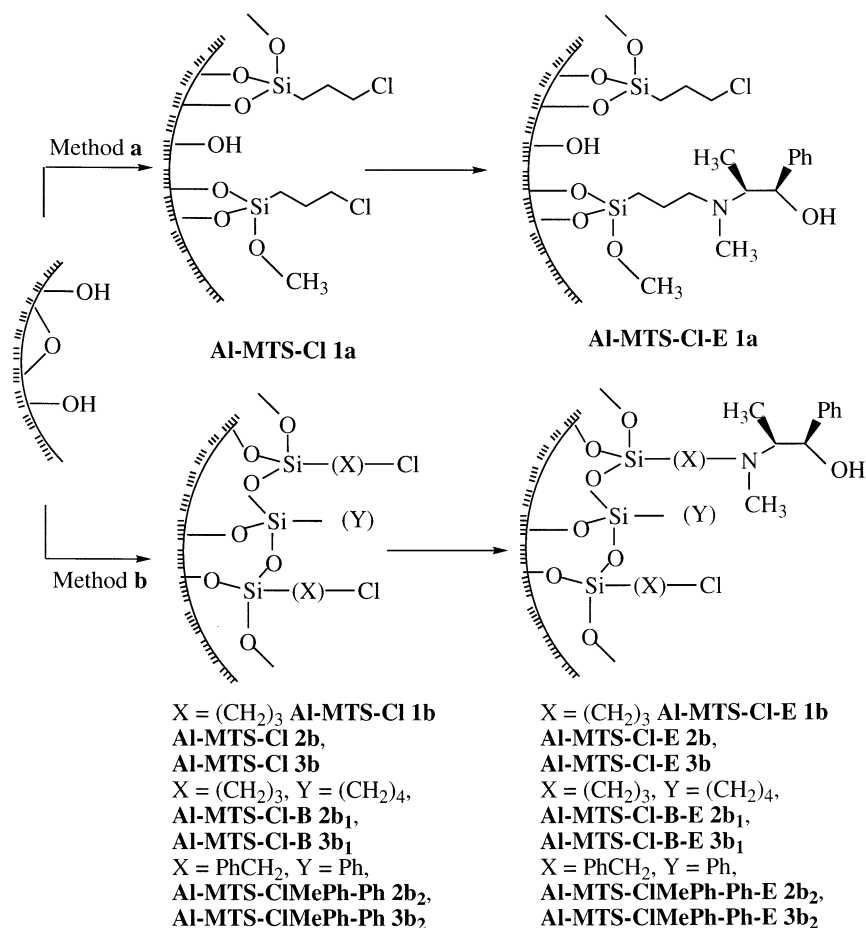
**2.1.2. Synthesis of the hybrid materials.** The synthesized supports were activated at 550°C for 12 h under a flow of synthetic air, in order to eliminate the template before surface modification. Two methods (methods **a** and **b**) were used for covalent anchorage of the coupling halogeno moiety. On the other hand, various types of halogeno moieties were grafted. Then, halogen substitution by (–)-ephedrine led to the chiral auxiliaries (Scheme 1).

In the general case, 3-chloropropyltrimethoxysilane (CPTMS) was used. The method described up to now (method **a**) was performed in anhydrous conditions<sup>47</sup> (toluene, 130°C, 4 h, under nitrogen flow) and led to Al-MTS-Cl **1a**, given for comparison. The new Al-MTS-Cl **1b**, Al-MTS-Cl **2b** and Al-MTS-Cl **3b** were obtained by a surface sol–gel method<sup>54</sup> (method **b**) in the presence of water. In the latter case, water was added with *p*-toluenesulfonic acid and ammonium fluoride as catalysts after stirring aluminosilicate with CPTMS for 2 h at room temperature (Section 5). By reaction of chloro-hybrids with an excess of (–)-ephedrine in refluxing xylene for 6 h, chiral auxiliaries Al-MTS-Cl-E **1a**, Al-MTS-Cl-E **1b**, Al-MTS-Cl-E **2b** and Al-MTS-Cl-E **3b** were obtained.

The effect of site proximity was studied for large mean pore diameter supports. Dilution of halogeno moieties

**Table 1.** Textural characteristics of the supports

Supports	<i>S</i> (m <sup>2</sup> g <sup>−1</sup> )	<i>V</i> <sub>mp</sub> (mL g <sup>−1</sup> )	4 <i>V</i> / <i>S</i> (nm)
MTS <b>1</b>	833	0.76	3.6
MTS <b>2</b>	822	1.71	8.3
MTS <b>3</b>	791	1.57	4–12



**Scheme 1.** Covalent grafting of (–)-ephedrine on the surface of Al-MTS supports by methods **a** (CPTMS, toluene, anhydrous conditions, 130°C, 4 h) and **b** (CPTMS, toluene, H<sub>2</sub>O, NH<sub>4</sub>F-*p*TsOH, 25°C, 2 h and 60°C, 4 h).

was performed by competitive grafting of CPTMS and butyltrimethoxysilane by method **b**. Solids Al-MTS-CI-B 2b<sub>1</sub> and Al-MTS-CI-B 3b<sub>1</sub> were obtained which led to Al-MTS-CI-B-E 2b<sub>1</sub> and Al-MTS-CI-B-E 3b<sub>1</sub> after reaction with (–)-ephedrine.

Rigidification of the anchorage link together with dilution of the catalytic sites was performed by competitive grafting of *para*-chloromethylphenyltrimethoxysilane and phenyltrimethoxysilane by method **b**. Al-MTS-CiMePh-Ph 2b<sub>2</sub> and Al-MTS-CiMePh-Ph 3b<sub>2</sub> were synthesized and led to Al-MTS-CiMePh-Ph-E 2b<sub>2</sub> and Al-MTS-CiMePh-Ph-E 3b<sub>2</sub> after reaction with (–)-ephedrine at 80°C.

