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Synthesis of novel well-defined chain-end-functionalized polystyrenes with dendritic chiral ephedrine moieties and their applications as highly enantioselective diethylzinc addition to *N*-diphenylphosphinoyl arylimines

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Abstract—A series of novel well-defined chain-end-functionalized polystyrenes having 2, 4, 8, and 16 chiral ephedrine moieties dendritically distributed at their hyperbranched chain-ends were quantitatively synthesized. Their well-defined architectures were fully confirmed by elemental analysis, FTIR, SEC as well as by ^{1}H and ^{13}C NMR spectroscopies. These polymers were precisely controlled in the molecular weight and molecular weight distribution as well as well-defined in chain-end-functionalities. These dendritic chiral polymers serve as highly enantioselective chiral ligands in the enantioselective addition of diethylzinc to a series of *N*-diphenylphosphinoyl arylimines. Among them, chiral dendrimer having eight ephedrine moieties at the chain-ends afforded the corresponding enantiomerically enriched phosphinoylamides in good to high yields with enantioselectivities up to 93% ee. The obtained enantioselectivities are comparable with those obtained by using *N*-benzylephedrine and its corresponding copolymer as chiral ligands.

1. Introduction

The synthetic usefulness of enantiomerically pure amines[1] has stimulated great interest in developing methods for their asymmetric preparation.[2] The addition of organometallics to imines is a powerful method for the asymmetric synthesis of chiral amines.[3] We have previously reported on the enantioselective addition of allylmetal reagents to imines using various chiral ligands including chiral amino alcohols and their corresponding copolymers, which afforded the enantioenriched homoallylic amines in quantitative yields with enantioselectivities up to 96% ee[4]. Diastereoselective allylation of chiral imines activated by Lewis acids has been also reported by us and the corresponding optically active secondary homoallylic amines with perfect diastereoselectivities were obtained.[5] Moreover, very recently, we have reported on an efficient dual catalytic enantioselective diethylzinc addition to the exocyclic C=N double bond of some 4-arylideneamino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-ones using chiral β-amino alcohols derived from norephedrine,[6a] and their corresponding copolymers,[6b] in the presence of Lewis acids as activators. The addition products 4-(1-arylpropyl)amino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-ones were obtained in high yields with enantioselectivities up to 92% ee.[6] Subsequent reductive cleavage of the 1,2,4-triazinyl heterocyclic ring led smoothly to the corresponding free amines without any significant loss of enantiomeric purity.[6]

Since Soai and co-workers reported on the MOPEP (an ephedrine derivative)-mediated addition of diethylzinc to *N*-diphenylphosphinoyl imine,[7] enantioselective alkylations of *N*-diphenylphosphinoyl imines with dialkylzinc reagents that employ chiral amino alcohols,[8] polymeric chiral amino alcohols,[9] and chiral dendrimers[10] as chiral ligands have been described.

Meanwhile, dendrimers represent a new and fascinating class of regular highly branched and well-defined macromolecules.[11] When the well-designed chiral functionalities are loaded in the core or at the chain-ends of the dendrimers, these functionalities are expected to be positioned on the surface and they are expected to act as chiral ligands in asymmetric synthesis.[10,12,13] However, the dendrimer backbone structure may cause unfavorable interactions with the chiral

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sites and consequently may reduce the enantioselectivity. Thus, highly enantioselective synthesis utilizing chiral dendrimers has been a challenge.

However, Hirao and co-workers recently developed an attractive iterative methodology based on a divergent approach, by which well-defined chain-end-functionalized polystyrenes with a definite number of benzyl bromide (BnBr) functionalities dendritically distributed at their chain ends were prepared.[11e,i,j,14,15] These BnBr-end-functionalized polystyrenes were found to be a new class of functionalized polymers, which can be utilized as an interesting precursory polymers leading to novel special-shaped polymers with branched architecture. Based on the above-mentioned methodology, we have recently reported on the successful synthesis of novel well-defined chain-end-functionalized polystyrenes with a definite number of perfluorooctyl (C_8F_{17}) groups dendritically distributed or linearly aligned in a double line at the chain-ends, by various addition reactions of polystyryllithium to specially designed 1,1-diphenylethylene derivatives, followed by introduction of the C_8F_{17} groups, and examined their surface segregation behaviors of C_8F_{17} groups.[15]

Thus, in continuous to our interest in the attractive characteristics of dendrimers, we wish to report herein on the successful synthesis of a novel series of chain-end-functionalized polystyrenes with a definite number of chiral ephedrine moieties dendritically distributed at their chain-ends, by attractive iterative methodology based on a divergent approach, by which well-defined chain-end-functionalized polystyrenes with a definite number of BnBr functionalities were prepared, followed by introduction of the ephedrine moieties. The preliminary application of these chiral polymers as a highly enantioselective diethylzinc addition to a series of *N*-diphenylphosphinoyl arylimines was also reported.

