Catalysis Letters Vol. 82, No. 3–4, October 2002 (©2002)

Design of silica-supported dendritic chiral catalysts for the improvement of enantioselective addition of diethylzinc to benzaldehyde

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Received 12 March 2002; accepted 22 May 2002

This article describes an efficient method to design a heterogeneous catalyst for the enantioselective addition of diethylzinc to benzaldehyde. Combining the immobilization of a dendrimer on a silica surface with the introduction of a long alkyl spacer at the periphery of the dendrimer is found to be effective in improving the conversion, selectivity and enantioselectivity.

KEY WORDS: dendrimer; immobilization; asymmetric synthesis; chiral ligand; organic–inorganic hybrid; alkylation; secondary alcohol.

1. Introduction

Enantioselective addition of dialkylzinc reagents to aldehydes is one of the most important and fundamental methods that affords optically active secondary alcohols [1,2]. 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 insoluble supports in an attempt to combine the practical advantages of a heterogeneous catalyst with the efficiency of a homogeneous system. However, the efficiency of the heterogenized catalysts depends mainly on the nature of the support and is less than satisfactory compared with their homogeneous counterparts. With organic polymer supports, enantiomeric excesses are high but rates are generally lower due to the intrinsic feature of polymeric materials that reactions taking place on the interior surface of a porous catalyst particle encounter resistance to mass transport through the pores. On the other hand, immobilization of chiral ligands on inorganic supports has attracted little attention. In the case of silica gels, the reported values of rates, selectivities and enantioselectivities are found to be low [3].

In recent years, 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. There have been investigations involving changes in the pore size, the composition of the support, end-capping of the surface, and the dilution of the catalytic sites to improve the activity, selectivity and enantioselectivity [4–6]. It has been claimed that two factors such as the suppression of the activity of the naked surface toward the formation of racemic alcohols and the accessibility to the catalytic sites are of prime importance [5].

Dendrimers are highly-branched macromolecules and they are generally described as having a structure of spherical shape with a high degree of symmetry. By combining chirality or asymmetry with their highly-symmetric nature, dendrimers render themselves attractive for the design of asymmetric catalysts. Different from conventional polymers, when chiral functionalities are introduced at the periphery of a dendrimer, approximately the same chiral environments are envisaged. However, chiral dendrimers have rarely been utilized in asymmetric synthesis and the reaction performance has been found to be unsatisfactory [7]. In the enantioselective ethylation of benzaldehyde with chiral dendrimer catalysts, both the chemical yields and the enantiomeric excess decrease with increase in the generation of dendrimers because of the multiple interactions on the dendritic surface at higher generations [8].

Recently, we have found that silica-supported dendritic chiral catalysts are effective for the enantioselective addition of diethylzinc to benzaldehyde [9]. It was observed that the reaction performance is strongly dependent on the control of hyper-branching and the symmetric hyper-branching is a prerequisite to suppressing the racemic reaction taking place on the mineral surface and to maintaining the accessibility of reagents to the active sites high. In this regard, a desirable dendritic chiral catalyst constructed on the surface of silica can be obtained by appropriate balancing between the amino group content of initiator sites and the number of dendrimer generations.

From the viewpoint of the suppression of the racemic reaction, it may be conceivable that immobilization of a

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1011-372X/02/1000-0249/0

perfectly symmetric dendrimer would be more effective than our previous method, *i.e.,* stepwise propagation of a dendrimer on a silica support, because the propagation of a dendrimer on a silica surface at higher generations is hardly as high as that of the theoretical value due to steric crowding [9–11]. However, it is noteworthy that the use of a ready-made dendrimer is accompanied by an intrinsic problem of a chiral dendrimer catalyst. Dense packing caused by the multiple interactions on the dendritic surface at higher generations will bring about not only diffusional resistance but also different chiral environments [7,8].

In line with our previous study, we have developed here another type of silica-supported dendritic chiral catalyst to achieve two goals: suppression of the unfavorable racemic reaction caused by the surface silanol groups and weakening of the multiple interactions between the chiral functionalities at the periphery of the dendrimer.

2. Experimental

2.1. Materials and reagents

Ultrafine silica was supplied by Aldrich. The specific surface area and particle size were 500 m^2/g and 2–25 μm, respectively. It was dried *in vacuo* at 110 °C for 24 h before use. Methyl acrylate (Aldrich) and all the solvents used were distilled just before use. 3-Glycidoxypropyltrimethoxysilane (Aldrich), 1,6-diaminohexane (Fluka), (1*R*,2*R*)-(+)-1-phenylpropylene (Aldrich), 1.1 M diethylzinc solution in toluene (Aldrich), benzaldehyde (Aldrich) and *n*th generation polyamidoamine (PAMAM) dendrimers (Aldrich) were used without further purification.

