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Application of well-defined chain-end-functionalized polystyrenes with dendritic chiral ephedrine moieties as reagents for highly catalytic enantioselective addition of dialkylzincs to aldehydes

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Abstract—A series of well-defined chain-end-functionalized polystyrenes having a definite number of chiral ephedrine moieties dendritically distributed at the periphery of their hyperbranched chain-ends were evaluated as chiral catalysts for the enantioselective addition of dialkylzinc reagents to aldehydes. These dendritic macromolecules worked well as homogeneous chiral catalysts and exhibited high catalytic activity and enantioselectivity very similar to those observed for the corresponding monomeric chiral catalysts. The optimum amount of chiral catalyst was found to be 5 mol %. A profound number effect of the chiral ephedrine moieties was observed, and PS(Ephed)$_8$ having eight chiral ephedrine moieties at the periphery was found to be superior to other dendritic chiral catalysts. The enantioselectivity reached a value of 95% in the addition of diisopropylzinc to 3-phenylpropanal. The dendritic chiral catalysts could be easily recovered from the reaction solution by using a solvent precipitation method, and the recovered catalyst showed no significant loss of its catalytic activity or enantioselectivity.

1. Introduction

One of the major challenges in organic synthesis is the asymmetric preparation of organic compounds by means of forming carbon–carbon bonds through asymmetric catalysis.[1] Among the different strategies, the catalytic enantioselective 1,2-addition of organometallics to carbonyl compounds is probably the most straightforward and useful manner of achieving this goal.[2] Since Soai et al. have reported the chiral ephedrine-catalyzed dialkylzinc addition to benzaldehyde,[3] numerous elegant investigations have established the broad utility of using several chiral β-amino alcohols,[4] and their polymer-supported analogues[5] as chiral catalysts. However, a major problem associated with most homogeneous chiral catalyst systems is the separation and recycling of the expensive chiral catalyst. Although linear polymeric chiral catalysts with an enantioselectivity parallel to that of the monomeric chiral catalysts have been developed, their efficiency for asymmetric catalysis has been limited due to the nature of one catalytic site per repeating unit.[6] Moreover, unfortunately, most of the insoluble polymer-supported chiral catalysts often suffered from low catalytic activity and enantioselectivity.[7] In recent years, the utility of using dendronized chiral β-amino alcohols in the catalytic asymmetric dialkylzinc addition to aldehydes has been surveyed.[8]

Meanwhile, dendrimers or dendronized polymers are among the most exciting molecular architectures that have been recently developed, and they have paved the way for a new class of materials with promising applications.[9] The dendritic rods can thus be used as ideal scaffolds for the immobilization of chiral catalysts, yielding structurally well-defined recyclable catalysts.[10] Unlike ordinary polymers, chiral dendrimers are characterized by their elaborate structure, which allows us to precisely control their molecular size, shape, and the numbers and positions of functional groups.[11] Organometallic dendrimers offer an attractive avenue for catalyst development because of their ease of characterization and their solubility in most

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common organic solvents. Thus, the unique feature of this strategy is that the catalytic reactions are carried out in a homogeneous manner (one phase) under appropriate reaction conditions and the immobilized catalysts can be separated from the reaction mixture afterwards by using a solvent precipitation method (two-phase). In general, catalyst efficiency is expected to be superior with a dendritic complex, since they could also overcome the dense packing problem that exists in the linear polymeric catalysts without sacrificing the advantage of easy recovery by either filtration or precipitation.[10,11] Thus, dendronized chiral polymers may bridge the gap between homogeneous and heterogeneous catalysis. Due to their unique structure and size, potential applications are manifold and include their use as catalyst supports for asymmetric synthesis.[8,10,12]

Over the course of our continuing study on asymmetric synthesis using recyclable chiral ligands and catalysts,[13,14] we became interested in the attractive characteristics of dendrimers. As a part of our research, we are interested in the precise synthesis of a novel special shaped macromolecules with different architectures including chain-end and in-chain-functionalized polystyrenes with a definite number of benzyl halide functionalities by means of living anionic polymerization.[15,16] Thus, we have recently successfully synthesized a novel series of chain-end-functionalized polystyrenes with a definite number of chiral ephedrine moieties dendritically distributed at their hyperbranched chain-ends PS(Ephed)$_n$ (Fig. 1), by an attractive iterative methodology based on a divergent approach, by which well-defined chain-end-functionalized polystyrenes with a definite number of benzyl bromide functionalities were prepared, followed by the introduction of the ephedrine moieties.[17] The preliminary application of these dendritic chiral polymers in the highly enantioselective diethylzinc addition to a series of *N*-diphenylphosphinoyl arylimines has also been reported.[17]

As an extension of our research program aimed at developing practical immobilized chiral catalysts, we herein report the first application of the above-mentioned chiral dendrimers PS(Ephed)$_n$ as chiral catalysts in the dialkylzinc addition reaction to aldehydes. Our design demonstrated that the chiral dendrimers serve as highly active homogeneous chiral catalysts and allow for significantly more facial catalyst recovery when compared to the corresponding non-polymeric catalysts.

2. Results and discussion

As has been mentioned in the preceding section, we have recently described the synthesis and application of a new kind of dendronized polymers with chiral ephedrine incorporation at the polystyrene hyperbranched chain-ends PS(Ephed)$_n$ as highly effective chiral ligands for the enantioselective diethylzinc addition to a series of *N*-diphenylphosphinoyl imines[17] (Fig. 1 and Scheme 1). According to our previous study,[17] all dendronized chiral polymers used were found to be highly active chiral ligands and the addition products were obtained with high enantioselectivities (up to 93% ee). It was noted that higher enantioselectivities of the addition products were observed when the generation of the pendant dendron that includes the chiral moieties was increased from two to eight, while dendronized polymers with a higher generation of sixteen ephedrine moieties PS(Ephed)$_{16}$ drove the asymmetric ethylation reaction to a lower yield and enantioselectivity. In continuation of this study, the catalytic efficiency of the dendronized chiral polymers PS(Ephed)$_2$–PS(Ephed)$_{16}$ as chiral