**2.1.3. Characterization of the hybrid materials.** Halogen and nitrogen loadings were determined by both elemental analyses and thermogravimetry. The results are expressed relatively to the weight of dry initial silica content (Table 2).

Table 2 shows that surface functionalization with CPTMS by method **b** (entries 3, 5, 11) leads to a two times higher amount of chloride moieties than by

method **a** (entry 1) whatever the support. Substitution of halogen by (–)-ephedrine is performed with a lower yield for solids synthesized by method **b** and leads to a similar amount of (–)-ephedrine whatever the support (entries 4, 6, 12). The sum of nitrogen and remaining halogen loadings corresponds to the initial halogen loading for all the solids. As expected, lower amounts of replaceable alkyl halide functions (Al-MTS-CI-B 2b<sub>1</sub> and Al-MTS-CI-B 3b<sub>1</sub>, entries 7 and 13) are obtained by dilution of alkyl halide moieties by butyl functions. Loadings in the same range are obtained for, on the one hand, Al-MTS-CI-B 2b<sub>1</sub> (entry 7) and Al-MTS-CiMePh-Ph 2b<sub>2</sub> (entry 9) and, on the other hand, Al-MTS-CI-B 3b<sub>1</sub> (entry 13) and Al-MTS-CiMePh-Ph 3b<sub>2</sub> (entry 15). The high reactivity of chlorophenyl functions leads to a slightly higher amount of catalytic sites for Al-MTS-CiMePh-Ph-E 2b<sub>2</sub> (entry 10) and Al-MTS-CiMePh-Ph-E 3b<sub>2</sub> (entry 16) than for Al-MTS-CI-B-E 2b<sub>1</sub> (entry 8) and Al-MTS-CI-B-E 3b<sub>1</sub> (entry 14), respectively. In each case loading is notably lower after dilution.

Textural properties from nitrogen adsorption isotherms are described in Table 3.

**Table 2.** Halogen and amine loadings of the hybrid materials

Entry	Solids	$N_{\text{Xi}}^a \times 10^3$ (mol g <sup>-1</sup> )	$N_{\text{Xr}}^a \times 10^3$ (mol g <sup>-1</sup> )	$N_{\text{N}}^a \times 10^3$ (mol g <sup>-1</sup> )	Substitution (%)
1	Al-MTS-Cl <b>1a</b>	2.1	–	–	–
2	Al-MTS-Cl-E <b>1a</b>	–	0.8	1.3	62
3	Al-MTS-Cl <b>1b</b>	4.4	–	–	–
4	Al-MTS-Cl-E <b>1b</b>	–	2.5	1.9	43
5	Al-MTS-Cl <b>2b</b>	4.3	–	–	–
6	Al-MTS-Cl-E <b>2b</b>	–	2.4	1.9	44
7	Al-MTS-Cl-B <b>2b<sub>1</sub></b>	1.3	–	–	–
8	Al-MTS-Cl-B-E <b>2b<sub>1</sub></b>	–	0.9	0.5	38
9	Al-MTS-ClMePh-Ph <b>2b<sub>2</sub></b>	0.8	–	–	–
10	Al-MTS-ClMePh-Ph-E <b>2b<sub>2</sub></b>	–	0.1	0.7	85
11	Al-MTS-Cl <b>3b</b>	4.6	–	–	–
12	Al-MTS-Cl-E <b>3b</b>	–	2.5	2.1	45
13	Al-MTS-Cl-B <b>3b<sub>1</sub></b>	2.1	–	–	–
14	Al-MTS-Cl-B-E <b>3b<sub>1</sub></b>	–	1.6	0.9	42
15	Al-MTS-ClMePh-Ph <b>3b<sub>2</sub></b>	1.6	–	–	–
16	Al-MTS-ClMePh-Ph-E <b>3b<sub>2</sub></b>	–	0.3	1.2	80

<sup>a</sup> Loadings are calculated relative to the weight of dry initial silica content.

**Table 3.** Effect of the structure of the support on the textural characteristics of the hybrid materials

Entry	Solids	$S$ (m <sup>2</sup> g <sup>-1</sup> )	$V_{\text{mp}}$ (mL g <sup>-1</sup> )	Mean pore diameter (nm)
1	Al-MTS-Cl <b>1a</b>	756	0.42	2.2
2	Al-MTS-Cl-E <b>1a</b>	689	0.30	1.7
3	Al-MTS-Cl <b>1b</b>	– <sup>a</sup>	0.21	–
4	Al-MTS-Cl-E <b>1b</b>	– <sup>a</sup>	0.07	–
5	Al-MTS-Cl <b>2b</b>	559	0.79	5.6
6	Al-MTS-Cl-E <b>2b</b>	440	0.64	5.8
7	Al-MTS-Cl-B <b>2b<sub>1</sub></b>	470	0.68	5.8
8	Al-MTS-Cl-B-E <b>2b<sub>1</sub></b>	543	0.82	6.0
9	Al-MTS-ClMePh-Ph <b>2b<sub>2</sub></b>	552	0.73	5.3
10	Al-MTS-ClMePh-Ph-E <b>2b<sub>2</sub></b>	586	0.78	5.3
11	Al-MTS-Cl <b>3b</b>	539	0.68	– <sup>b</sup>
12	Al-MTS-Cl-E <b>3b</b>	302	0.44	– <sup>b</sup>
13	Al-MTS-Cl-B <b>3b<sub>1</sub></b>	550	0.70	– <sup>b</sup>
14	Al-MTS-Cl-B-E <b>3b<sub>1</sub></b>	459	0.59	– <sup>b</sup>
15	Al-MTS-ClMePh-Ph <b>3b<sub>2</sub></b>	585	0.67	– <sup>b</sup>
16	Al-MTS-ClMePh-Ph-E <b>3b<sub>2</sub></b>	451	0.57	– <sup>b</sup>

<sup>a</sup> BET equation used for the determination of surface area is inoperative.

