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Best design of heterogenized β-aminoalcohols for improvement of enantioselective addition of diethylzinc to benzaldehyde

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Covalent immobilization of (1*R*,2*S*)-(−)-ephedrine, used as a model molecule of β-aminoalcohols, on the surface of MCM-41-type mesoporous aluminosilicates, performed by a new sol–gel method, leads to chiral auxiliaries which show greatly enhanced rates and ee's compared to those reported up to now in the enantioselective addition of diethylzinc to benzaldehyde.

Increasing interest has been devoted to the design of heterogeneous asymmetric catalysts.[1] One major method involves heterogenization of homogeneous catalysts by their immobilization on organic polymers or inorganic supports.[2] However, the efficiency of the catalysts of the heterogenized catalysts is different compared with their homogeneous counterparts. This is the case for chiral β-aminoalcohols used in the enantioselective addition of dialkylzincs to aldehydes[3] in C–C bond forming reactions. The efficiency of such catalysts depends mainly on the native of the support. Since the pioneering work of Frechet[4] who used polymer-bound chiral aminoalcohols, various authors have described such immobilization on organic polymers.[5,6] Ee's are high, and only slightly lower than those obtained in homogeneous conditions but rates are notably lower. On the other hand, immobilization on mineral surfaces has attracted little attention. Our first results using (−)-ephedrine supported on MCM-41-type mesoporous silicas[7] were in good agreement with precedent results of Soai *et al.*[8] using silica gel or alumina supported (−)-ephedrine. Lower rates, selectivities and enantioselectivities were obtained compared with homogeneous catalysis. Investigations involving changes in the pore size,[9] the composition[10] of the support, end-capping of the surface[9] and the dilution of the catalytic sites[9,10] failed to improve the ee's significantly. These results indicate significant activity of the naked surface towards the formation of racemic alcohols.

The aim of this work was to decrease the negative effects of the uncovered mineral surface by increasing the coverage by organics on the inner surface of the pores.[11] In this work, the synthesis of high surface densities of chloropropyl groups covalently grafted on mesoporous micelle templated aluminosilicates (Al-MTS) of various initial pore diameters is performed. The hybrid inorganic–organic materials resulting from halogen substitution by (−)-ephedrine are applied in the enantioselective addition of diethylzinc to benzaldehyde.

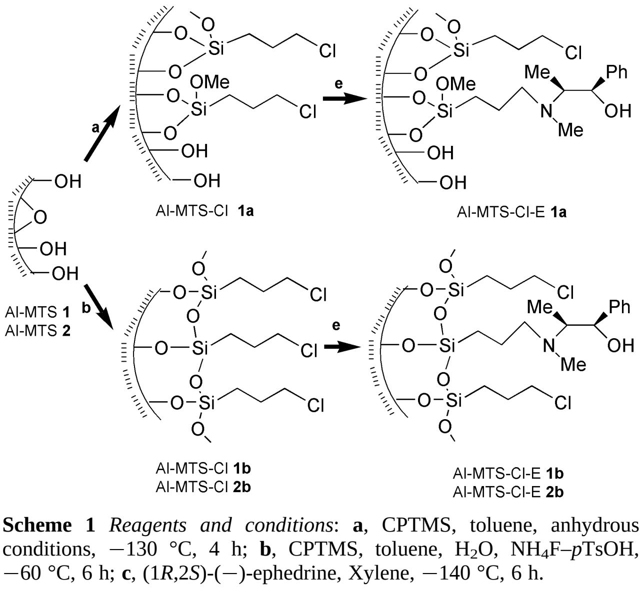
Two mesoporous aluminosilicates of the same composition (Si/Al = 27) and 3.6 (Al-MTS **1**, S = 833 m^2 g^{-1}, V = 0.76 mL g^{-1})[12] and 8.3 nm (Al-MTS **2**, S = 822 m^2 g^{-1}, V = 1.71 mL g^{-1})[13] mean initial pore diameter were used as supports, respectively. In order to remove the template, the as-synthesized solids were activated before surface modification at 550 °C for 12 h under a flow of synthetic air. Up to now, covalent anchorages have been performed in anhydrous conditions, by silylation (method **a**) with 3-chloropropyltrimethoxysilane (CPTMS) (Al-MTS-Cl **1a**) followed by the nucleophilic substitution of chlorine by the basic amino group of (−)-ephedrine (Al-MTS-Cl-E **1a**). Alternatively, grafting of the coupling CPTMS agent by the sol–gel method[11,14] (method **b**, Al-MTS-Cl **1b**, Al-MTS-Cl **2b**) and reaction with (−)-ephedrine leads to new hybrid materials (Al-MTS-Cl-E **1b**, Al-MTS-Cl-E **2b**) (Scheme 1).

