

Dendritic chiral auxiliaries on silica: a new heterogeneous catalyst for enantioselective addition of diethylzinc to benzaldehyde

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This article reports the first work on the use of silica supported dendritic chiral auxiliaries for the enantioselective addition of diethylzinc to benzaldehyde: the control of dendrimer propagation on the silica surface is of prime importance to obtain enhanced conversion, selectivity, and enantioselectivity.

Enantioselective addition of dialkylzinc reagents to aldehydes is one of the most important and fundamental methods that afford optically active secondary alcohols.¹ In addition to the efforts for the design of effective chiral ligands, increasing interest has been directed to their heterogenization *via* immobilization of chiral ligands on solid supports. Compared to organic polymers, however, immobilization of chiral ligands on inorganic supports has attracted little attention. In the case of silica gels, reported values for the reaction rate, selectivity, and enantioselectivity are found to be fairly low.²

Recently, attempts have been made to overcome the drawbacks associated with the irregular texture and heterogeneous chemical nature of silica gel by employing mesoporous silicas as supports.³ It has been claimed that two important features are the suppression of the formation of racemic alcohols on the naked surface and the enhancement of the accessibility of reactants to the catalytic sites.

Dendrimers are highly branched macromolecules and they are generally described to have a structure of spherical shape with a high degree of symmetry. By combining the chirality or asymmetry with their highly symmetrical nature, dendrimers render themselves attractive for the design of asymmetric catalysts. However, chiral dendrimers have rarely been utilized in asymmetric synthesis and the reaction performance has been found unsatisfactory.⁴ In the enantioselective ethylation of benzaldehyde with chiral dendrimer catalysts, both the chemical yields and the enantiomeric excess decrease with increasing generation of dendrimers because of the multiple interactions on the dendritic surface at higher generations.⁵ To relieve the multiple interactions between the end groups at the periphery of higher generations, introduction of an alkyl chain as a spacer⁵ or use of a rigid hydrocarbon backbone⁶ has been proposed.

In this work, we have developed silica supported dendritic chiral auxiliaries for the enantioselective addition of diethylzinc to benzaldehyde. To our knowledge, this is the first report that utilizes a solid-phase synthesis of dendritic materials having chiral function at the periphery to carry out the enantioselective addition of diethylzinc to benzaldehyde.

The preparation of dendritic chiral auxiliaries on silica was conducted by the following three steps: (1) preparation of initiator sites, (2) dendrimer propagation, and (3) immobilization of chiral auxiliaries at the periphery of the dendrimer.

The introduction of amino groups onto the silica surface, *i.e.*, preparation of an 'initiator site' (G_0) was accomplished by the treatment of surface silanol groups with 3-aminopropyltriethoxysilane under reflux of xylene. Two types of initiator sites were prepared containing 0.24 (G_0L) and 0.9 mmol g⁻¹ (G_0H) of amino groups, respectively.

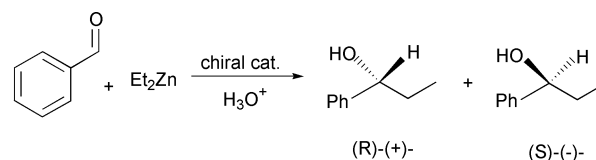
The construction of polyamidoamine dendrimer on silica support was performed by repeating the two steps pioneered by Tomalia and co-workers.⁷ The Michael addition of methyl

acrylate to the surface amino groups as an initiator site (G_0) gives rise to the formation of the amino propionate ester ($G_{0.5}$).

Table 1 The amino group content of dendrimer constructed silica^a

Initiator sites (G_0 , mmol g ⁻¹ SiO ₂)	Generation	Amino group content (mmol g ⁻¹ SiO ₂)	
		Theoretical	Observed
0.9	1 (G_1H)	1.8	1.22
	2 (G_2H)	3.6	1.62
	3 (G_3H)	7.2	1.84
	4 (G_4H)	14.4	2.26
0.24	1 (G_1L)	0.48	0.45
	2 (G_2L)	0.96	0.84
	3 (G_3L)	1.92	1.46
	4 (G_4L)	3.84	1.89

^a The content of amino groups was determined by elemental analysis, acid-base titration, and UV-vis spectroscopy. To obtain UV-vis spectra, 4-nitrobenzaldehyde was linked to terminal amino groups *via* imine formation.⁹

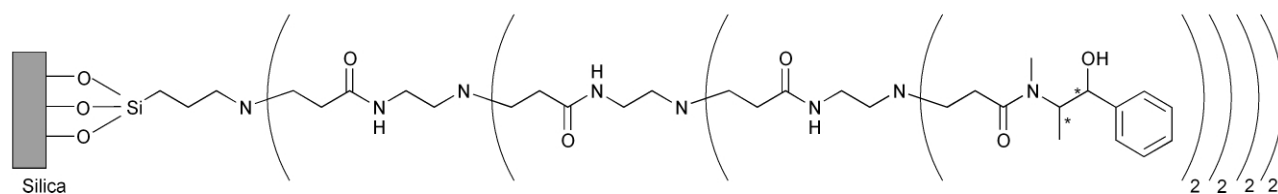


Scheme 1

Table 2 Experimental results of enantioselective addition of diethylzinc to benzaldehyde^a