2. Results and discussion

As mentioned in the preceding section, we have recently developed an iterative methodology based on a divergent approach, by which chain-end-functionalized polystyrenes with a definite number of BnBr functionalities dendritically distributed at their chain ends were prepared.[15] Since these polymers have reactive BnBr functionalities at their chain ends, it may be possible to introduce new chiral functionalities at the chain ends by the reaction with suitable chiral reagents. For this purpose, chain-end-functionalized polystyrenes having a definite number of 2, 4, 8, and 16 BnBr moieties at their chain-ends, **PS(BnBr)$_2$–PS(BnBr)$_{16}$**, respectively, were first synthesized by the previously reported method (Fig. 1).[14b–d,15] Thus, the utility of attaching a chiral moiety via the reactive benzyl bromide functionalities in the BnBr-end-functionalized polystyrenes was examined.

From literature survey on the dialkylzinc addition to *N*-diphenylphosphinoyl imines using chiral *N*-alkyl-*N*-benzylnorephedrines as chiral ligands, *N*-benzylephedrine was found to be the most highly enantioselective chiral ligand.[9,10] Therefore, the chiral ephedrine moiety was chosen to be introduced at the functional dendrimer. Thus, the reaction of chain-end-functionalized polystyrenes **PS(BnBr)$_2$–PS(BnBr)$_{16}$** that have two–sixteen BnBr moieties, respectively, at their chain ends with ephedrine **1** was examined (Scheme 1). The anchoring reaction proceeded virtually quantitatively affording the corresponding chain-end-functionalized polystyrenes having the same number of ephedrine moieties, **PS(Ephed)$_2$–PS(Ephed)$_{16}$**, respectively, at their chain-ends. The resulting chiral dendrimers were all readily purified by reprecipitation from their THF solutions to methanol and isolated in quantitative yields. They have been fully characterized by elemental analysis, FTIR, SEC as well as by ^{1}H and ^{13}C NMR spectroscopies.

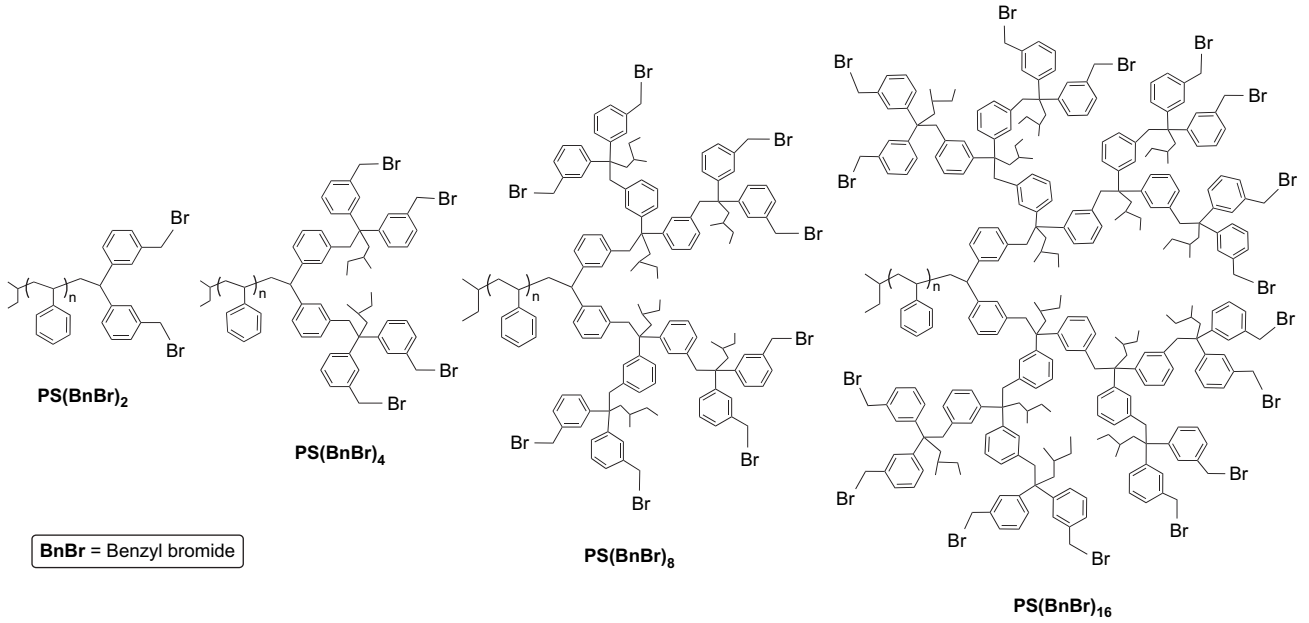
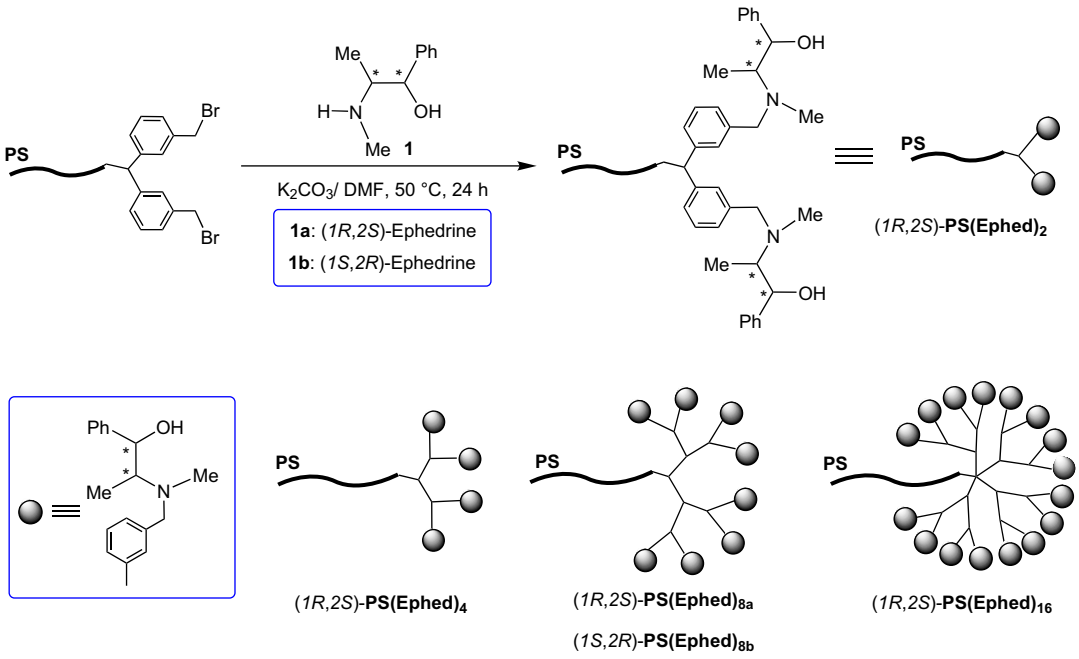