2.2. Preparation of silica-supported dendritic chiral catalysts

As shown in figure 1, the preparation of silica-supported dendritic chiral catalysts was carried out in four steps: (1) grafting of an epoxide linker on a silica support, (2) immobilization of the *n*th generation dendrimer, (3) introduction of a long alkyl spacer and (4) immobilization of chiral auxiliaries at the periphery of the dendrimer.

The grafting of an epoxide linker on a silica support (G_0) was conducted by the treatment of surface silanol groups with 3-glycidoxypropyltrimethoxysilane (GPTMS) under reflux of toluene. A typical example is as follows: 20 g of freshly dried silica in toluene (100 ml) was refluxed and stirred for 3 h with GPTMS (0.15 mol). After cooling to room temperature, the mixture was filtered and washed thoroughly with toluene and methanol, and this was followed by Soxhlet extraction with methanol for 24 h. The resulting product

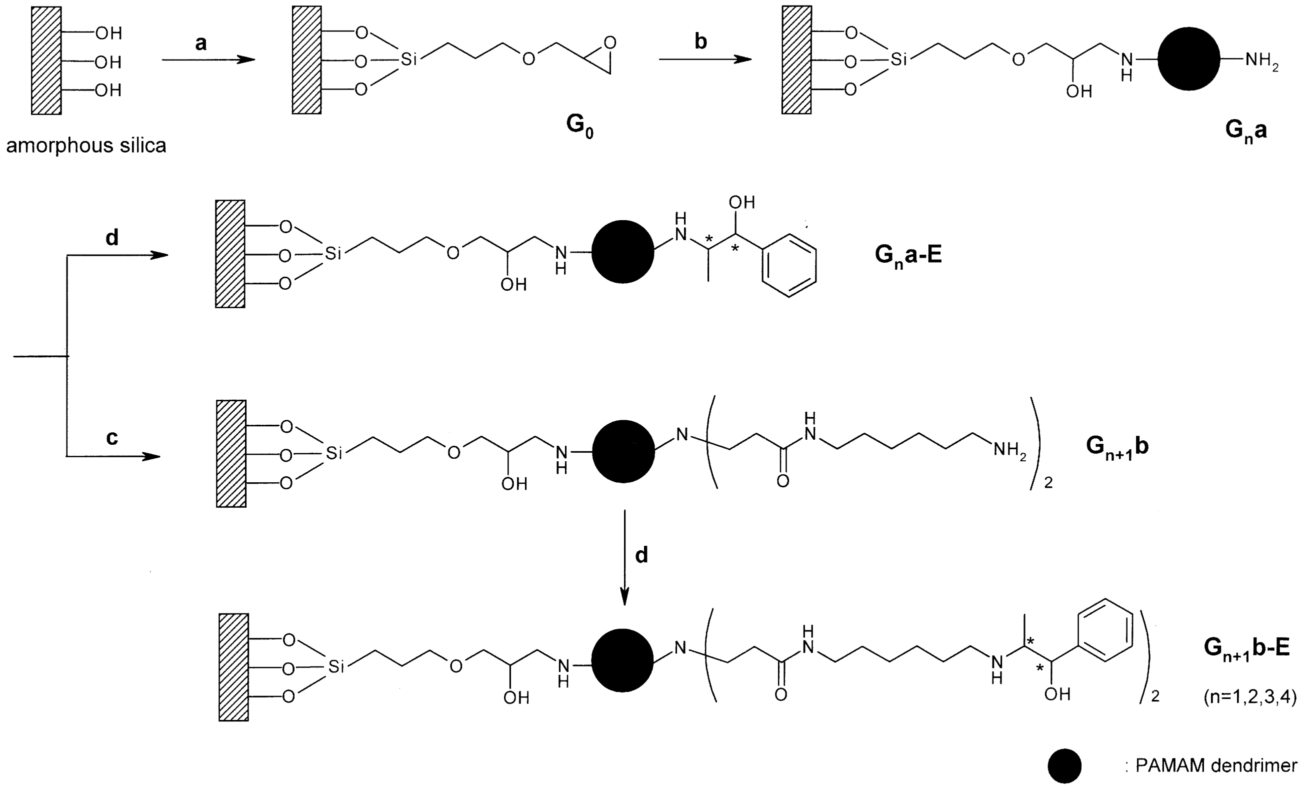

Figure 1. Preparation of silica-supported dendritic chiral catalysts. (a) 3-Glycidoxypropyltrimethoxysilane, toluene, reflux, 3 h; (b) *n*th generation PAMAM dendrimer, methanol, reflux, 4 h; (c) (i) excess of methyl acrylate, methanol, 50 °C, 3 days, (ii) excess of 1,6-diaminohexane, methanol, 50 °C, 3 days; (d) (1*R*,2*R*)-(+)-1-phenylpropylene oxide, hexane, reflux, 3 h.

was dried under vacuum at 110 °C. Elemental analysis showed that 0.97 mmol/g of GPTMS was constructed on the silica surface.