Entry	Catalyst ^b	Conversion (%)	Selectivity (%)	ee (%), (R)
1	Without catalyst	45	57	0
2	(-)-Ephedrine	91.3	98	62
3	$G_{0.5}H-E$	82.7	92.2	11.8
4	$G_{1.5}H-E$	79	88.2	8
5	$G_{2.5}H-E$	70	88.4	6.5
6	$G_{3.5}H-E$	67.6	84.8	3.7
7	$G_{4.5}H-E$	66	85.2	2.8
8	$G_{0.5}L-E$	63	85	11
9	$G_{1.5}L-E$	77	91	23.8
10	$G_{2.5}L-E$	86.2	94.9	40.5
11	$G_{3.5}L-E$	88.5	97.6	56
12	$G_{3.5}L-E^c$	92	98	59.7
13	$G_{3.5}L-E$ (recycle 1) ^d	86	97.2	53.8
14	$G_{3.5}L-E$ (recycle 2) ^d	80	97	50.4
15	$G_{3.5}L-E$ (recycle 3) ^{d,e}	85.3	98	56.2
16	$G_{4.5}L-E$	83.6	98	42.2

^a All the reactions were carried out in toluene at 0 °C for 48 h using 2.2 molar equiv. of diethylzinc and 5 mol% of catalyst. ^b Amine content of initiator sites; H = 0.9 mmol NH₂ g⁻¹ SiO₂, L = 0.24 mmol NH₂ g⁻¹ SiO₂. ^c 6.6 molar equiv. of diethylzinc. ^d The recovery of catalyst was carried out in a manner similar to the one reported elsewhere.^{10c} ^e Additional fresh catalyst was supplemented for the loss during recycling.



Scheme 2 $G_{3.5}L-E$ propagated from G_0L containing $0.24 \text{ mmol NH}_2 \text{ g}^{-1} \text{ SiO}_2$.

Subsequent amidation of the resulting ester moieties with an excess of ethylenediamine affords the first generation of dendrimer constructed silica (G_1). Both the Michael addition and the amidation reactions were repeated to propagate the second (G_2), third (G_3), and fourth generation (G_4) dendrimers on the silica surface in a similar manner.

Table 1 shows the amino group content of the n th generation dendrimer constructed silica. It is found that the propagation of dendrimer on the silica surface at higher generations is not so high as the theoretical value due to the incomplete propagation caused by the steric crowding.⁸ However, it should be noted that the propagation on G_0L is more effective than that on G_0H .

Dendritic chiral catalysts were prepared *via* the reactions of various dendrimers ($G_{n.5}H$, $G_{n.5}L$) with (1*R*, 2*S*)-ephedrine under reflux of hexane. The immobilization of chiral ligand on dendritic supports affords two series of catalysts, $G_{n.5}H-E$ and $G_{n.5}L-E$. Regardless of the catalyst used, the reaction yielded 1-phenyl-1-propanol as the major product (Scheme 1). Benzyl alcohol is formed *via* the reduction of benzaldehyde by diethylzinc in the absence of catalyst and this reaction proceeds slowly in a competitive way.

As may be noticed in Table 2, the reaction performance is strongly dependent upon both the number of generations and the amino group content of initiator sites. In all the cases with $G_{n.5}H-E$ series, the conversion, selectivity, and enantioselectivity decreased with an increase in the number of generations. The irregular hyper-branching caused by the incomplete propagation gives rise not only to a diffusional resistance but also to a different chiral environment. Moreover, the irregular branching appears not to be effective in preventing the reactant from approaching to the native support on which the unfavorable racemic alkyl transfer reaction proceeds and thus decreases the enantioselectivity significantly.

On the other hand, the reactions with $G_{n.5}L-E$ series exhibit different characteristics compared to those with $G_{n.5}H-E$ series. The increase in the number of generations brings about an increase in the conversion, going from 63 ($G_{0.5}L-E$) to 88.5% ($G_{3.5}L-E$). This indicates that a large portion of active sites can exist at the periphery of dendrimers and be exposed to the reaction mixture so that they are easily accessible. When the fourth generation is reached ($G_{4.5}L-E$; *cf.* entry 13 of Table 2), however, the steric hindrance caused by the hyper-branching becomes significant enough to partially restrict the access of reagents to active sites. This may lead to a decrease in the catalytic activity.

The most conspicuous feature of the reactions with the $G_{n.5}L-E$ series is the change in the enantioselectivity. Unlike the case of the $G_{n.5}H-E$ series, the enantioselectivity is found to increase as the number of generations increases. When the reaction is carried out in the presence of $G_{3.5}L-E$ (Scheme 2), the enantioselectivity is increased to 56% (*cf.* entry 11 of Table 2). In addition, the reaction performance can be improved to the level of the homogeneous counterpart by increasing the diethylzinc concentration (*cf.* entry 12 of Table 2). Similar

observations have also been reported in the homogeneous system by other groups.^{5,6}

The high enantioselectivity may originate from a unique feature of the dendritic catalyst. Presumably, the globularly hyper-branched nature of the dendritic backbone effectively prevents the reagents from having access to the native mineral surface which is responsible for the production of racemic alcohol. In addition, the multiple interactions between end groups may be weakened because the dendrimer is propagated on the rigid solid support. Consequently, the chiral ligand may take its preferred conformation more easily. In the reaction with $G_{4.5}L-E$, however, the enantioselectivity is observed to be lower and this suggests that the multiple interactions between end groups become more pronounced in this case.

On the basis of these results, it is evident that symmetric hyper-branching is prerequisite to suppress the unfavorable racemic reaction taking place on the naked surface. Furthermore, the control of hyper-branching is important not only to maintain the accessibility of reagents to the active sites high but also to relieve the multiple interactions between the chiral active sites. In this regard, an appropriate balance between the two factors, the amino group content of initiator sites and the number of generations, is of prime importance to obtain higher values of the conversion, selectivity and enantioselectivity. Furthermore, the heterogeneous dendritic chiral catalyst can also be recycled and reused without a significant loss of catalytic activity. This new organic-inorganic hybrid catalyst is considered to be one of the most effective catalysts for the enantioselective addition of diethylzinc to benzaldehyde.

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