Figure 1. .Structure of the chain-end-functionalized polystyrenes having 2, 4, 8, and 16 benzyl bromide moieties **PS(BnBr)$_n$**.



Scheme 1. .General pathway for the synthesis of chain-end-functionalized polystyrenes with a definite number of chiral ephedrine moieties **PS(Ephed)$_n$**.

The analytical results of the resulting chiral dendrimers **PS(Ephed)$_2$–PS(Ephed)$_{16}$** in comparison with their precursory polymers are summarized in Table 1.

Quantitative degree of ephedrine-end-functionalization was confirmed by FTIR and ^{1}H NMR analyses, both of which indicated that the bromomethyl groups in the starting polymers **PS(BnBr)$_2$–PS(BnBr)$_{16}$** had quantitatively reacted with ephedrine. The FTIR absorption band attributed for the C–Br bond of the BnBr moiety that should appear at 1208 cm^{-1} had completely disappeared after the reaction and a new absorption band at 3345 cm^{-1} attributed for the hydroxyl group of the ephedrine moiety clearly appeared. Moreover, ^{1}H NMR analysis showed that the resonance peaks attributed for the methylene protons of the BnBr moieties (in the range of 4.32–4.40 ppm) had completely disappeared and new resonance peaks were observed at 3.69–3.91 ppm attributed for the methylene protons of the benzylephedrine moieties, in addition to the resonance peaks assigned for the other protons of ephedrine moieties (see Supplementary data). The degree of ephedrine-end-functionalization was determined by comparing the relative intensities of the ^{1}H NMR resonance peak at 3.69–3.91 ppm with that assigned for methylene protons of the benzylephedrine moiety with those observed 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 end functionalities of chiral ephedrine moieties thus determined were found to be in quite agreement with those predicted (Table 1).

Table 1. Synthesis of chain-end-functionalized polystyrenes with a definite number of chiral ephedrine moieties **PS(Ephed)$_n$** in compared with their precursory polymers[a]

Entry	Polymer	M_n (kg/mol)[b]			M_w/M_n SEC	Functionality[c]	
		Calcd	SEC	^{1}H NMR		Calcd	^{1}H NMR
1	**PS(BnBr)$_2$**	19.67	19.63	19.81	1.02	2	1.98
2	**PS(BnBr)$_4$**	20.36	20.22	20.39	1.03	4	3.99
3	**PS(BnBr)$_8$**	21.73	21.93	21.71	1.03	8	8.00
4	**PS(BnBr)$_{16}$**	24.48	24.28	24.43	1.03	16	15.99
5[d]	**PS(Ephed)$_2$**	19.84	19.86	20.00	1.03	2	1.99
6[d]	**PS(Ephed)$_4$**	20.70	20.75	20.82	1.04	4	4.00
7[d]	**PS(Ephed)$_{8a}$**	22.40	22.39	22.44	1.03	8	7.99
8[d]	**PS(Ephed)$_{8b}$**	22.40	22.41	22.45	1.04	8	8.00
9[d]	**PS(Ephed)$_{16}$**	25.82	25.83	25.89	1.03	16	15.98

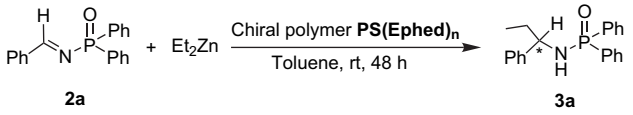
[a] In all cases, the isolated yields after reprecipitation were ca. 100%.
[b] In all cases, the M_n values of polystyrene main chains determined by SEC were always ~19.3 kg/mol.
[c] Functionality of benzyl bromide and chiral ephedrine moieties.
[d] In all cases, (1*R*,2*S*)-ephedrine was used except for entry 8 in which (1*S*,2*R*)-ephedrine was used as chiral moiety.