Loadings of grafted chloroalkylsiloxanes (Al-MTS-Cl **1a**, **1b**, **2b**) or ephedrine moieties (Al-MTS-Cl-E **1a**, **1b**, **2b**) have been calculated from elemental and thermogravimetric analyses. They depend mainly on the grafting method used, the sol–gel method **b** leading to notably higher amounts of organics on the surface.

Textural properties are recorded in Table 1. Method **a** leads to conservation of the mesoporosity after modification by organics. As shown previously[7,9,10] textures are maintained after grafting of halogens and substitution by (−)-ephedrine. However, a decrease in the residual mesoporous volume is observed. In the case of method **b**, the porosity of hybrids Al-MTS-Cl **1b** and Al-MTS-Cl-E **1b** becomes a microporosity. Increasing the initial pore diameter allows high residual mesoporous volumes to be obtained even after immobilization of a high density of organic functions by method **b** (Al-MTS-Cl **2b**, Al-MTS-Cl-E **2b**, Table 1).

Enantioselective addition of diethylzinc to benzaldehyde conducted in the presence of these solid chiral auxiliaries leads to the formation of (*R*)- or (*S*)-1-phenylpropan-1-ol (Scheme 2). All experiments were performed at 0 °C using the same weight of solid chiral auxiliary (0.29 g) and 2.3 eq. of Et_2Zn to benzaldehyde.[9,10] Results are shown in Table 2.

Such chiral auxiliaries are efficient in the enantioselective transfer of an ethyl group to benzaldehyde. The best results are obtained using (−)-ephedrine anchored on the Al-MTS **2** support (entry 11) and it is worth noting that ee and activity are close to those obtained in homogeneous catalysis (entries 2 and 3). On the other hand, efficiency depends on the synthetic method and on the initial pore diameter of the support. The



Scheme 1 *Reagents and conditions*: **a**, CPTMS, toluene, anhydrous conditions, −130 °C, 4 h; **b**, CPTMS, toluene, H_2O, NH_4F–*p*TsOH, −60 °C, 6 h; **c**, (1*R*,2*S*)-(−)-ephedrine, Xylene, −140 °C, 6 h.

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Table 1 Characterization of hybrid inorganic–organic mesoporous aluminosilicates

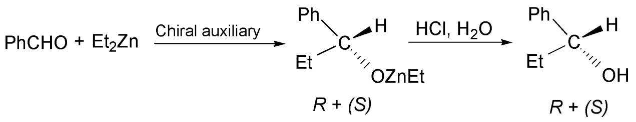
Materials	Cl loading[a]/ mmol g^{-1}	N loading[a]/ mmol g^{-1}	Cl density[b]/ 10^6 mol/m^{-2}	S^{c}_{BET}/ m^2 g^{-1}	V^{c}_{mp}/ mL g^{-1}	Mean pore diameter[c]/nm
Al-MTS-Cl **1a**	2.1	—	2.3	756	0.42	2.2
Al-MTS-Cl-E **1a**	0.8	1.3		689	0.30	1.7
Al-MTS-Cl **1b**	4.4	—	—		0.21[d]	
Al-MTS-Cl-E **1b**	2.5	1.9			0.07[d]	
Al-MTS-Cl **2b**	4.3	—	7.7	559	0.77	5.5
Al-MTS-Cl-E **2b**	2.4	1.9		440	0.62	5.5

[a] Loadings are calculated relatively to the weight of dry initial silica content. [b] Densities are expressed by the ratio of the loading to the surface area of the naked support. [c] N_2 adsorption and desorption isotherms were collected on a Micromeritics ASAP 2000 apparatus at 77 K, after outgassing samples at 423 K for 8 h. Mean pore diameters are calculated by the $4V_{\mathrm{mp}}/S_{\mathrm{BET}}$ ratio. [d] BET equation used for the determination of surface area is inoperative.