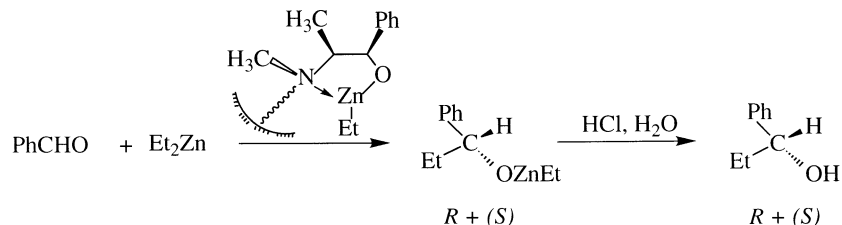
<sup>b</sup> Taking into account the large variation of pore diameters, they are not calculated.

Grafting of organic moieties onto the naked support leads to a decrease in the residual mesoporous volume whatever the method used. However, by method **a** mesoporosity is maintained (entries 1 and 2), while by method **b** it is lost for hybrids synthesized from Al-MTS **1** support (entries 3 and 4, Al-MTS-Cl **1b** and Al-MTS-Cl-E **1b**). The BET equation used for the determination of surface area becomes inoperative taking into account that the step characteristic of type IV isotherms according to the IUPAC classification disappears and that the initial mesoporosity tends to microporosity after grafting of organics by method **b**. Regular mesoporosity is maintained for hybrids **2b**, **2b<sub>1</sub>**, **2b<sub>2</sub>** while hybrids **3b**, **3b<sub>1</sub>**, **3b<sub>2</sub>** present isotherms analogous to that of the support Al-MTS **3**. Functionalization of supports Al-MTS **2** and Al-MTS **3** by method **b** and substitution by (–)-ephedrine lead to hybrid materials with high residual mesoporous volumes slightly lower from the irregular Al-MTS **3** support than from the regular Al-MTS **2** support.

## 2.2. Enantioselective addition of diethylzinc to benzaldehyde

Enantioselective alkylation of benzaldehyde (BA) with diethylzinc (Scheme 2) was performed with an excess of diethylzinc ([Et<sub>2</sub>Zn]/[BA]=2.3) at 0°C under a nitrogen flow, with the same weight of solid chiral auxiliary (0.29 g) whatever the hybrid material used. The solid was activated at 25°C under vacuum for 1 h before use. The experimental has been described previously.<sup>47</sup>

Results are shown in Table 4. The amount of chiral auxiliary is calculated relative to the total weight of hybrid material. Taking into account that with excess of diethylzinc the kinetics are first order with BA concentration and zero order with diethylzinc concentration, like in homogeneous catalysis,<sup>44</sup>  $k_{\text{obs}}$  is obtained by fitting BA% versus time (h) by an exponential regression. Activities are related with reaction rates ( $k_{\text{obs}}$  h<sup>-1</sup> for benzaldehyde consumption). Selectivities



**Scheme 2.** Enantioselective addition of diethylzinc to benzaldehyde.

**Table 4.** Heterogeneous alkylation of benzaldehyde with diethylzinc

Entry	Solid	(–)-Ephedrine <sup>a</sup> (mol%)	$k_{\text{obs}} \times 10^2$ (h <sup>-1</sup> )	$k_{\text{obs}(R+S)}^b$ $\times 10^2(\text{h}^{-1})$	Selectivity <sup>c</sup> (%)	E.e. <sup>d</sup> (%)
1	Without catalyst	–	1.2	0.6	51	0
2	(–)-Ephedrine	8.5	57.0	51.0	97	62
3	(–)- <i>N</i> -Propyl-ephedrine	8.5	68.0	67.0	98	76
4	Al-MTS-Cl-E <b>1a</b>	13.6	17.0	15.8	93	47
5	Al-MTS-Cl-E <b>1b</b>	15.4	11.4	10.7	94	54
6	Al-MTS-Cl-E <b>2b</b>	16.8	55.2	54.1	98	64
7	Al-MTS-Cl-B-E <b>2b<sub>1</sub></b>	4.7	19.2	18.4	96	62
8	Al-MTS-CIMePh-Ph-E <b>2b<sub>2</sub></b>	7.4	30.6	29.1	95	61
9	Al-MTS-Cl-E <b>3b</b>	17.1	27.6	26.2	95	55
10	Al-MTS-Cl-B-E <b>3b<sub>1</sub></b>	8.7	30.6	29.4	96	59
11	Al-MTS-CIMePh-Ph-E <b>3b<sub>2</sub></b>	12.0	25.2	24.2	96	58

<sup>a</sup> The amount of chiral auxiliary is calculated relative to the total weight of hybrid material.

<sup>b</sup>  $k_{\text{obs}(R+S)} = k_{\text{obs}} \times \text{selectivity}$ .

<sup>c</sup> % selectivity =  $100 ([R]+[S])/([R]+[S]+[\text{PhCH}_2\text{OH}])$ .

<sup>d</sup> % e.e. =  $100 ([R]-[S])/([R]+[S])$ .

refer to 1-phenylpropan-1-ol formation relative to the total amount of products taking into account the formation of benzyl alcohol as a by-product (% selectivity =  $100 ([R]+[S])/([R]+[S]+[\text{PhCH}_2\text{OH}])$ ) and enantioselectivities to (*R*)-1-phenylpropan-1-ol formation when (–)-ephedrine is used as the chiral auxiliary (% e.e. =  $100 ([R]-[S])/([R]+[S])$ ).