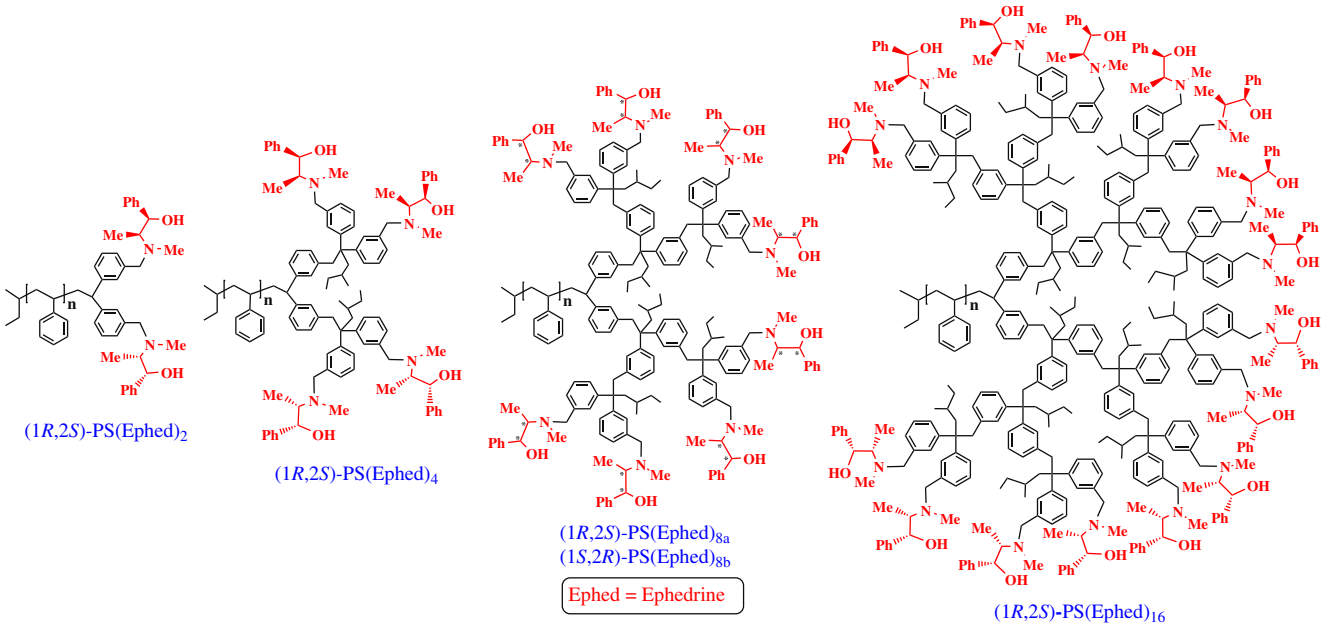
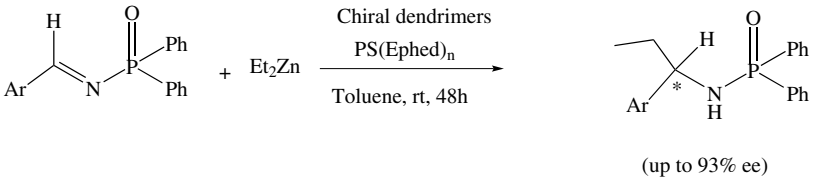


Figure 1. Structures of chain-end functionalized polystyrenes having 2, 4, 8, and 16 chiral ephedrine moieties PS(Ephed)$_n$.

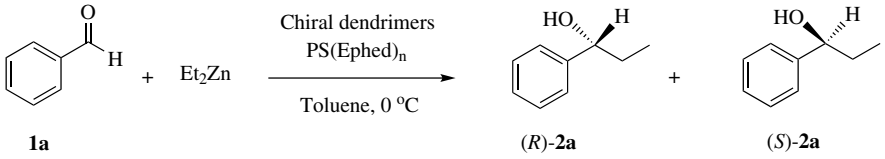


Scheme 1. Diethylzinc addition to *N*-diphenylphosphinoyl imines using chiral dendrimers Ps(Ephed)$_n$.

catalysts in the enantioselective addition of dialkylzincs to aldehydes was further examined.

As pointed out in the literature, when chiral dendrimers with heteroatoms in their polymeric backbones were used as chiral ligands in the enantioselective dialkylzinc addition to aldehydes, an excess amount of dialkylzinc reagents should be used due to the unfavorable coordination that may occur with the dialkylzinc, and may also result in reducing the enantioselectivity of the addition products.[8b,f,g] Therefore, it is necessary to avoid any unfavorable coordination between the dialkylzinc reagents and the framework of the dendrimer. Thus, we have devised the above-mentioned chiral dendrimers PS(Ephed)$_2$–PS(Ephed)$_{16}$ that are shown in Figure 1 with hydrocarbon backbone chains (i.e., without any heteroatoms either in the polystyrene main chain or in the dendritic chain-ends). In this case, the polymer backbone hardly coordinates with the dialkylzinc reagent and each chiral site of the dendritic chiral catalyst is anticipated to work independent of other chiral sites.

In order to optimize the reaction conditions, the enantioselective diethylzinc addition reaction to benzaldehyde **1a** using the above-mentioned macromolecular chiral catalysts PS(Ephed)$_2$–PS(Ephed)$_{16}$ was chosen as the model reaction (Scheme 2). The results are summarized in Table 1. Under the same reaction conditions, the asymmetric diethylzinc addition to benzaldehyde **1a** in the presence of catalytic amounts of chiral dendrimers PS(Ephed)$_2$–PS(Ephed)$_{16}$ (5 mol %; based on the total number of chiral ephedrine moieties at the periphery, relative to benzaldehyde) in toluene at 0 °C for 48 h was first examined (Table 1, entries 1, 4, 7, and 8, respectively). As can be seen, when chiral dendrimer PS(Ephed)$_2$, bearing two stereogenic sites at the periphery, was used as a chiral catalyst, the corresponding enantiomerically enriched (*R*)-1-phenyl-1-propanol **2a** was obtained with a chemical yield of 63% and an enantioselectivity of 72% ee (Table 1, entry 1). The same reaction using chiral dendrimer PS(Ephed)$_4$ afforded the addition product (*R*)-**2a** with a higher ee value of 78% ee and chemical yield of 77% (Table 1, entry 4). Interestingly, the chemical yield as well as the enantioselectivity of the addition



Scheme 2. Catalytic asymmetric addition diethylzinc to benzaldehyde using chiral dendrimers PS(EPhed)$_n$.