Immobilization of the *n*th generation dendrimer on G_0 affords the dendrimer grafted silica. For this, 3 g of G_0 in methanol (20 ml) was refluxed with 3 ml of the *n*th generation dendrimer solution (10 wt% dendrimer in methanol) for 4 h. The resulting sample was isolated by filtration and washed with methanol three times. The residual solvent was removed *in vacuo* affording silica with the *n*th generation dendrimer constructed (G_na).

To extend the chain length, the terminal ethylenediamine was substituted by 1,6-diaminohexane. Michael addition of G_na with methyl acrylate gives rise to the formation of terminal ester groups ($G_{n.5}$a). Subsequent amidation of the resulting product with 1,6-diaminohexane completes the reaction (G_{n+1}b). Michael addition was carried out as follows: 1 g of G_na and methyl acrylate (20 equivalents to amino groups) in methanol (20 ml) were stirred at 50 °C for 3 days under nitrogen. The suspension was cooled, filtered and washed with methanol three times. The resulting product ($G_{n.5}$a) was dried under vacuum. The amidation of terminal ester groups with 1,6-diaminohexane was conducted as follows: into a flask that contained the resulting silica ($G_{n.5}$a), 20 ml of methanol and 1,6-diaminohexane (20 times larger than the content of terminal ester groups) were added and stirred at 50 °C for 3 days under nitrogen. The resulting sample was isolated by filtration and washed with methanol three times. The residual solvent was removed *in vacuo* affording the alkyl-spacer-introduced dendrimers (G_{n+1}b).

Introduction of chiral functionalities at the periphery of the dendrimer was carried out by the reactions of various silica-supported dendrimers (G_na and G_{n+1}b) with (1*R*,2*R*)-(+)-1-phenylpropylene oxide (10 equivalents to amino groups) under reflux of hexane for 3 h. The reaction affords two series of catalysts, G_na-E and G_{n+1}b-E. Hexane was selected to prevent a retro-Michael reaction possibly proceeding at higher temperatures (*i.e.*, >100–120 °C) [12]. After cooling, the modified solid was filtered, washed with ether and methanol thoroughly, and dried *in vacuo*.

2.3. *General procedure for the enantioselective addition of diethylzinc to benzaldehyde*

The catalyst was dried under vacuum at 90 °C for 24 h. Then, a mixture of catalyst (G_na-E or G_{n+1}b-E, 5 mol%) and diethylzinc (2 ml of 1.1 M solution in toluene, 2.2 mmol) was stirred at 25 °C under an atmosphere of dry nitrogen for 1 h, and then cooled to 0 °C. A solution of benzaldehyde (1 mmol) in toluene (0.9 ml) was slowly added and the resulting mixture was stirred at 0 °C for 48 h. The reaction was quenched by the addition of 1 M HCl solution. After the removal of catalyst by filtration, the organic layer was separated and the aqueous layer was extracted with toluene. The combined organic layers were dried with $MgSO_4$ and then analyzed using a Varian CP-3380 gas chromatograph (GC) equipped with a chiral column (CP-cyclodextrin-β-2,3,6-M-19).

The recovery of catalyst was carried out in a manner similar to that reported elsewhere [13]. The recovered catalyst from the filtration was stirred for 4 h in a 4 : 1 mixture of THF–1 M HCl. The catalyst was filtered off and washed successively with water and a 4 : 1 mixture of THF–1 M NaOH, filtered off, and washed successively with water and methanol. After being dried *in vacuo*, the catalyst was reused.

3. Results and discussion

We examined the enantioselective addition of diethylzinc to benzaldehyde in the presence of two families of dendritic chiral catalysts. Regardless of the catalyst used, the reaction yielded 1-phenyl-1-propanol as the major product as shown in figure 2. Benzylalcohol is formed *via* the reduction of benzaldehyde by diethylzinc in the absence of catalyst and this reaction proceeds slowly in a competitive way.

As summarized in table 1, there are striking differences between the two series of dendrimer catalysts in promoting the reaction. In all the cases with G_na-E series (entries 2–5), the conversion, selectivity and enantiomeric excess decreased with an increase in the number of generations. The decrease in catalytic activity indicates that the access of reagents to active sites is restricted due to the steric hindrance as the packing becomes denser at higher generations. Furthermore, the denser packing of the end groups at higher generations brings about the presence of a number of different frozen-in conformations [7,8]. Consequently, it seems hardly achievable for a chiral catalyst to adopt its preferred conformation, which results in a poor enantiomeric excess. The possibility of surface reaction can be excluded because the hyper-branching of dendritic backbone is more crowded at higher generations.