Changing the grafting method from **a** to **b** leads to an increase in e.e. for Al-MTS **1** support with no increase in the activity (entries 4 and 5). The activities and enantioselectivities obtained with (–)-ephedrine grafted by method **b** onto Al-MTS **2** and **3** notably increase and reach those achieved using homogeneous catalysis (entry 6). Activities are in general higher with hybrids **2b** than with **3b**. They depend on the (–)-ephedrine loading in the former case only. Enantioselectivities are slightly higher with hybrids **2b**. No effect either of dilution of the catalytic sites or of rigidification of the anchoring arm appears.

The catalyst can be reused after removal of the products with a syringe, various washings of the solid with the reaction solvent in the reaction pot, under nitrogen and reintroduction of reactants (Table 5).

E.e.s and activities previously obtained with hybrids as catalysts, lower than in homogeneous catalysis, were related with the effect of the uncovered mineral surface.<sup>47</sup> Thus, the activity of naked supports and chloro-

functionalized surfaces in the model reaction was probed. The results are summarized in Table 6.

Under the same conditions with the same weight of solid (0.29 g), naked surface activity depends on the mean pore diameter of the support and is markedly higher for Al-MTS **2** (Table 6, entry 4) and **3** (entry 8) than for Al-MTS **1** (entry 1). On the other hand, it appears that activity of the mineral surface is better decreased by grafting organics via method **b** (entry 3) rather than method **a** (entry 2). However, this difference may be related either to the higher loading (Table 2, entries 1 and 3) or to the smaller available residual volume (Table 3, entries 2 and 4). For hybrids characterized by a high residual mesoporous volume, the effect of passivation may be expressed as the ratio of hybrid to support activity (Table 6). It is higher for hybrids synthesized with dilution of active centers by butyl groups (**2b<sub>1</sub>**, **3b<sub>1</sub>**) or with rigidification of anchoring arms (**2b<sub>2</sub>**, **3b<sub>2</sub>**) than for hybrids **2b** and **3b** functionalized only with CPTMS. Selectivity decreases with activity (entries 6, 7, 10, 11) by the formation of

**Table 5.** Catalyst recycling

Run	Chiral auxiliary (mol%)	$k_{\text{obs}}$ (h <sup>-1</sup> )	Selectivity (%)	E.e. (%)
1	4.7	0.192	96	62
2	4.7	0.156	95	64
3	4.7	0.150	95	65

**Table 6.** Activity of the uncovered mineral surface in the model reaction

Entry	Solid	$k_{\text{obs}} \times 10^2 \text{ (h}^{-1}\text{)}$	$k_{\text{obs}(R+S)r}^a \times 10^2 \text{ (h}^{-1}\text{)}$	Selectivity <sup>b</sup> (%)	$\frac{k_{\text{obs}(R+S)r \text{ hybrid}}}{k_{\text{obs}(R+S)r \text{ support}}}$
1	Al-MTS <b>1</b>	16.8	13.9	83	–
2	Al-MTS-Cl <b>1a</b>	10.8	8.9	82	0.64
3	Al-MTS-Cl <b>1b</b>	5.4	4.5	84	0.32
4	Al-MTS <b>2</b>	25.8	22.4	87	–
5	Al-MTS-Cl <b>2b</b>	6.6	5.7	86	0.25
6	Al-MTS-Cl-B <b>2b<sub>1</sub></b>	3.3	2.6	78	0.12
7	Al-MTS-ClMePh-Ph <b>2b<sub>2</sub></b>	4.8	3.8	79	0.17
8	Al-MTS <b>3</b>	26.4	22.4	85	–
9	Al-MTS-Cl <b>3b</b>	8.4	7.1	85	0.32
10	Al-MTS-Cl-B <b>3b<sub>1</sub></b>	4.5	3.5	77	0.16
11	Al-MTS-ClMePh-Ph <b>3b<sub>2</sub></b>	5.4	4.3	79	0.19

<sup>a</sup>  $k_{\text{obs}(R+S)r} = k_{\text{obs}} \times \text{selectivity}$ .

<sup>b</sup> % selectivity =  $100([R]+[S])/([R]+[S]+[\text{PhCH}_2\text{OH}])$ .

benzyl alcohol from the uncatalyzed reaction (51% selectivity).

### 3. Discussion

Heterogeneous enantioselective alkylation of benzaldehyde with diethylzinc catalyzed by  $\beta$ -amino alcohols supported on silica gel, alumina, MTS or Al-MTS materials is presently less powerful than the homogeneous reaction. The activities of hybrid catalysts were low and ligand accelerated effects similar to those observed in homogeneous catalysis were not known. Our preceding results showed that the rates were governed by naked support activity<sup>47</sup> and that moderate enantioselectivities resulted from accessible uncovered mineral surface. In order to prevent this negative effect increase of loading of  $\beta$ -amino alcohol moieties was performed by surface polymerization of alkoxy silanes by hydrolysis of alkoxy moieties and condensation of the resulting hydroxyl groups (surface sol–gel, method **b**). However, covering of the mineral surface by organics may have some drawbacks such as decreased diffusion inside the pores and increased site–site and/or site–surface interactions. These factors have to be controlled to enhance both catalyst activity and enantioselectivity in the model reaction.