Interestingly, the SEC profile of the resulting dendritic chiral polymers showed also sharp and symmetric monomodal distributions (M_w/M_n being less than 1.04) similar to that of the corresponding BnBr-end-functionalized polymers before the end-functionalization reaction. Neither shoulder nor tailing was observed. As expected, the M_n values that determined by each of SEC and ^{1}H NMR analyses agreed quite well with those predicted (Table 1). Thus, the anchoring reaction of chiral ephedrine moiety proceeded quantitatively as it was desired within analytical limits. It is interesting to note that in this polymer series, the molecular weight of polystyrene main chain remained unchanged (M_n ~19.3 kg/mol), while the dendritic branched chain-end that includes the chiral moiety increases in both size and molecular weight as the reaction sequence was repeated.

As stated in literature, when chiral dendrimers with heteroatoms in the dendrimer backbones are used as chiral ligands in the dialkylzinc addition to each of aldehydes[10d,16] and imines,[10] the heteroatoms in the backbones may cause

unfavorable coordination with the dialkylzinc reagents and may also reduce the enantioselectivity of the addition products. Thus, in order to attain high enantioselectivity, it is necessary to avoid any unfavorable coordination between the dialkylzinc reagents and the framework of the dendrimer. Therefore, we have devised the above-mentioned chiral dendrimers **PS(Ephed)$_n$** with hydrocarbon backbone structure (Scheme 1). In this case, the backbone hardly coordinates with the diethylzinc and each chiral site of the dendritic ligands is expected to work independently of other chiral sites.

In order to evaluate the most efficient dendrimer as chiral ligand, the enantioselective diethylzinc addition reaction to *N*-diphenylphosphinoyl benzaldimine **2a** as a standard substrate using chiral dendrimers **PS(Ephed)$_2$**–**PS(Ephed)$_{16}$**, in toluene at room temperature for 48 h, was first examined (Scheme 2). The obtained results are summarized in Table 2. When chiral dendrimer **PS(Ephed)$_2$**, bearing two chiral sites at the chain ends, was used as chiral ligand in the enantioselective diethylzinc addition to the C=N double bond of benzaldimine **2a**, the corresponding enantiomerically enantioenriched (*R*)-*N*-diphenylphosphinoylamide (*R*)-**3a** was obtained in chemical yield of 53% with 81% ee (Table 2, entry 1). The same reaction using dendritic chiral polymer **PS(Ephed)$_4$** that have four chiral sites afforded the addition product (*R*)-**3a** with slightly higher enantioselectivity (84% ee) and in an isolated yield of 71% (Table 2, entry 3). Interestingly, the use of **PS(Ephed)$_{8a}$** with eight ephedrine moieties at the polystyrene chain ends afforded the addition product (*R*)-**3a** with more higher enantioselectivity (90% ee) and with much better chemical yield of 92% (Table 2, entry 5). More interestingly, **PS(Ephed)$_{16}$**, having 16 ephedrine moieties at the chain ends, drove the asymmetric ethylation reaction of **2a** with an enantioselectivity of 79% ee with chemical yield of 78% (Table 2, entry 6).



2a **3a**

Scheme 2. Enantioselective diethylzinc addition to *N*-diphenylphosphinoyl benzaldimine **2a** in the presence of chiral dendrimers **PS(Ephed)$_n$**.

As can be seen from the results that are shown in Table 2, under the same reaction conditions, the enantioselectivity of the addition product **3a** obtained by using **PS(Ephed)$_{8a}$** (entry 5) was higher than that observed in case of using **PS(Ephed)$_{16}$** (entry 6) as chiral ligand. This is probably due to the fact that the environments of active sites at the polystyrene chain ends of **PS(Ephed)$_{8a}$** might have enough space to work as a chiral ligand, while the active chiral sites of **PS(Ephed)$_{16}$** interfere either with each others and/or with the polymer backbone chains. It is interesting to note that on performing the diethylzinc addition reaction to imine **2a** in the presence of excess amount of **PS(Ephed)$_{16}$** (1.5 molar equiv, based on the total number of ephedrine moieties against the imine **2a**), the addition product **3a** was obtained in higher yield of 93% without considerable change in the enantioselectivity (80% ee, Table 2, entry 7). More interestingly, on performing the diethylzinc addition reaction to benzaldimine **2a** using each of **PS(Ephed)$_2$** and **PS(Ephed)$_4$**, but for longer reaction times (Table 1, entries 2 and 4, respectively), the addition product **3a** was obtained in higher yields with slightly higher enantioselectivities.

Table 2. Enantioselective diethylzinc addition to *N*-diphenylphosphinoyl imine **2a** using chiral dendrimers **PS(Ephed)$_n$**[a]

Entry	Dendritic chiral ligand	Reaction time (h)	Yield[b] (%)	ee[c] (%)	Config.[d]
1	**PS(Ephed)$_2$**	48	53	81	*R*
2	**PS(Ephed)$_2$**	90	85	83	*R*
3	**PS(Ephed)$_4$**	48	71	84	*R*
4	**PS(Ephed)$_4$**	72	90	85	*R*
5	**PS(Ephed)$_{8a}$**	48	92 (91)[e](74)[f]	90 (92)[e](89)[f]	*R*
6	**PS(Ephed)$_{16}$**	48	78	79	*R*
7[a]	**PS(Ephed)$_{16}$**	48	93	80	*R*
8	**PS(Ephed)$_{8b}$**	48	91	90	*S*