On the other hand, the reactions with G_{n+1}b-E series (entries 6–12) exhibit different characteristics. Irrespective of generations, enhanced reaction performances were obtained with G_{n+1}b-E series compared with those with G_na-E series. This indicates that the introduction of an alkyl spacer not only renders the access

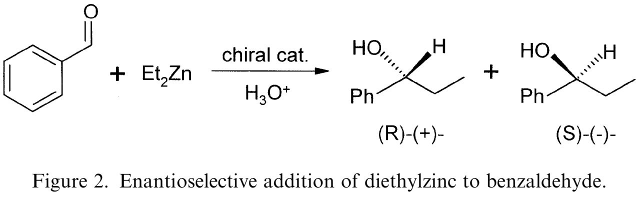

Figure 2. Enantioselective addition of diethylzinc to benzaldehyde.

Table 1
Experimental results of enantioselective addition of diethylzinc to benzaldehyde

Entry	Catalyst	Conversion (%)	Selectivity (%)	ee (%) (*R*)
1	Without catalyst	45	57	0
2	G_1a-E	79.7	96.4	13.2
3	G_2a-E	73.3	96	7.2
4	G_3a-E	71.3	91.5	5.2
5	G_4a-E	65.5	87.2	2.3
6	G_2b-E	77.3	97.2	15.5
7	G_3b-E	83.8	98.4	35.9
8	G_4b-E	85	98	37
9	G_4b-E (recycle 1)	82	98	34
10	G_4b-E (recycle 2)	78	97.6	28.8
11	G_4b-E (recycle 3)[a]	84	98	34.2
12	G_5b-E	68	95.3	17.6

[a] Additional fresh catalyst was supplemented for the loss during recycling.

of reactant to the catalytic active sites easier but also effectively imparts the unfavorable intramolecular interactions between the chiral active sites. The latter suggests that respective chiral ligands at the periphery of the dendrimer are expected to operate independently and consequently exhibit approximately the same chiral environment. Similar observations have also been reported in a homogeneous system [8]. When the fifth generation is reached (G_5b-E, entry 12), however, the multiple interactions between end groups become more pronounced. This may lead to a decrease in the reaction performance. It should be noted that although a decrease in the reaction performance is observed at higher generation, it is evident that the use of an alkyl chain as a spacer leads to an enhancement of catalytic performance. In the case of G_na-E series an increase of enantioselectivity was not observed at higher generations.

It is noteworthy that although it has been reported that this particular type of chiral catalyst formed by the epoxide ring-opening shows a moderate to low enantiomeric excess [14], we have used the chiral dendrimer catalyst to investigate the viability of our strategy for the suppression of the racemic reaction taking place on the mineral surface and for the relaxation of multiple interactions between chiral active sites. It is natural that the enantioselectivity mainly depends on the nature of a chiral ligand, and therefore the moderate enantiomeric excess obtained in this study can be improved by the use of an effective chiral ligand. In our previous report, we have shown that in the reaction with an ephedrine immobilized chiral dendrimer catalyst, the reaction performance can be improved to the level of its homogeneous counterpart [9].

In order to confirm the feasibility of catalyst recycling, after the reaction with G_4b-E was completed, the catalyst was filtered, washed thoroughly and reused three times. Although the catalytic performance of the recovered catalyst slightly decreased as the catalyst recycle was repeated (entries 9 and 10), it should be noted that the decrease in the catalytic performance may be caused by the loss of catalyst during the catalyst regeneration. When additional fresh catalyst was supplemented (entry 11), the reaction performance became as good as that of the fresh one. This indicates that the silica-supported dendritic chiral catalyst can be reused without apparent loss of catalytic activity.

4. Conclusions

A new silica-supported dendritic chiral catalyst has been developed for the enantioselective addition of diethylzinc to benzaldehyde. It has been found that the participation of surface silanol groups in the racemic reaction can be effectively suppressed by the immobilization of the dendrimer on the silica support. Moreover, the substitution of terminal ethylenediamine with a long alkyl chain spacer is effective to relieve the multiple interactions between the end groups. Therefore, our strategy of combining the immobilization of a dendrimer on a silica surface with the introduction of a long alkyl spacer may be considered as one of the most effective methods to design a heterogeneous chiral catalyst for the enantioselective addition of diethylzinc to benzaldehyde.

The present strategy may be applied to various asymmetric alkylation systems in which optically active ligands can be used as a chiral inducer. Moreover, it is worth noting that the application of the silica-supported dendrimer catalysts may not be restricted to the asymmetric synthesis but can be expanded to many of the heterogeneous catalytic reactions because the use of the dendritic catalysts is obviously advantageous over the conventional catalysts in the sense that the diffusional resistance is reduced and the active sites are formed almost uniformly.

Acknowledgment

Financial aid from the Brain Korea 21 Program supported by the Ministry of Education is gratefully acknowledged.

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