#### 3.1. Characterization of chiral inorganic–organic Al-MTS auxiliaries

Covalent grafting of coupling haloalkyl functions with CPTMS onto the surface of supports of similar composition and surface area by method **b**, allows increased surface loading (Table 2, entries 1, 3). Substitution of chlorine by (–)-ephedrine, even performed with a yield lower than for hybrids synthesized by method **a** and probably related with steric hindrance around the halogen, leads to higher densities of chiral auxiliary and similar for the three supports (entries 4, 6, 12). As observed for hybrids highly functionalized by method **a**, the total number of organic moieties is maintained after reaction with (–)-ephedrine indicating that direct immobilization of (–)-ephedrine on the surface does not occur.<sup>46</sup>

However, increased loading infers decrease of available residual volume, which is particularly noticeable after reaction with (–)-ephedrine. Thus, when Al-MTS **1** support is used (Table 3, entries 1, 3 and 2, 4), hybrids present a super microporosity in place of the initial mesoporosity. It is worth noting that mesoporosity is maintained after functionalization of Al-MTS **2** (entries 5, 6) and Al-MTS **3** (entries 11, 12) with an available volume slightly lower from the Al-MTS **3** support characterized by an irregular mesoporosity (0.44 mL/g) than from the regular one (0.64 mL/g). In the latter case the regular structure is preserved as for the other hybrids, **2b<sub>1</sub>**, **2b<sub>2</sub>** characterized by dilution of the sites or/and rigidification of the anchoring arm. Calculation of the diluent number present some difficulties due to the presence of remaining methoxy groups not hydrolyzed in the grafting process. The evaluation based on <sup>13</sup>C NMR spectroscopic analyses shows that the total number of grafted moieties (halogen plus diluent) is nearly equal to the number of chloro moieties for undiluted solids. Thus, before reaction with (–)-ephedrine a similar loading onto each support is obtained whatever the grafted species, halogen and diluent moieties. The halogen to diluent ratio depends on the relative amounts of the corresponding alkoxy silanes used in the grafting process (Section 5). The residual mesoporosity of chloro hybrids for the two supports can be accounted for by the initial mesoporosity of the supports (Table 1). After reaction with (–)-ephedrine the higher pore volumes of hybrids **2b<sub>1</sub>**, **2b<sub>2</sub>**, with regard to **3b<sub>1</sub>**, **3b<sub>2</sub>**, respectively, may therefore be explained by their lower (–)-ephedrine loading (Table 3).

#### 3.2. Enantioselective addition of diethylzinc to benzaldehyde

**3.2.1. Activities.** In homogeneous catalysis the chiral auxiliary not only directs the stereoselectivity, but also accelerates the reaction markedly (Table 4, entries 1–3).<sup>2,3</sup> With heterogeneous organic–inorganic hybrids synthesized either by silylation (method **a**) or those reported by Soai et al.,<sup>43</sup> this marked effect on the reaction rate was not observed. Whatever the support

composition,<sup>47</sup> catalyst activity (Al-MTS-Cl-E **1a**, Table 4, entry 4) was only slightly higher than that of the naked support (Al-MTS **1**, Table 6, entry 1) or that of the parent hybrid (Al-MTS-Cl **1a**, Table 6, entry 2). This activity may even be lower in some cases.<sup>45,47</sup> The larger the uncovered surface was, the higher the activity of the corresponding solid was in agreement with the competitive participation of the inorganic surface to the overall catalytic activity.

Taking into account that grafting performed by silylation under anhydrous conditions proceeded mainly on the hydrophobic portion of the surface<sup>55</sup> with preservation of the hydrophilic part, total coverage of the surface was aimed at<sup>54</sup> in order to lower the intrinsic activation by residual silanols. Therefore, increasing the loading on the inorganic surface leads to a decrease in the surface activity (Al-MTS-Cl **1b**, Table 6, entry 3). In the case of the small pore support, the drawback is the concomitant decrease of the catalyst activity (Al-MTS-Cl-E **1b**, Table 4, entry 5). Although the former result with Al-MTS-Cl **1b** may imply better coverage of the surface, the latter with Al-MTS-Cl-E **1b** can be explained by the low residual volume of this hybrid and/or by the inaccessibility of the catalytic sites inside the pores with increased loading.

Using silicic mesoporous supports of 5.2 nm pore diameter in place of 3.5 nm led to increased rate without any effect on the enantioselectivity.<sup>45</sup> Likewise, naked Al-MTS **2** (Table 6, entry 4) and Al-MTS **3** (entry 8) are much more active than Al-MTS **1** (entry 1). This increase for supports of the same composition and surface area may possibly be explained by diffusional constraints in the latter case. After grafting the coupling agent by method **b** on large pore supports, all hybrids (Table 6, entries 5–7, 9–11) are much less active than the corresponding supports. For these hybrids which present high residual volume, the high loading implies an effective passivation of the surface whatever the grafted species. On the other hand, solid chiral auxiliaries synthesized from large pore supports show high activity (Table 4, entries 6–11), notably higher than that of the parent chloro grafted Al-MTS (Table 6, entries 5–7, 9–11). This strong increase in activity is logically related to catalytic site accessibility and efficiency.

Benzaldehyde consumption ( $k_{\text{obs}}$ ,  $\text{h}^{-1}$ ) provides enantiomeric 1-phenylpropan-1-ol, racemic 1-phenylpropan-1-ol and benzyl alcohol, the formation of which takes place in a competitive way.<sup>44</sup> For surfaces without chiral auxiliaries, the rate of formation of racemic alcohols is given by:

$$k_{\text{obs}(R+S)r} = k_{\text{obs}} \times \text{selectivity (Table 6)}.$$

The overall 1-phenylpropan-1-ol formation is expressed by:

$$k_{\text{obs}(R+S)} = k_{\text{obs}} \times \text{selectivity} = k_{\text{obs}(R+S)e} + k_{\text{obs}(R+S)r} + k_{\text{obs}(R+S)\text{without catal}} \quad (\text{Table 4}).$$

If  $k_{\text{obs}(R+S)\text{without catal}}$  can be disregarded in front of

$k_{\text{obs}(R+S)e} + k_{\text{obs}(R+S)r}$  the efficiency of chiral catalytic sites is expressed by:

$$k_{\text{obs}(R+S)e} = k_{\text{obs}(R+S)} - k_{\text{obs}(R+S)r}$$

Variation of the initial rate of formation of the enantiomeric alcohols ( $r_0 = k_{\text{obs}(R+S)e} \times [\text{BA}]_0$ ) versus the number of catalytic sites is shown in Fig. 1. A linear correlation is obtained for hybrids synthesized by method **b** and characterized by an initial regular mesoporosity. The turn over frequency ( $\text{TOF} = 3.4 \text{ h}^{-1}$ ) is measured by the slope of the linear plotting. On the contrary, increasing the loading of catalytic sites on the surface of the irregular mesoporous supports results in a slight decrease of activity.