[a] All reactions were performed in toluene at room temperature using 3.0 molar equiv of diethylzinc and equimolar amounts of chiral polymer (based on the total number of ephedrine moieties against the imine) and imine **2a**, except for entry 7, which was performed using 1.5 molar equiv of chiral polymer.
[b] Refers to the isolated yields after flash chromatography (hexane/ethyl acetate).
[c] Determined by HPLC analysis on a chiral column (Chiralpak AD).
[d] The absolute configuration was assigned to be *R* by comparing the retention time on HPLC with those reported in literature (see Section 4).
[e] Values in parenthesis are obtained from the same reaction using 1.0 molar equiv of (1*R*,2*S*)-*N*-benzylephedrine as chiral ligand.[8a,10b]
[f] Values in parenthesis are obtained by using *N*-vinylbenzylephedrine copolymerized with styrene and divinylbenzene as chiral ligand.[9]

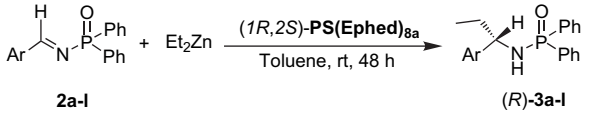
Although number effect of the chiral end-functional groups on each of the reaction yield and enantioselectivity of the addition product **3a** has not been clear yet, the above mentioned set of results was found to be in agreement with the previous finding reported by Hirao et al.[17] It has been found that the conformation of the polystyrene main chain within the polystyrene end-functionalized with dendritic moieties in nonpolar solvents strongly depends on the number of the end-functional moieties and consequently on their molecular weights. As can be seen from Table 1, the molecular weight of the dendritically branched end chains that include the chiral moieties are increased 6-times by repeating the functionalization reaction sequence on going from two to eight end-functional groups. Moreover, the volume ratio of the dendritically branched chain-ends relative to the polystyrene main chain for **PS(Ephed)$_8$** is seen to be high and comparable with the block copolymer. Therefore, the dendritic end-functional groups in case of chiral dendrimer **PS(Ephed)$_8$** can act as a block copolymer in solutions. Considering the above-mentioned factors, tentatively, it is supposed that the chain conformation for **PS(Ephed)$_8$** as a chiral ligand may be more preferable for segregation of the end-functional chiral groups from the polystyrene main chain similar to an immiscible block copolymers.

It is worth to mention that all the dendritic chiral polymers used in this study are soluble in toluene and worked well as homogeneous chiral ligands during the reaction. Interestingly, the enantioselectivity observed in the diethylzinc addition reaction to imine **2a** using chiral dendrimer **PS(Ephed)$_{8a}$** (90% ee, Table 2, entry 5) was high as those obtained not only by using (1*R*,2*S*)-*N*-benzylephedrine (92% ee, entry 5)[8a,10b] but also by using polystyrene supported with the same chiral moiety (89% ee, entry 5)[9]

as chiral ligand. More interestingly, the enantioselectivity thus obtained by using **PS(Ephed)$_{8a}$** (90% ee, entry 5) was found to be higher than that obtained from the same reaction using the chiral dendrimer having the same chiral moiety but with carbosilane backbone structure (86% ee).[10c]

Since in asymmetric synthesis it is important that both enantiomers of a given compound can be prepared, the dendritic chiral ligand **PS(Ephed)$_{8b}$**, prepared by the reaction of **PS(BnBr)$_8$** with chiral monomer (1*S*,2*R*)-ephedrine **1b**, was examined in the enantioselective ethylation of phosphinoyl imine **2a**. Chiral polymer **PS(Ephed)$_{8b}$** worked well as chiral polymer **PS(Ephed)$_{8a}$** and led smoothly to the desired secondary chiral amine **3a** with almost the same chemical yield and enantioselectivity, but with reversed stereoselectivity (Table 2, entry 8).

The above-mentioned primarily results obtained from the diethylzinc addition reaction to *N*-diphenylphosphinoyl benzaldimine **2a** prompted us to further examine the generality of the diethylzinc addition reaction to a series of *N*-diphenylphosphinoyl arylimines in the presence of the dendritic chiral ligand **PS(Ephed)$_{8a}$** that showed the best result, under the optimized experimental conditions shown in Table 2, entry 5. The results of diethylzinc addition reactions to a series of *N*-diphenylphosphinoyl arylimines (**2a–l**) displayed in Scheme 3 are summarized in Table 3.



Scheme 3. Enantioselective diethylzinc addition to *N*-diphenylphosphinoyl arylimines **2a–l** using dendritic chiral ligand (1*R*,2*S*)-**PS(Ephed)$_{8a}$**.