Table 1. Catalytic enantioselective diethylzinc addition to benzaldehyde **1a** using chiral dendrimers PS(Ephed)$_2$–PS(Ephed)$_{16}$[a]

Entry	Chiral dendrimer		Reaction time (h)	Alcohol		
		(mol %)		Yield[b] (%)	ee[c] (%)	Config.[d]
1	PS(Ephed)$_2$	5	48	63	72	(*R*)
2	PS(Ephed)$_2$	7	48	79	76	(*R*)
3	PS(Ephed)$_2$	10	48	88	79	(*R*)
4	PS(Ephed)$_4$	5	48	77	78	(*R*)
5	PS(Ephed)$_4$	7	48	89	82	(*R*)
6	PS(Ephed)$_4$	10	48	90	83	(*R*)
7	PS(Ephed)$_{8a}$	5	48	94 (98)[e]	90 (92)[e]	(*R*)
8	PS(Ephed)$_{16}$	5	48	86	84	(*R*)
9	PS(Ephed)$_2$	5	96	86	75	(*R*)
10	PS(Ephed)$_4$	5	72	90	79	(*R*)
11	PS(Ephed)$_{8a}$	10	48	95	91	(*R*)
12[f]	PS(Ephed)$_{8a}$	5	48	93	89	(*R*)
13	PS(Ephed)$_{8b}$	5	48	95	90	(*S*)

[a] All reactions were performed in toluene at 0 °C using 2.2 M equiv of diethylzinc.
[b] Yields after purification by column chromatography (hexane/ethyl acetate = 4:1).
[c] Determined by HPLC analysis on a chiral stationary phase (Chiralcel OD-H).
[d] The absolute configurations were assigned by comparing the sign of their specific rotations with those reported in the literature.[4c,d,i,5b,c,18]
[e] Data in parentheses are obtained from the same reaction using (1*R*,2*S*)-*N*-benzylephedrine.[5e]
[f] Recovered chiral catalyst was used.

product **2a** was increased markedly on using PS(Ephed)$_{8a}$ that having eight ephedrine moieties (90% and 94% ee, respectively, Table 1, entry 7). More interestingly, chiral dendrimer PS(Ephed)$_{16}$, with sixteen ephedrine moieties at the periphery of the hyperbranched chain-ends, drove the asymmetric ethylation reaction of **1a** with an enantioselectivity of 84% ee and a chemical yield of 86% (Table 1, entry 8).

As can be seen from the results that are shown in Table 1 (entries 1, 4, 7, and 8), under the same reaction conditions, the enantioselectivity of the addition product **2a** obtained from using PS(Ephed)$_{8a}$ (entry 7) was higher than that observed when using PS(Ephed)$_{16}$ (entry 8) as chiral catalysts. It can be speculated that the lower enantioselectivity of **2a** that was obtained from using PS(Ephed)$_{16}$ (entry 8) as a chiral catalyst resulted from the highly condensed packing of the chiral moieties at the periphery of the dendrimer, which might cause the interference of the active chiral sites at the periphery of PS(Ephed)$_{16}$ either with each other and/or with the polymer backbone chains, while the environments of chiral sites at the polystyrene hyperbranched chain-ends of PS(Ephed)$_{8a}$ might have enough space to work more independently as chiral catalysts.

The influence of the molar ratios of the dendritic chiral catalyst was also examined to establish whether there is any relationship between its molar ratios with the enantiomeric excess of the resulting secondary alcohol. The results obtained are also included as shown in Table 1. On performing the diethylzinc addition reaction to benzaldehyde **1a** in the presence of higher molar ratios of PS(Ephed)$_2$ (7 and 10 mol %; Table 1, entries 2 and 3, respectively), the addition reaction turned out to be faster while the chemical yield as well as the enantioselectivity of the addition product **2a** was increased markedly, but still lower than those values obtained from the same reaction using 5 mol % of PS(Ephed)$_{8a}$ (entry 7). The same observation could also be seen using higher molar ratios of PS(Ephed)$_4$ (7 and 10 mol %; Table 1, entries 5 and 6, respectively); the chemical yield was significantly increased with increasing the molar ratio from 5 to 10 mol % of PS(Ephed)$_4$, while no considerable change in the enantioselectivity of the addition product with increasing the molar ratio of PS(Ephed)$_4$ from 7 to 10 mol % of chiral dendrimer PS(Ephed)$_4$ (entry 6) was observed. However, on performing the diethylzinc addition reaction to benzaldehyde **1a** using 5 mol % of chiral dendrimers PS(Ephed)$_2$ and PS(Ephed)$_4$ as chiral catalysts, but for longer reaction times (Table 1, entries 9 and 10, respectively), significant increases in the chemical yields and slightly higher enantioselectivities of the addition product **2a** were observed. Interestingly, the diethylzinc addition reaction to benzaldehyde **1a** using a higher molar ratio of chiral catalyst PS(Ephed)$_{8a}$ (10 mol %) afforded the addition product **2a** with almost the same enantioselectivity (91% ee, entry 11) similar to that observed in the same reaction using 5 mol % of PS(Ephed)$_{8a}$ (90% ee, entry 7).

The above-mentioned set of experiments clearly revealed that increasing the number of chiral ephedrine moieties at the periphery and consequently the size of the pendant dendritic chain-ends improved not only the chemical yield but also the enantioselectivity of the addition product. It is interesting to note that the same behavior was also observed during our previous study on the enantioselective diethylzinc addition to *N*-diphenylphosphinoyl imines using the same chiral dendrimers.[17]

Although the origin of reasons behind the remarkable number effect of the chiral moieties at the periphery of the hyperbranched chain-ends on the chemical yields and enantioselectivities of the addition product remains unclear, a tentative explanation can be discussed on the basis of our previous finding on similar dendrimers.[19] It has been found that the conformation of the polystyrene main chain within the polystyrene end-functionalized with hyperbranched dendritic moieties in nonpolar solvents strongly depends on the number of end-functional moieties and consequently on the molecular weight of the dendritic hyperbranched chain-ends. However, the molecular weight of the hyperbranched dendritic chain-ends that include the chiral moieties is increased six times going from PS(Ephed)$_2$ to PS(Ephed)$_8$. Thus, the volume ratio of the dendritically hyperbranched chain-ends in the case of PS(Ephed)$_8$ relative to the polystyrene main chain is seen to be high and apparently was found to be comparable with the block copolymer. Therefore, it is possible to state that the dendritic hyperbranched chain-ends in the case of chiral dendrimer PS(Ephed)$_8$ can behave as a block copolymer in solutions. Considering the above-mentioned factors, it is supposed that the chain conformation for PS(Ephed)$_8$ may be more preferable for segregating the end-functional chiral moieties from the polystyrene main chains and can behave similarly to immiscible block copolymers. Further investigation to address the detailed mechanism of the enhanced stereoselectivity of the addition products by increasing the number of chiral moieties at the hyperbranched chain-ends, together with the size of the hyperbranched dendritic moieties, is now the focus of our interest.