The activity of chiral sites is correlated with the amount of chiral auxiliary for the regular pore diameter support. As in homogeneous catalysis, reaction rate increases with the number of sites even if a slight flattening can be noticed for Al-MTS-Cl-E **2b**, which presents the higher density of (–)-ephedrine moieties. That means that all the sites are accessible in the range of densities used. Moreover, the diluent effect of catalytic sites by butyl chains which could enhance the site activity by preventing the formation of dimers,<sup>15,16</sup> may not be evidenced by the activity of the site. Thus, the role and formation of dimers are not evidenced in our case. The rigidity of the anchoring arm which suppresses the possible interaction of (–)-ephedrine with the surface, does not affect the activity of the site. Coating by method **b** together with dilution of the sites prevents (–)-ephedrine interaction with the surface. Hybrid **2b<sub>1</sub>** may be reused without significant loss of activity (Table 5). However, the activity remains lower than in homogeneous catalysis for which the TOF lies between 6.7

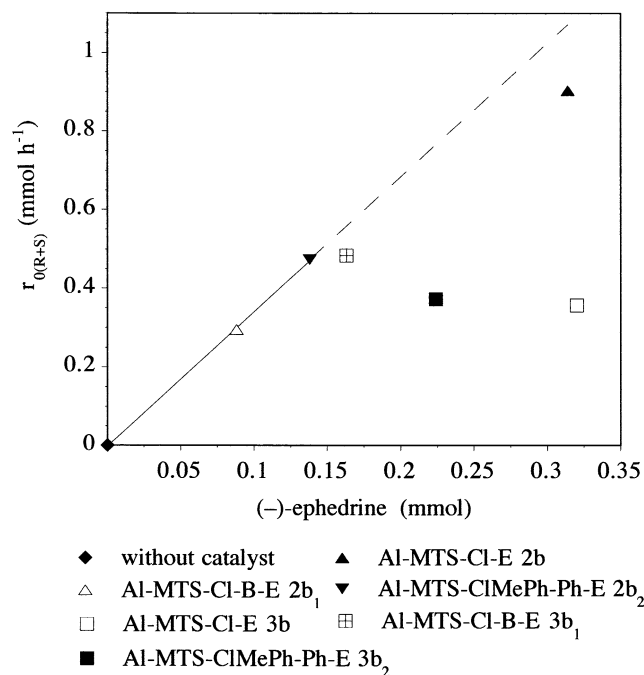


Figure 1. Chiral site efficiency versus number of sites.



$h^{-1}$  for (–)-ephedrine and  $8 h^{-1}$  for (–)-*N*-propyl-ephedrine which can be considered as the analogue of grafted (–)-ephedrine.

On the other hand, the efficiency of catalysts obtained by grafting (–)-ephedrine on the Al-MTS **3** support does not depend on or slightly decreases with the amount of chiral auxiliary (Fig. 1). The activity of Al-MTS-Cl-B-E **3b**<sub>1</sub>, the less heavily loaded hybrid of the series and the loading of which is close to that of Al-MTS-Cl-MePh-Ph-E **2b**<sub>2</sub>, is located near the correlation obtained for the regular support. This result indicates that nearly all of the catalytic sites are well accessible. Increasing the number of sites has no effect on the efficiency, suggesting undesirable interactions between catalytic sites or diffusional limitations. Comparison with the regular support shows that high activity can be observed with high loading on the surface. Therefore, increasing the number of sites on the irregular support without concomitant increase of activity is probably related to the inaccessibility of the added catalytic sites. Grafting of ligands in small and irregular pores can limit access to the corresponding catalytic sites.<sup>56</sup> Thus, our results illustrate the role of a large regular mesoporosity for minerals used as supports for grafting organics which favors access to the surface sites.

**3.2.2. Enantioselectivities.** The enantioselectivities depend only slightly on the reaction solvent<sup>44</sup> contrary to that observed with polymeric supports and the e.e.s are constant throughout the reaction. Moreover, the enantioselectivity does not depend on the mass of hybrid used<sup>46</sup> and the same enantioselectivities were obtained using two hybrids, the overall activity of which is very different but for which the ratio of surface ( $k_{\text{obs}(R+S)r}$ ) to overall activity ( $k_{\text{obs}(R+S)}$ ) is of the same order of magnitude.<sup>45</sup> Taking into account that e.e.s do not vary with conversion, they can be expressed as a function of the rate of formation of each enantiomer as:

$$\text{e.e.} = k_{\text{obs}(R-S)e} / (k_{\text{obs}(R+S)e} + k_{\text{obs}(R+S)r} + k_{\text{obs}(R+S)\text{without catal}})$$

where  $k_{\text{obs}(R-S)e}$  depicts the difference of the formation rate of *R* and *S* enantiomers,  $k_{\text{obs}(R+S)e}$  stands for the efficiency of chiral sites,  $k_{\text{obs}(R+S)r}$  that of the mineral surface and  $k_{\text{obs}(R+S)\text{without catal}}$  the participation of the reaction without catalyst.

$$\text{e.e.} = k_{\text{obs}(R-S)e} / k_{\text{obs}(R+S)}$$

which can be written:

$$\text{e.e.} = (k_{\text{obs}(R-S)e} / k_{\text{obs}(R+S)e}) \times (k_{\text{obs}(R+S)e} / k_{\text{obs}(R+S)})$$

where  $(k_{\text{obs}(R-S)e} / k_{\text{obs}(R+S)e})$  is the enantiomeric excess which can be obtained with the same chiral auxiliary in homogeneous conditions (e.e.<sub>hom</sub>).