Table 3. Enantioselective diethylzinc addition to *N*-diphenylphosphinoyl arylimines **2a–l** using chiral dendrimer (1*R*,2*S*)-**PS(Ephed)$_{8a}$**[a]

Entry	Imine	(Ar)	Addition product	Yield (%)[b]	ee (%)[c,d]
1	**2a**	Phenyl	**3a**	92	90
2	**2b**	2-Me–C_6H_4	**3b**	86	88
3	**2c**	3-Me–C_6H_4	**3c**	90	91
4	**2d**	4-Me–C_6H_4	**3d**	90	93
5	**2e**	2-MeO–C_6H_4	**3e**	93	91
6	**2f**	4-MeO–C_6H_4	**3f**	89	92
7	**2g**	4-Cl–C_6H_4	**3g**	89	89
8	**2h**	4-Br–C_6H_4	**3h**	92	90
9	**2i**	2-Furyl	**3i**	83	79
10	**2j**	3-Pyridyl	**3j**	84	77
11	**2k**	1-Naphthyl	**3k**	86	83
12	**2l**	2-Naphthyl	**3l**	93	90
13[e]	**2d**	4-Me–C_6H_4	**3d**	91	93
14[a]	**2d**	4-Me–C_6H_4	**3d**	59	53

[a] All reactions were performed in toluene at room temperature for 48 h using 3.0 molar equiv of diethylzinc and equimolar amounts of chiral polymer (based on the total number of the ephedrine moieties against imine) and imine **2**, except for entry 14, which was performed using 0.5 molar equiv of chiral polymer.

[b] Refers to the isolated yields after flash chromatography (hexane/ethyl acetate).

[c] Determined by HPLC analysis on a chiral column (Chiralcel OD or Chiralpak AD) under the conditions that is described in Section 4.

[d] The absolute configuration was assigned by comparing the retention time on HPLC with those reported in literature (see Section 4).

[e] Recovered dendritic chiral polymer was used.

As expected, chiral dendrimer **PS(Ephed)$_{8a}$** promotes the highly enantioselective addition of diethylzinc to all aromatic substituted phosphinoyl imines **2a–l** to afford the corresponding enantiomerically enriched (*R*)-*N*-diphenylphosphinoylamides **3a–l** with yields of 83–93% and enantioselectivities up to 93% ee (Table 3). It is interesting to note that phosphinoyl imines bearing *para*-substituents on their phenyl groups would provide the corresponding *N*-phosphinoylamides with relatively higher enantioselectivity than their analogues having *ortho*- or *meta*-substituted phenyl groups. For example, the diethylzinc addition reaction to imine **2d**, having a *para*-methylphenyl group, afforded the addition product **3d** with a relatively higher enantioselectivity of 93% ee (Table 3, entry 4) than that of 88 and 91% ee given by its analogues **2b** and **2c**, which possessed an *ortho*- and *meta*-methylphenyl groups, respectively (Table 3, entries 2 and 3). Phosphinoyl imines **2i** and **2j** with heteroatom rings (2-furyl and 3-pyridyl, respectively) were also ethylated smoothly to afford the corresponding enantiomerically enriched (*R*)-**3i** and (*R*)-**3j**, respectively (Table 3, entries 9 and 10, respectively). Moreover, phosphinoyl imine **2l** bearing a 2-naphthyl group provided the corresponding addition product **3l** with a much higher enantioselectivity than that observed in the same addition reaction to imine **2k** having 1-naphthyl group (Table 3, entries 12 and 11, respectively). Thus, dendritic chiral polymer **PS(Ephed)$_{8a}$** also acts as a highly enantioselective chiral ligand for the diethylzinc addition to *N*-diphenylphosphinoyl arylimines and at the best, the enantioselectivity of the addition product **3d** with a *p*-tolyl substituent, obtained from the diethylzinc addition to imine **2d**, reached to 93% ee (Table 3, entry 4).

Since dendritic chiral polymer **PS(Ephed)$_{8a}$** was found to be efficient as a chiral ligand, we examined the re-use of the ligand in the asymmetric diethylzinc addition reaction. The chiral polymer was easily and quantitatively recovered by silica gel column chromatography followed by reprecipitation from its THF solution to a mixture of methanol and HCl. As shown in Table 3, the diethylzinc addition reaction to imine **2d** using the recovered polymer **PS(Ephed)$_{8a}$** afforded the addition product **3d** (entry 13) without any significant loss in the enantioselectivity as in entry 4.

As it has been cited in literature, a stoichiometric amount of the chiral β-amino alcohol usually is required to assure high yield and enantioselectivity in the enantioselective dialkylzinc addition to *N*-diphenylphosphinoyl imines.[8a,b,10] Since we have used in this study an equimolar amount of the dendritic chiral polymer **PS(Ephed)$_{8a}$**, based on the total number of the chiral sites at the periphery, against imines, the obtained high yields and enantioselectivities of the addition products suggested that nearly all of the chiral sites at the periphery of dendritic ligand **PS(Ephed)$_{8a}$** worked effectively. Thus, like in the reaction using monomeric chiral ligands,[8a] the eight parts in situ formed ethylzinc alkoxides of the amino alcohols (active chiral sites) can operate independently and can form an appropriate reaction field for the highly enantioselective addition of diethylzinc to imines. It is worth to mention that in the diethylzinc addition to imine **2d**, the use of a lesser amount of chiral dendrimer **PS(Ephed)$_{8a}$** (0.5 molar equiv against imine **2d**) resulted in a significant decrease

in each of the chemical yield and the enantioselectivity of the addition product (*R*)-**3d** (Table 3, entry 14).

To the best of our knowledge, the present method is the first example for the synthesis of such kind of chain-end-functionalized polystyrenes having dendritic chiral moieties at their chain-ends and their application as chiral ligands to the enantioselective dialkylzinc addition to imines.