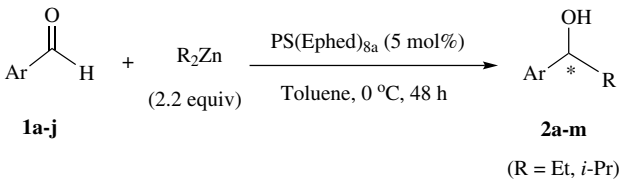
An important feature of the design of dendronized polymeric catalysts is the easy and reliable separation of the chiral catalyst based on its rather large molecular size with a rigid cylinder structure and different solubilities in various organic solvents. Unlike the corresponding crosslinked polystyrene-supported chiral ligands and most common linear polymers, the dendritic chiral polymers PS(Ephed)$_n$ used in this study are well soluble in most common organic solvents such as THF, toluene, and chloroform, but they are insoluble in methanol. This different solubility provides a convenient and reliable method for the isolation of the addition products, as well as the recovery of the dendritic catalysts by a precipitation method. Herein, chiral dendrimer PS(Ephed)$_{8a}$ was used for a recycling experiment. Upon completion of the reaction, a THF solution of the resulting residue thus obtained after the workup of the reaction mixture was added into a mixture of MeOH and HCl. The chiral catalyst PS(Ephed)$_{8a}$ was precipitated quantitatively and recovered by filtration process (see Section 4). Thus, the isolation of the addition products as well as the recovery of dendritic chiral catalyst was very easy. Interestingly, as shown in Table 1, the diethylzinc addition reaction to benzaldehyde **1a** using the

recovered dendronized polymer PS(Ephed)$_{8a}$ afforded the addition product **2a** with a comparable result to that of entry 7 (Table 1, entry 12). It is more interesting to note that the high enantioselectivity observed in the asymmetric diethylzinc addition to benzaldehyde **1a** using chiral dendrimer PS(Ephed)$_{8a}$ (90% ee, Table 1, entry 7) was found to be comparable to that reported for the same reaction using the corresponding monomeric chiral catalyst (1*R*,2*S*)-*N*-benzylephedrine (92% ee, Table 1, entry 7)[5e] under otherwise identical reaction conditions.

Since in the asymmetric reactions it is important that both enantiomers of a given compound can be prepared, the dendritic chiral catalyst PS(Ephed)$_{8b}$ having eight (1*S*,2*R*)-ephedrine moieties at the hyperbranched chain-ends was examined in the catalytic enantioselective ethylation of benzaldehyde **1a**. Dendritic chiral catalyst PS(Ephed)$_{8b}$ worked well as in the case of using PS(Ephed)$_{8a}$ and led smoothly to the desired secondary alcohol **2a** with almost the same chemical yield and enantioselectivity, but with reversed stereoselectivity (Table 1, entry 13).

Once the dendronized chiral catalyst PS(Ephed)$_8$, bearing eight chiral sites of ephedrine moieties, has been found to be the best catalyst for the enantioselective diethylzinc addition to benzaldehyde **1a**, its catalytic efficiency was further demonstrated in the dialkylzinc addition reaction to a series of substituted aldehydes. The dialkylzinc addition reactions were performed under the optimal reaction conditions that were identified for the diethylzinc addition reaction to **1a** using dendritic chiral catalyst PS(Ephed)$_{8a}$ as specified in Table 1 (entry 7). The collective results of dialkylzinc addition reactions to a series of aldehydes **1a**–**j** that are displayed in Scheme 3 are summarized in Table 2. The obtained results revealed that the dendritic chiral catalyst PS(Ephed)$_{8a}$ promotes the highly enantioselective addition of dialkylzincs to all aromatic substituted aldehydes **1a**–**j**.

In the presence of a catalytic amount of PS(Ephed)$_{8a}$ (5 mol %), the enantioselective addition of diisopropylzinc (*i*-Pr$_2$Zn) to benzaldehyde **1a** afforded the addition product (*R*)-2-methyl-1-phenylpropan-1-ol **2b** with slightly higher enantioselectivity (92% ee, entry 2) than that observed in the same reaction using diethylzinc (90% ee, entry 1). Interestingly, the diethylzinc addition to 2-naphthylaldehyde **1c** afforded the addition product (*R*)-1-(2′-naphthyl)-1-propanol **2d** with a slightly higher enantioselectivity of 91% ee (entry 4) than that observed with its analogue 1-naphthylaldehyde **1c** (89% ee, Table 2, entry 3). The same tendency was also observed in the diisopropylzinc addition to 1- and 2-naphthylaldehydes **1b**,**c** (entries 5 and 6, respectively). More interestingly, the enantioselectivity of the addition reactions was found to be subjected to a remote electronic effect; the enantioselectivity remarkably increases with more reactive substrates. The catalytic enantioselective diisopropylzinc addition to an aldehyde possessing an electron-withdrawing group at the *para* position of the aromatic ring proceeded with slightly higher enantioselectivity than the addition to an aldehyde with an electron-donating group (compare entries 11 vs 7 and 9 and 12 vs 8 and 10, respectively, Table 2); however, the difference in enantioselectivities for the *ortho*- and *para*-isomers **1d**,**e**, **1f**,**g**, and **1h**,**i**, was negligible (entries 7–12, respectively). For example, an electron-donating group (MeO) turned out to reduce the level of asymmetric induction rather more than an electron-withdrawing substituent (Cl) both in the *para* (compare entries 10 vs 12 in Table 2) and *ortho* series (compare entries 9 vs 11 in Table 2). This phenomenon was found to be in quite good accordance with the earlier reports by some groups,[18a,21] who observed the enhancement of enantioselection for benzaldehyde bearing strongly electron-withdrawing groups. Most importantly, the diisopropylzinc addition to 3-phenylpropanal **1j** proceeded in a highly enantioselective manner to give the corresponding secondary alcohol, 2-methyl-5-phenyl-3-pentanol, **2m** with a high enantioselectivity of 95% ee (entry 13). Thus, dendritic chiral catalyst PS(Ephed)$_{8a}$ proved to induce the formation of the secondary alcohols **2a**–**m** with high enantioselectivities (87–95% ee).



Scheme 3. Catalytic asymmetric dialkylzinc addition to aldehydes using chiral dendrimer Ps(Ephed)$_{8a}$.

It should be mentioned that the obtained high yields and enantioselectivities of the addition products suggested that nearly all chiral sites at the periphery of the dendritic hyperbranched chain-ends of catalyst PS(Ephed)$_{8a}$ worked effectively. Thus, the observed selectivity clearly demonstrated that, similar to the reaction using almost the same molar ratios of the corresponding monomeric chiral ligand,[5e] the eight parts in situ formed alkylzinc alkoxides of the amino alcohols (active sites) can operate independently, as in solution system, and can form an appropriate reaction field for the highly enantioselective addition of dialkylzinc to aldehydes.