Taking into account that  $k_{\text{obs}(R+S)\text{without catal}}$  can be disregarded before  $(k_{\text{obs}(R+S)e} + k_{\text{obs}(R+S)r})$  and that  $k_{\text{obs}(R+S)e} = k_{\text{obs}(R+S)} - k_{\text{obs}(R+S)r}$  the expression of e.e. becomes:

$$\text{e.e.} = \text{e.e.}_{\text{hom}} (1 - k_{\text{obs}(R+S)r} / k_{\text{obs}(R+S)})$$

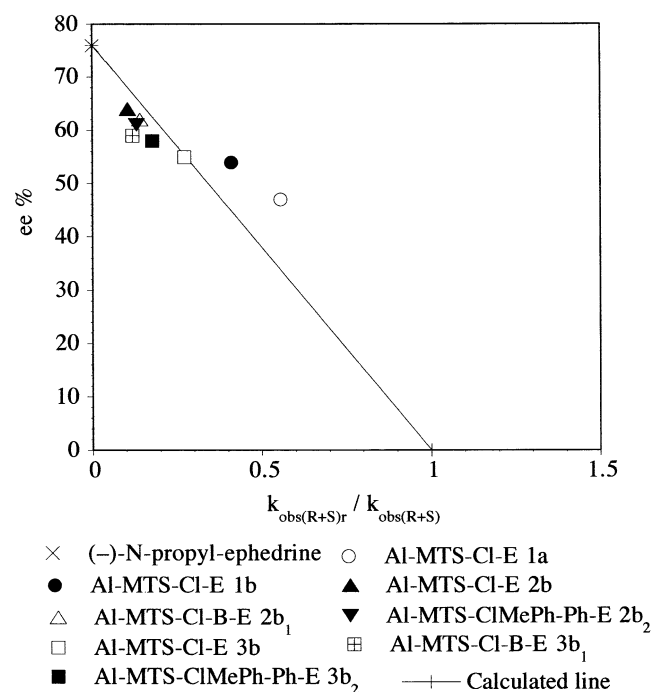
This relation leads to a linear correlation between e.e. and the ratio  $k_{\text{obs}(R+S)r} / k_{\text{obs}(R+S)}$  the limits being for e.e. = 0 if  $k_{\text{obs}(R+S)r} = 0$  and e.e. = 76% if  $k_{\text{obs}(R+S)r} = 0$ .

Variation of enantioselectivities with  $k_{\text{obs}(R+S)r} / k_{\text{obs}(R+S)}$  is shown in Fig. 2.

The lower the ratio is, the higher the enantioselectivity is. Our results are in good agreement with the model proposed. Thus, they can be accounted for by either the lowering of the activity of the mineral surface and/or an increase in the activity of the chiral sites. Coating of the surface of Al-MTS **1** support by method **b** leads to increased enantioselectivities. However, the efficiency of chiral catalytic sites of Al-MTS-Cl-E **1b** is notably decreased by the poor accessibility and therefore the increase in e.e. is moderate. The same surface and overall activities with **2b**<sub>2</sub> and **3b**<sub>1</sub> hybrids lead to similar enantioselectivities. On the other hand, the enantioselectivity obtained with the hybrid **2b** (64%) notably higher than with **3b** (55%) is better explained by the higher activity of chiral sites than by the lower activity of the mineral surface. It is worth noting that enantiomeric excesses are maintained after reuse of hybrid **2b**<sub>1</sub> (Table 5).

#### 4. Conclusions

The efficiency of covalently linked (–)-ephedrine on the mineral surface of mesoporous aluminosilicates as a chiral ligand in the enantioselective alkylation of benzaldehyde with diethylzinc is controlled by various factors including the activity of the naked surface towards the formation of racemic alcohols and the accessibility of the chiral catalytic sites. The mineral surface activity



**Figure 2.** Effect of the ratio of the mineral surface to the overall activity on enantioselectivity.

was decreased by grafting organic residues to the surface by a surface sol–gel method. The accessibility of the chiral sites was increased by using a support of high initial mean pore diameter characterized by a regular mesoporosity. On the other hand, no effects of dilution of the catalytic sites or rigidification of the grafting arms were shown. These new hybrids present a good activity notably higher than those reported up to now with grafted (–)-ephedrine. The efficiency of the more heavily loaded hybrid is close to that obtained in homogeneous catalysis and is very interesting if we take into account the fact that activity is practically unaffected by catalyst loading. Enantioselectivities, related with the ratio of mineral to overall activity of production of (*R*)- and (*S*)-1-phenylpropan-1-ol are slightly lower than in homogeneous catalysis. This was explained by remaining activity of the mineral surface and by a low activity of the chiral sites for high loadings onto the support with irregular mesoporosity. Moreover, the use of (–)-ephedrine as the chiral auxiliary limits the obtained e.e.s which could be increased by immobilization of another more efficient chiral auxiliary such as DAIB. The advantages provided by these hybrid catalysts are now highlighted: the mineral serves to enhance the catalytic site accessibility via modeling of the pore size of the support, whilst, as with organic polymers, the presence of grafted polymer renders the mineral surface chemically inert and suppresses side reactions catalyzed by surface silanols.