3. Conclusion

A novel series of well-defined chain-end-functionalized polystyrenes having 2, 4, 8, and 16 chiral ephedrine moieties dendritically distributed at their chain ends were prepared and evaluated as chiral ligands in the diethylzinc addition to a series of *N*-diphenylphosphinoyl arylimines. Among them, chiral dendrimer **PS(Ephed)$_8$** having eight ephedrine moieties at the chain ends worked very well as efficient chiral ligand affording the addition products in good to high yields with enantioselectivities up to 93% ee. The obtained enantioselectivities are comparable with those obtained by using the corresponding *N*-benzylephedrine in solution system. We believe that the results reported herein would provide guidelines for the design future of dendritic chiral catalysts and ligands for the enantioselective asymmetric synthesis. Further applications toward the immobilization of other chiral ligands as well as other asymmetric reactions are now the focus of our continuing efforts.

4. Experimental

4.1. General

All reactions were performed under a nitrogen atmosphere. The reagents (>98% purities) were purchased from Aldrich Co. and used as received unless otherwise stated. DMF and toluene were freshly distilled over CaH_2 under a nitrogen atmosphere. Chain-end-functionalized polystyrenes with benzyl bromide moieties were synthesized by following the previously reported method.[14b–d,15] *N*-Diphenylphosphinoyl arylimines **2a–l** were prepared following literature procedures.[8a,d,e,i-k,10a,18,19a] The addition products *N*-diphenylphosphinoylamides **3a–l** are known compounds.[8a,c–e,f,h,j,k,m,n,9c,10a,c,d,19b–d,20] The benzyl bromide- and 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 $CDCl_3$. 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. Calibration curves were made with standard polystyrene samples to determine the M_n and M_w/M_n values. FTIR spectra were recorded on a JEOL JIR-AQS20 M FTIR 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 with a Perkin–Elmer 341 Polarimeter in a 10-cm cell. HPLC analyses were carried out on a chiral column (Chiralcel OD or Chiralpak AD, 25 cm, ca. 20 °C), with a 254 nm UV detector and a flow rate of 1.0 mL/min with the eluent indicated.

4.2. 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 (**1**, 0.3 g, 1.8 mmol) in DMF (5 mL) was added dropwise 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=21.71×10^3 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 2 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 methylene protons of the benzylephedrine moieties, with those at 0.17–0.84 ppm attributed for the methyl protons of the *sec*-butyl groups (initiator fragment). The ^{1}H NMR resonances attributed for the other protons of the chiral moiety were also taken into consideration. The functionalities of ephedrine moieties thus determined were found to be in quite agreement to those predicted (Table 1).

4.2.1. PS(Ephed)$_2$. ^{1}H NMR: δ=0.49–0.83 (br m, 6H, CH(C*H*$_3$)CH$_2$C*H*$_3$), 1.08–2.32 (br m, 578H, C*H*$_2$C*H*+C*H*$_3$N+C*H*$_3$CHN), 2.87–2.99 (br m, 2H, CH$_3$C*H*N), 3.46–3.56 (br s, 1H, ArC*H*Ar), 3.72–3.83 (br m, 4H, ArC*H*$_2$N), 4.78–4.90 (br m, 2H, C*H*OH), 6.30–7.25 (br m, 949H, Ar*H*); ^{13}C NMR: 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; FTIR (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.

4.2.2. PS(Ephed)$_4$. ^{1}H NMR: δ=0.39–0.82 (br m, 18H, CH(C*H*$_3$)CH$_2$C*H*$_3$), 1.09–2.35 (br m, 590H, C*H*$_2$C*H*+C*H*$_3$N+C*H*$_3$CHN), 2.95–3.34 (br m, 9H, ArC*H*Ar+(Ar)$_2$-CC*H*$_2$Ar+CH$_3$C*H*N), 3.71–3.86 (br m, 8H, ArC*H*$_2$N), 4.76–4.89 (br m, 4H, C*H*OH), 6.16–7.27 (br m, 975H, Ar*H*); ^{13}C NMR: 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; FTIR (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.

4.2.3. PS(Ephed)$_8$. ^{1}H NMR: 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+$(Ar)_2CCH_2$Ar+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: 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; FTIR (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.

4.2.4. PS(Ephed)$_{16}$. ^{1}H NMR: 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+$(Ar)_2$C-CH_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: 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; FTIR (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.

4.3. Enantioselective diethylzinc addition to *N*-diphenylphosphinoyl imines 2 using dendritic chiral polymers PS(Ephed)$_n$