To the best of our knowledge, the present method is the first example for the application of such a type of well-defined macromolecular dendritic chiral catalysts as unique soluble chiral catalysts for the enantioselective dialkylzinc addition to aldehydes. Interestingly, the chemical yields obtained and enantioselectivities, in most cases, were found to be not only higher than those obtained when using the corresponding polymer-supported ephedrine[5b,c,e,f,22] but also higher than those obtained from using several dendronized polymers having the same chiral ephedrine moiety with either hydrocarbon[8b,c,23] or silicon[8e,f,24] backbone structures.

3. Conclusion

We have described the first application of chain-end-functionalized polystyrenes bearing dendritic chiral β-amino alcohol moieties at the periphery of their hyperbranched

Table 2. Catalytic enantioselective addition of dialkylzinc reagents to aldehydes using dendritic chiral catalyst PS(Ephed)$_{8a}$[a]

Entry	Aldehyde		R_2Zn	Alcohol		
		(Ar)			Yield[b] (%)	ee[c,d] (%)
1	**1a**	Ph	Et_2Zn	**2a**	94	90
2	**1a**	Ph	*i*-Pr_2Zn	**2b**	93	92
3	**1b**	1-Naphthyl	Et_2Zn	**2c**	90	89
4	**1c**	2-Naphthyl	Et_2Zn	**2d**	91	91
5	**1b**	1-Naphthyl	*i*-Pr_2Zn	**2e**	92	90
6	**1c**	2-Naphthyl	*i*-Pr_2Zn	**2f**	90	92
7	**1d**	2-Me–C_6H_4	*i*-Pr_2Zn	**2g**	91	89
8	**1e**	4-Me–C_6H_4	*i*-Pr_2Zn	**2h**	93	91
9	**1f**	2-MeO–C_6H_4	*i*-Pr_2Zn	**2i**	88	87
10	**1g**	4-MeO–C_6H_4	*i*-Pr_2Zn	**2j**	89	88
11	**1h**	2-Cl–C_6H_4	*i*-Pr_2Zn	**2k**	93	92
12	**1i**	4-Cl–C_6H_4	*i*-Pr_2Zn	**2l**	91	94
13	**1j**	$PhCH_2CH_2$	*i*-Pr_2Zn	**2m**	94	95

[a] All reactions were performed in toluene at 0 °C for 48 h using 2.2 M equiv of dialkylzinc and 5 mol % of chiral dendrimer PS(Ephed)$_{8a}$.
[b] Isolated yields after flash chromatography.
[c] The ee values were determined by HPLC analysis using a chiral stationary phase (Chiralcel-OD, Chiralcel OB-H or Chiralpak-AD column).
[d] Absolute configurations were determined by comparing the sign of their specific rotations with those reported in the literature.[4a,c,d,h,i,5b,c,e,f,18,20]

chain-ends as a new type of hybrid catalysts, with the potential of combining the advantages of linear polymer and perfect dendrimer chiral catalyst, for the enantioselective dialkylzinc addition to aldehydes. They exhibited high catalytic activity and enantioselectivity very similar to those observed with the corresponding monomeric chiral *N*-benzyl ephedrine in solution system. The number of chiral moieties at the periphery of pendant dendrons has a major impact on the catalytic properties. Chiral dendrimer PS(Ephed)$_8$ showed high catalytic activity and enantioselectivity affording the addition products with enantioselectivities up to 95% ee. The immobilized chiral catalysts could be easily recovered from the reaction solution by using solvent precipitation. We believe that this study provides a new direction for the future design and synthesis of highly efficient macromolecular chiral catalysts for asymmetric synthesis. The design, synthesis, and reactivity of other dendronized chiral ligands and catalysts are now the focus of our continuing efforts.

4. Experimental

4.1. General

All reactions were performed under nitrogen atmosphere. All reagents (>98% purities) were purchased from Aldrich Co and used as received unless otherwise stated. Tetrahydrofuran (THF) was refluxed over sodium wire, distilled over $LiAlH_4$ under a nitrogen atmosphere and finally distilled from its sodium naphthalene under high vacuum (10^{-6} torr). DMF and toluene were freshly distilled over CaH_2 under dry nitrogen. Styrene was washed with 5% NaOH, dried over $MgSO_4$, and distilled over CaH_2 under reduced pressure, and after adding Bu_2Mg (3 mol %), styrene was finally distilled under high vacuum (10^{-6} torr). All polymerizations were carried out under high vacuum conditions (10^{-6} torr) in sealed glass reactors equipped with break seals. 1,1-Bis(3-*tert*-butyldimethylsilyloxymethylphenyl)- ethylene was prepared according to the procedure previously reported.[16a] The benzyl bromide- and chiral ephedrine-end-functionalized polystyrenes have been designated by PS(BnBr)$_n$ and PS(Ephed)$_n$, and the subscript numbers are corresponding to the number of the terminal benzyl bromide and ephedrine moieties, respectively.

^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX (300 MHz for ^{1}H and 75 MHz for ^{13}C) in $CDCl_3$ at 25 °C with TMS as the internal standard. Size-exclusion chromatograms (SEC) were measured with a TOSOH HLC-8020 at 40 °C equipped with ultraviolet (254 nm) and refractive index detections. THF was used as a carrier solvent at a flow rate of 1.0 mL/min 40 °C. Calibration curves were made with standard polystyrene samples to determine M_n and M_w/M_n values. FT-IR spectra were recorded on a JEOL JIR-AQS20M FT-IR spectrophotometer. Flash chromatography was performed on deactivated silica gel (Matrix 60A, 37–70 μm) and the spots were detected with UV model UVGL-58. Optical rotations were measured on materials isolated either by bulb-to-bulb distillation or by column chromatography. Optical rotations were measured using a Perkin–Elmer 341 Polarimeter in a 10 cm cell at 25 °C. HPLC analyses were carried out using a DIACEL Chiralcel-OD, Chiralcel OB-H or Chiralpak-AD column (0.46×25 cm^2) with Shimadzu LC-6A with a 254 nm UV detector.