## 5. Experimental

General procedures were described previously.<sup>45</sup> *para*-Chloromethylphenyltrimethoxysilane and phenyltrimethoxysilane were purchased from ABCR GMBH & Co.

### 5.1. Grafting of coupling halogeno moieties

Grafting of siloxanes on Al-MTS surface by method **a** has been described previously.<sup>47</sup> In method **b** aluminosilicate was stirred with CPTMS (6.5 mmol/g) for 2 h at room temperature under a nitrogen flow. Then, water (3 mol H<sub>2</sub>O/CPTMS) was added with *p*-toluenesulfonic acid and ammonium fluoride (0.05:0.05 mol/CPTMS) as catalysts. The mixture was warmed at 25°C for 2 h and at 60°C for 4 h. Water was removed by azeotropic distillation and the solids were washed and dried. Grafting by method **b**<sup>54</sup> was performed with CPTMS and butyltrimethoxysilane for Al-MTS-Cl-B **2b**<sub>1</sub> (1:3 ratio) and Al-MTS-Cl-B **3b**<sub>1</sub> (1:1 ratio), *para*-chloromethylphenyltrimethoxysilane and phenyltrimethoxysilane for Al-MTS-ClMePh-Ph **2b**<sub>2</sub> (1:4 ratio) and Al-MTS-ClMePh-Ph **3b**<sub>2</sub> (1:1 ratio). In order to prevent decomposition during azeotropic distillation, the reaction temperature was lowered to 60°C for 2 h for Al-MTS-ClMePh-Ph **2b**<sub>2</sub> and **3b**<sub>2</sub>.

Elemental analyses (%):

Al-MTS-Cl **1a**: C, 7.51; Cl, 5.64; Si, 34.90%. Al-MTS-Cl-E **1a**: C, 16.7; Cl, 2.07; N, 1.24; Si, 31.20%.

Al-MTS-Cl **1b**: C, 11.30; Cl, 10.22; Si, 33.47%. Al-MTS-Cl-E **1b**: C, 19.97; Cl, 4.68; N, 1.40; Si, 26.20%.

Al-MTS-Cl **2b**: C, 11.87; Cl, 9.86; Si, 32.46%. Al-MTS-Cl-E **2b**: C, 23.40; Cl, 5.02; N, 1.53; Si, 28.90%.

Al-MTS-Cl-B **2b**<sub>1</sub>: C, 16.03; Cl, 2.96; Si, 31.30%. Al-MTS-Cl-B-E **2b**<sub>1</sub>: C, 19.11; Cl, 1.97; N, 0.43; Si, 32.18%.

Al-MTS-ClMePh-Ph **2b**<sub>2</sub>: C, 22.36; Cl, 1.90; Si, 32.95%. Al-MTS-ClMePh-Ph-E **2b**<sub>2</sub>: C, 24.41; Cl, 0.31; N, 0.67; Si, 31.12%.

Al-MTS-Cl **3b**: C, 11.92; Cl, 10.30; Si, 32.79%. Al-MTS-Cl-E **3b**: C, 22.17; Cl, 4.85; N, 1.56; Si, 28.86%.

Al-MTS-Cl-B **3b**<sub>1</sub>: C, 14.05; Cl, 4.93; Si, 34.99%. Al-MTS-Cl-B-E **3b**<sub>1</sub>: C, 18.96; Cl, 3.60; N, 0.79; Si, 32.61%.

Al-MTS-ClMePh-Ph **3b**<sub>2</sub>: C, 20.59; Cl, 3.60; Si, 31.86%. Al-MTS-ClMePh-Ph-E **3b**<sub>2</sub>: C, 25.99; Cl, 0.70; N, 1.09; Si, 30.03%.

### 5.2. (–)-*N*-propylephedrine

Propionyl chloride (1.25 mL, 0.013 mol) and 2 M aqueous solution of NaOH (0.014 mol) were added dropwise to a solution of (–)-ephedrine (0.013 mol) in diethyl ether (5 mL) at 0°C. The white precipitate was dissolved by addition of THF (8.5 mL) and stirring was maintained at 0°C for 40 min. The mixture was extracted with methylene chloride. The organic layers were combined and washed with sodium bicarbonate then dried over MgSO<sub>4</sub>. After evaporation of the solvent, a solution of the oil (1 g) in THF (5 mL) was treated under magnetic stirring with a solution of BH<sub>3</sub> (0.013 mol) in THF for 30 min at 0°C. The mixture was allowed to react at room temperature for 4 h. After dropwise addition of 6 mL of HCl 6 M, the solvent was evaporated. The obtained precipitate was dissolved in water and the mixture was adjusted to pH 9 with NaOH 10 M. (–)-*N*-propylephedrine (41% yield) was obtained after extraction with diethyl ether, drying with MgSO<sub>4</sub> and solvent evaporation. GC–MS (OV-1) *t*<sub>R</sub> = 5.8 min, *m/z* = 56, 77, 100, 105, 117, 160. <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ ppm from TMS) δ = 0.88 (m, 6H, CCH<sub>3</sub>), δ = 1.45 (2H, CH<sub>2</sub>) δ = 2.25 (s, 3H, CH<sub>3</sub>N), δ = 2.42 (2H, CH<sub>2</sub>N), δ = 2.79 (m, 1H, CHN), δ = 4.80 (d, 1H, HCφ), δ = 7.30 (m, 5H, aromatic H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, δ ppm from TMS) δ = 9.8 (CH<sub>3</sub>), 11.6 (CH<sub>3</sub>), 20.4 (CH<sub>2</sub>) 38.7 (CH<sub>3</sub>N), 56.7 (CH<sub>2</sub>N), 63.5 (CHN), 72.8 (CHO), 126.0–126.6–127.8 (tertiary aromatic C), 142.6 (quaternary aromatic C).

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