Table 2 Alkylation of benzaldehyde with diethylzinc

Entry	Materials	(−)-Ephedrine (mol%)[a]	k^{b}_{obs}/h^{-1}	Selectivity[c] (%)	Ee[d] (%)
1	Without catalyst	—	1.2 10^{-2}	51	0
2	(−)-Ephedrine	8.5	0.53	98	65
3	(−)-*N*-Propylnorephedrine	8.5	0.68	98	76
4	Al-MTS **1**	—	0.17	84	0
5	Al-MTS-Cl **1a**	—	0.11	82	0
6	Al-MTS-Cl-E **1a**	13.6	0.17	93	47
7	Al-MTS-Cl **1b**	—	0.05	84	0
8	Al-MTS-Cl-E **1b**	15.4	0.11	94	54
9	Al-MTS **2**	—	0.26	87	0
10	Al-MTS-Cl **2b**	—	0.07	86	0
11	Al-MTS-Cl-E **2b**	16.8	0.55	98	64

[a] The number of catalytic sites is calculated relative to the total weight of hybrid material. [b] Fitting of BA (%) *versus* time (h) by an exponential regression leads to k_{obs} (h^{-1}). [c] % selectivity = 100 ([*R*] + [*S*])/([*R*] + [*S*] + [PhCH$_2$OH]). [d] (%) Ee = 100 ([*R*] − [*S*])/[*R*] + [*S*].



Scheme 2

inorganic surface of the support catalyzes the racemic alkyl transfer (entries 4 and 9) as shown by comparison with the uncatalyzed reaction (Table 2, entry 1) and the activity increases with the mesoporous volume (Table 1). Coverage of the surface by chloropropyl moieties leads to a decrease in the activity whatever the support (entries 4, 5 and 7 for Al-MTS **1**, entries 9 and 10 for Al-MTS **2**). The higher the coverage is, the lower the activity of the mineral surface. Solids derived from Al-MTS **1** show a slight increase in activity after modification by (−)-ephedrine; the activity of the high density solid (entry 8) is lower than that of the low density auxiliary (entry 6). Taking into account the low residual volume of the high density Al-MTS-Cl-E **1b**, we believe that accessibility to the catalytic sites is limited by diffusional constraints and that the reaction mainly proceeds on the external surface and at the pore opening. An increase in the mean pore diameter of the support allows the synthesis of high density hybrids with conservation of available mesoporous volumes. Hence, Al-MTS-Cl-E **2b** shows the highest activity obtained up to now, concomitant with good enantioselectivity related to the organic coverage of the mineral surface. It can be assumed that the catalytic sites located on the inner surface of the pores are active in the reaction. Bae *et al.*[15] reported recently the use of new chiral heterogeneous catalysts based on mesoporous silica, either MCM-41 or SBA-15 based catalysts. They attempted to improve ee's by using a more selective ligand than (−)-ephedrine and by addition of butyllithium as an extra metal reagent. It is worth noting that ee's were improved only in the latter case using a lithium salt in place of zinc alcoholate as the catalyst. Our approach based on the comprehension of the various effects led to the synthesis of the first inorganic–organic hybrid chiral auxiliaries, the efficiency of which can be compared with that obtained in homogeneous catalysis. Moreover, these catalysts may be reused three times without loss of enantioselectivity. In summary, two factors determine the design of new inorganic–organic chiral auxiliaries effective in C–C bond formation: firstly, the coverage of the surface by organics in order to suppress the activity towards the racemic reaction and secondly, the accessibility to the catalytic sites by using inorganic supports with large mesopore diameters.

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