4.2. Synthesis of chain-end-functionalized polystyrenes with 2, 4, 8, and 16 benzyl bromide moieties PS(BnBr)$_n$

The title chain-end-functionalized polystyrenes were synthesized following our previously reported procedures.[16,17] Polystyrene end-functionalized with two benzyl bromide moieties PS(BnBr)$_2$ was first synthesized by the following typical experimental procedure: A solution of styrene (10.82 g, 104 mmol) in *tert*-butyl benzene (42.6 mL) was polymerized with *sec*-BuLi (0.534 mmol, 5.71 mL of a heptane solution) at 0 °C for 20 min and then at room temp for 4 h. The reaction mixture was then chilled to −78 °C, and 48.7 mL of THF was first added followed by a solution of

1,1-bis(3-*tert*-butyldimethylsilyloxymethylphenyl)ethylene (0.31 g, 0.649 mmol) in THF (7.82 mL). The reaction mixture was left at −78 °C for additional 30 min and then terminated with degassed methanol. The resulting polymer was precipitated in methanol, purified by reprecipitation from its THF solution with methanol three times, and freeze-dried from its absolute benzene solution for 24 h.

The two 3-*tert*-butyldimethylsilyloxymethylphenyl (SMP) functionalities thus introduced at the polystyrene chain-ends were transformed into two benzyl bromide functionalities by the following typical experimental procedure: The resulting SMP-end-functionalized polystyrene (4.2 g, 0.425 mmol per two SMP functionalities) reacted with a mixture of LiBr (1.85 g, 21.25 mmol) and $(CH_3)_3SiCl$ (2.88 g, 26.56 mmol) in a mixed solvent of chloroform (125 mL) and acetonitrile (47 mL) at 40 °C for 24 h. After quenching and usual workup, the polymer was precipitated in methanol and purified by reprecipitation from its THF solution with methanol two times. After being freeze-dried in vacuo from its absolute benzene solution for 24 h, chain-end-functionalized polystyrene with two benzyl bromide moieties $PS(BnBr)_2$ at the chain-ends was obtained.

A polystyrene end-functionalized with four benzyl bromide functionalities $PS(BnBr)_4$, was synthesized by the following typical procedure: The 1,1,-diphenylalkylanion was first synthesized by reacting 1.20 mmol of 1,1-bis(3-*tert*-butyldimethylsilyloxymethylphenyl)ethylene in THF (14.5 mL) with *sec*-BuLi (1.13 mmol, 3.67 mL in heptane) at −78 °C for 15 min. A solution of chain-end functionalized polystyrene with two benzyl bromide functionalities $PS(BnBr)_2$ (4.01 g, 0.42 mmol per two BMP groups) in THF (49.3 mL) was then added at −78 °C. The reaction mixture was left at −78 °C for an additional 2 h and terminated with degassed methanol. The polymer was then precipitated and reprecipitated three times from its THF solution to methanol and freeze-dried from its absolute benzene solution for 24 h. By the same procedure described previously, the resulting polymer with four SMP functionalities was reacted again with a mixture of LiBr and $(CH_3)_3SiCl$ in a mixed solvent of chloroform and acetonitrile (4:3, v/v) at 40 °C for 24 h to afford the corresponding chain-end-functionalized polystyrene having four benzyl bromide functionalities. Similarly, chain-end-functionalized polystyrenes $PS(BnBr)_8$ and $PS(BnBr)_{16}$ were successfully and quantitatively synthesized by repeating the reaction sequence two times more.

4.2.1. $PS(BnBr)_2$. ^1H NMR ($CDCl_3$): δ 0.49–0.83 (br m, 6H, $CH(CH_3)CH_2CH_3$), 1.09–2.37 (m, 563H, CH_2CH), 3.41–3.52 (br s, 1H, $ArCHAr$), 4.33–4.39 (br m, 4H, $ArCH_2Br$), 6.25–7.23 (m, 940H, ArH); ^{13}C NMR ($CDCl_3$): δ 11.37, 20.43, 20.89, 30.29, 31.16, 31.58, 33.73, 40.44, 41.78, 42.47, 42.63, 43.56, 43.91, 44.28, 44.88, 46.09, 46.49, 51.18, 76.49, 77.11, 77.31, 77.53, 125.57, 125.72, 126.72, 127.38, 127.50, 127.72, 128.03, 128.13, 128.34, 128.88, 129.66, 137.27, 145.17, 145.39, 145.77, 145.87, 145.98, 146.14, 149.07; FT-IR (KBr, cm^{-1}): 1208 (CH_2Br). Anal. Calcd for $C_{1511}H_{1515}Br_2$: C, 91.55; H, 7.65; Br, 0.79. Found: C, 91.48; H, 7.76; Br, 0.77.

4.2.2. $PS(BnBr)_4$. ^1H NMR ($CDCl_3$): δ 0.36–0.82 (br m, 18H, $CH(CH_3)CH_2CH_3$), 1.05–2.38 (br m, 577H, CH_2CH), 2.98–3.40 (br m, 5H, $ArCHAr + (Ar)_2CCH_2Ar$), 4.33–4.39 (br m, 8H, $ArCH_2Br$), 6.09–7.33 (m, 951H, ArH); ^{13}C NMR ($CDCl_3$): δ 11.41, 20.27, 20.59, 30.97, 31.54, 31.67, 33.74, 34.18, 40.39, 41.72, 42.46, 42.69, 43.57, 43.91, 44.28, 44.88, 46.09, 46.49, 50.89, 76.66, 77.07, 77.37, 125.57, 125.72, 127.39, 127.51, 127.73, 127.86, 128.05, 128.13, 128.33, 128.97, 137.74, 145.17, 145.28, 145.39, 145.77, 145.87, 145.98, 146.14, 149.08; FT-IR (KBr, cm^{-1}): 1208 (CH_2Br). Anal. Calcd for $C_{1543}H_{1553}Br_4$: C, 90.83; H, 7.62; Br, 1.55. Found: C, 91.02; H, 7.69; Br, 1.52.

4.2.3. $PS(BnBr)_8$. ^1H NMR ($CDCl_3$): δ 0.28–0.81 (br m, 42H, $CH(CH_3)CH_2CH_3$), 1.09–2.39 (br m, 583H, CH_2CH), 2.71–3.47 (br m, 13H, $ArCHAr + (Ar)_2CCH_2Ar$), 4.32–4.39 (br m, 16H, $ArCH_2Br$), 6.11–7.26 (br m, 981H, ArH); ^{13}C NMR ($CDCl_3$): δ 11.36, 20.28, 20.43, 30.29, 31.16, 31.58, 34.03, 40.44, 41.78, 42.65, 43.58, 44.26, 46.01, 46.51, 51.18, 76.68, 77.10, 77.31, 125.56, 125.71, 126.72, 127.38, 127.50, 127.72, 128.03, 128.11, 128.34, 128.88, 129.66, 137.27, 145.28, 145.39, 145.74, 145.76, 145.88, 145.98, 146.15, 149.06; FT-IR (KBr, cm^{-1}): 1208 (CH_2Br). Anal. Calcd for $C_{1620}H_{1642}Br_8$: C, 89.53; H, 7.56; Br, 2.88. Found: C, 89.50; H, 7.66; Br, 2.79.

4.2.4. $PS(BnBr)_{16}$. ^1H NMR ($CDCl_3$): δ 0.17–0.88 (br m, 90H, $CH(CH_3)CH_2CH_3$), 1.14–2.43 (br m, 698H, CH_2CH), 2.72–3.51 (br m, 29H, $ArCHAr + (Ar)_2CCH_2Ar$), 4.33–4.39 (br s, 32H, $ArCH_2Br$), 7.25–6.08 (br m, 1045H, ArH); ^{13}C NMR ($CDCl_3$): δ 11.36, 20.31, 20.44, 29.88, 30.27, 31.18, 34.02, 34.66, 40.43, 41.67, 42.60, 43.55, 43.93, 44.25, 45.93, 46.47, 50.14, 51.13, 76.67, 77.10, 77.30, 77.52, 125.56, 125.71, 126.73, 127.37, 127.49, 127.71, 128.02, 128.11, 128.33, 128.90, 129.67, 137.29, 145.16, 145.26, 145.37, 145.76, 145.86, 145.98, 146.12, 149.04; FT-IR (KBr, cm^{-1}): 1208 (CH_2Br). Anal. Calcd for $C_{1778}H_{1824}Br_{16}$: C, 87.36; H, 7.47; Br, 5.17. Found: C, 87.51; H, 7.49; Br, 5.20.

4.3. Synthesis of chain-end-functionalized polystyrenes with 2, 4, 8, and 16 chiral ephedrine moieties $PS(Ephed)_n$

Typical procedure for the synthesis of $PS(Ephed)_8$ is as follows: Under nitrogen atmosphere, a solution of ephedrine (0.3 g, 1.8 mmol) in DMF (5 mL) was added drop-wise within 5 min at 0 °C to a mixture of a DMF (20 mL) solution of chain-end-functionalized polystyrene with eight benzyl bromide moieties [$PS(BnBr)_8$ (0.5 g, $M_n = 21.71 \times 10^3$ g/mol, 0.18 mmol), based on eight BnBr moieties] and K_2CO_3 (0.25 g, 1.8 mmol). The reaction mixture was allowed to warm gradually to 50 °C and stirred further for 24 h. The reaction mixture was then allowed to return to room temperature and then poured into 1 N HCl methanolic solution (50 mL) to precipitate the polymer. The polymer was reprecipitated from its THF solution to methanol two times more followed by freeze-drying from its absolute benzene solution to afford the corresponding chiral polymer $PS(Ephed)_8$. The other dendritic chiral polymers $PS(Ephed)_2$, $PS(Ephed)_4$, and $PS(Ephed)_{16}$ were synthesized by the same procedure and under the same reaction conditions.

The degree of chiral ephedrine end-functionalization was determined by comparing the relative intensities of the ^{1}H NMR resonance peaks at 3.69–3.91 ppm assigned for the methylene protons of the benzyl ephedrine moieties, with those at 0.17–0.84 ppm attributed for the methyl protons of the *sec*-butyl groups (initiator fragment). The integral values of the ^{1}H NMR resonance peaks attributed for the other protons of ephedrine moieties were also taken into consideration. The functionalities of chiral ephedrine moieties thus determined were found to be in quite agreement to those predicted within analytical limits. The M_n values could be determined by ^{1}H NMR by using the resonances at 6.2–7.3 ppm (aromatic protons) and 0.17–0.84 ppm (methyl protons of the initiator fragment) and they were also found in quite well agreement with those calculated.

4.3.1. PS(Ephed)$_2$. ^{1}H NMR ($CDCl_3$): δ 0.49–0.83 (br m, 6H, CH(CH_3)CH_2CH_3), 1.08–2.32 (br m, 578H, $CH_2CH + CH_3N + CH_3CHN$), 2.87–2.99 (br m, 2H, CH_3CHN), 3.46–3.56 (br s, 1H, ArC*H*Ar), 3.72–3.83 (br m, 4H, ArCH_2N), 4.78–4.90 (br m, 2H, C*H*OH), 6.30–7.25 (br m, 949H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 9.85, 11.34, 20.28, 20.46, 29.85, 31.18, 33.77, 38.73, 40.59, 41.92, 43.50, 45.86, 46.59, 50.37, 59.14, 63.66, 73.52, 125.68, 125.83, 126.80, 127.22, 127.56, 127.81, 128.01, 128.25, 128.67, 129.07, 129.63, 133.46, 137.18, 140.21, 142.46, 145.09, 145.28, 145.58, 146.19, 149.17; FT-IR (KBr, cm^{-1}): 3345 (OH). Anal. Calcd for $C_{1533}H_{1545}N_2O_2$: C, 91.97; H, 7.73; N, 0.14. Found: C, 91.75; H, 7.61; N, 0.14.

4.3.2. PS(Ephed)$_4$. ^{1}H NMR ($CDCl_3$): δ 0.39–0.82 (br m, 18H, CH(CH_3)CH_2CH_3), 1.09–2.35 (br m, 590H, $CH_2CH + CH_3N + CH_3CHN$), 2.95–3.34 (br m, 9H, ArC*H*Ar + $(Ar)_2CCH_2Ar + CH_3CHN$), 3.71–3.86 (br m, 8H, ArCH_2N), 4.76–4.89 (br m, 4H, C*H*OH), 6.16–7.27 (br m, 975H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 9.84, 11.36, 20.33, 20.44, 29.99, 31.37, 34.12, 38.70, 40.82, 42.06, 44.52, 45.61, 47.22, 51.12, 59.17, 63.74, 73.67, 125.66, 125.77, 126.72, 127.30, 127.63, 127.74, 128.13, 128.38, 128.45, 128.76, 129.09, 133.67, 137.39, 140.24, 142.37, 145.18, 145.39, 145.68, 145.80, 146.29, 149.09; FT-IR (KBr, cm^{-1}): 3345 (OH). Anal. Calcd for $C_{1590}H_{1616}N_4O_4$: C, 91.66; H, 7.76; N, 0.27. Found: C, 91.72; H, 7.73; N, 0.26.

4.3.3. PS(Ephed)$_8$. ^{1}H NMR ($CDCl_3$): δ 0.18–0.79 (br m, 42H, CH(CH_3)CH_2CH_3), 1.11–2.33 (br m, 607H, $CH_2CH + CH_3N + CH_3CHN$), 2.79–3.50 (br m, 21H, ArC*H*Ar + $(Ar)_2CCH_2Ar + CH_3CHN$), 3.69–3.87 (br m, 16H, ArCH_2N), 4.73–4.90 (br m, 8H, C*H*OH), 6.20–7.23 (br m, 1027H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 9.91, 11.35, 20.30, 20.48, 30.17, 31.14, 33.98, 38.75, 41.18, 42.63, 44.39, 46.22, 46.97, 50.38, 59.08, 63.44, 73.59, 125.58, 125.73, 126.81, 127.39, 127.61, 127.89, 128.26, 128.35, 128.49, 128.76, 129.34, 133.59, 137.41, 140.07, 142.45, 145.33, 145.66, 145.84, 145.99, 146.31, 149.19; FT-IR (KBr, cm^{-1}): 3345 (OH). Anal. Calcd for $C_{1711}H_{1765}N_8O_8$: C, 91.10; H, 7.83; N, 0.50. Found: C, 91.23; H, 7.87; N, 0.49.

4.3.4. PS(Ephed)$_{16}$. ^{1}H NMR ($CDCl_3$): δ 0.17–0.84 (m, 90H, CH(CH_3)CH_2CH_3), 1.09–2.35 (m, 745H, $CH_2CH + CH_3N + CH_3CHN$), 2.81–3.55 (br m, 45H, ArC*H*Ar + $(Ar)_2CCH_2Ar + CH_3CHN$), 3.71–3.91 (br s, 32H, ArCH_2N), 4.72–4.89 (br m, 16H, C*H*OH), 6.18–7.25 (br m, 1133H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 9.89, 11.33, 20.29, 20.44, 30.22, 31.28, 34.19, 38.78, 40.88, 42.54, 43.93, 45.49, 47.14, 50.66, 59.12, 63.59, 73.44, 125.61, 125.87, 126.91, 127.34, 127.71, 127.93, 128.19, 128.37, 128.56, 128.89, 129.51, 133.75, 137.22, 139.97, 142.55, 145.29, 145.49, 145.70, 145.83, 146.28, 149.07; FT-IR (KBr, cm^{-1}): 3345 (OH). Anal. Calcd for $C_{1953}H_{2063}N_{16}O_{16}$: C, 90.21; H, 7.94; N, 0.86. Found: C, 89.98; H, 7.77; N, 0.85.

4.4. Typical procedure for the enantioselective addition of dialkylzinc reagents to aldehydes catalyzed by chiral dendrimers PS(Ephed)$_n$ (Table 2, entry 7)

To a dry toluene (2 mL) solution of a dendritic catalyst PS(Ephed)$_{8a}$ (Mol. Wt., 22.54×10^3 kg/mol; 0.14 g, 0.05 mmol, 5 mol %, based on the total number of ephedrine moieties at the periphery) at 0 °C was added a toluene solution of diethylzinc (2.2 mL of a 1 M toluene solution, 2.2 mmol) under a nitrogen atmosphere. After the reaction mixture was stirred for 20 min at 0 °C, a toluene solution of benzaldehyde (**1a**, 116 mg, 1 mmol) was added and the reaction mixture was stirred for a further 48 h at 0 °C. After being quenched with aqueous saturated NH_4Cl solution (5 mL), the reaction mixture was extracted with CH_2Cl_2 (10 mL × 3), washed with water and brine, and dried over anhydrous magnesium sulfate ($MgSO_4$). The solvent was evaporated to dryness under reduced pressure and the residue thus obtained was dissolved in THF (5 mL) and poured drop-wise into methanol (25 mL) to precipitate the polymer. After filtration, the precipitated polymer was washed thoroughly with methanol and the filtrate was evaporated to dryness under reduced pressure. The oil residue thus obtained was purified by flash column chromatography [developing eluent; hexane/ethyl acetate = 4:1 (v/v), $R_f = 0.45$] to afford the corresponding enantiomerically enriched optically active alcohol (*R*)-1-phenyl-1-propanol **2a** as a colorless oil (130 mg, 95%). The enantiomeric excess[4d,i,j,20f,h] was determined to be 90% by HPLC analysis using a DIACEL Chiralcel OD-H column (hexane/2-propanol 98:2, flow rate: 1 mL/min, 254 nm UV detector, 25 °C) $t_R = 11.93$ min for (*R*)-enantiomer and $t_R = 14.85$ min for (*S*)-enantiomer; $[\alpha]_D^{25} = +43.7$ (*c* 5.5, $CHCl_3$, 90% ee) {lit.[4c,d,i,5b,c,18] $[\alpha]_D^{22} = -47.6$ (*c* 6.11, $CHCl_3$) for 98% ee (*S*)-enantiomer}; ^{1}H NMR (300 MHz, $CDCl_3$)[18a,20b,g,h,21d,f]: δ 0.90 (t, $J = 7.5$ Hz, 3H, CH_3), 1.67–1.83 (m, 2H, CH_2), 2.05 (br s, 1H, O*H*), 4.58 (t, $J = 6.6$ Hz, 1H, PhC*H*(OH)Et), 7.25–7.39 (m, 5H, Ar-*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.14, 31.85, 76.05, 125.85, 127.43 (2C), 128.39 (2C), 144.57; *m*/*z*136 (M^+, 23%), 107 (100), 79 (93), 78 (17), 77 (49), 51 (33).

The chemical yields and the enantiomeric excesses of the addition products are indicated in Tables 1 and 2. The enantiomeric excesses of the addition products were determined by HPLC analysis using a DIACEL Chiralcel OD-H, Chiralcel OB-H, or Chiralpak AD column and by

comparison with those reported in the literature.[4d,i,j,18,20f] The addition products were established by comparison of their physical and spectroscopic data with those reported in the literature.[4d,18,20a,b,d,e,g,h,21d,f,25] The absolute configuration of the major enantiomer of the addition products was assigned either by comparing the retention times on HPLC[4d,i,j,18,20f,h] and/or by comparising the sign of their specific rotations with those reported in the literature.[4a,c,d,h,i,5b,c,e,f,18,20]

4.5. Recovery of the polymer

The recovered dendritic chiral polymer thus obtained from the dialkylzinc addition reaction through the filtration was precipitated from its THF solution in a 4:1 mixture of MeOH–2 M HCl followed by stirring for 4 h. The precipitated dendritic chiral polymer was filtered off followed by washing thoroughly with methanol. After being freeze-dried from its absolute benzene solution for 24 h, the recycled dendritic chiral polymer could be used in the enantioselective addition of dialkylzinc to aldehydes.

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