General procedure: under nitrogen atmosphere, a toluene solution (1 M) of diethylzinc (0.3 mmol, 0.3 mL) was added dropwise to a mixture of dendritic chiral polymer (0.1 mmol, based on the total number of ephedrine moieties) and *N*-diphenylphosphinoyl imine **2** (0.1 mmol) in toluene (5 mL) at 0 °C over a period of 10 min. After the complete addition, the reaction mixture was stirred for 48 h at room temperature followed by quenching with saturated aqueous NH_4Cl (5 mL). The reaction mixture was extracted with dichloromethane (10 mL×3) and the combined organic extracts were washed with water and brine and dried over anhydrous magnesium sulfate. After removal of the solvents, the residue thus obtained was purified by flash column chromatography (2.5% V/V triethylamine pretreated SiO_2) eluting with hexanes/ethyl acetate mixtures of increasing polarity (from 90:10 to 0:100) to afford first the corresponding diphenylphosphinoylamides **3** with the yields and enantioselectivities that are shown in Tables 2 and 3, followed by eluting the chiral polymer. The addition products **3a–l** were characterized by comparing their physical and spectroscopic data with those reported in the literature.[8a,d,e,j,k,m,n,9c,10a,19b–d] The absolute configuration of the major enantiomer was assigned based on comparing the HPLC retention time with the literature values.[8a,c–f,h,k,l,m,n,9c,10c,d,20] Racemic samples required for HPLC comparison were prepared by addition of EtMgBr in THF to *N*-diphenylphosphinoyl imines **2**.[19a]

4.3.1. *N*-(1-Phenylpropyl)-*P*,*P*-diphenylphosphinoylamide 3a.[8d,e,j,l,n,9c,20a,b] The enantiomeric excess was determined by HPLC on a chiral stationary phase (Chiralpak AD column, hexane/propan-2-ol 80:20); *R*-isomer, t_R 8.77 min and *S*-isomer, t_R 11.83 min.

4.3.2. *N*-[1-(2-Methylphenyl)propyl]-*P*,*P*-diphenylphosphinoylamide 3b.[20b] The enantiomeric excess was determined by HPLC on a chiral stationary phase (Chiralpak AD column, hexane/propan-2-ol 90:10); *R*-isomer, t_R 16.27 min and *S*-isomer, t_R 27.35 min.

4.3.3. *N*-[1-(3-Methylphenyl)propyl]-*P*,*P*-diphenylphosphinoylamide 3c.[8l–n,20a,b] The enantiomeric excess was determined by HPLC on a chiral stationary phase (Chiralpak AD column, hexane/propan-2-ol 90:10); *R*-isomer, t_R 10.78 min and *S*-isomer, t_R 19.89 min.

4.3.4. *N*-[1-(4-Methylphenyl)propyl]-*P*,*P*-diphenylphosphinoylamide 3d.[8l–n,10a,c,20a,b] The enantiomeric excess was determined by HPLC on a chiral stationary phase (Chiralpak AD column, hexane/propan-2-ol 92:8; *R*-isomer), t_R 21.78 min and *S*-isomer, t_R 27.49 min.

4.3.5. *N*-[1-(2-Methoxyphenyl)propyl]-*P*,*P*-diphenylphosphinoylamide 3e.[20a,b] The enantiomeric excess was determined by HPLC on a chiral stationary phase (Chiralpak AD column, hexane/propan-2-ol 90:10); *R*-isomer, t_R 21.59 min and *S*-isomer, t_R 27.12 min.

4.3.6. *N*-[1-(4-Methoxyphenyl)propyl]-*P*,*P*-diphenylphosphinoylamide 3f.[8k,l,n,20a,b] The enantiomeric excess was determined by HPLC on a chiral stationary phase (Chiralpak AD column, hexane/propan-2-ol 80:20); *R*-isomer, t_R 11.02 min and *S*-isomer, t_R 13.29 min.

4.3.7. *N*-[1-(4-Chlorophenyl)propyl]-*P*,*P*-diphenylphosphinoylamide 3g.[8d,n,10c,20a,b] The enantiomeric excess was determined by HPLC on a chiral stationary phase (Chiralpak AD column, hexane/propan-2-ol 80:20); *R*-isomer, t_R 11.13 min and *S*-isomer, t_R 12.81 min.

4.3.8. *N*-[1-(4-Bromophenyl)propyl]-*P*,*P*-diphenylphosphinoylamide 3h.[8k,m,20a,b] The enantiomeric excess was determined by HPLC on a chiral stationary phase (Chiralcel OD column, hexane/propan-2-ol 95:5); *R*-isomer, t_R 27.56 min and *S*-isomer, t_R 32.92 min.

4.3.9. *N*-[1-(2-Furyl)propyl]-*P*,*P*-diphenylphosphinoylamide 3i.[9c,20a,b] The enantiomeric excess was determined by HPLC on a chiral stationary phase (Chiralcel OD column, hexane/propan-2-ol 97:3); *R*-isomer, t_R 38.09 min and *S*-isomer, t_R 45.88 min.

4.3.10. *N*-[1-(3-Pyridyl)propyl]-*P*,*P*-diphenylphosphinoylamide 3j.[8k] The enantiomeric excess was determined by HPLC on a chiral stationary phase (Chiralcel AD column, hexane/propan-2-ol 90:10); *R*-isomer, t_R 30.35 min and *S*-isomer, t_R 47.55 min.

4.3.11. *N*-[1-(1-Naphthyl)propyl]-*P*,*P*-diphenylphosphinoylamide 3k.[9c,20a,b] The enantiomeric excess was determined by HPLC on a chiral stationary phase (Chiralcel

OD column, hexane/propan-2-ol 97:3); *R*-isomer, t_R 26.88 min and *S*-isomer, t_R 40.93 min.

4.3.12. *N*-[1-(2-Naphthyl)propyl]-*P*,*P*-diphenylphosphinoylamide 3l.[9c,10c,20a,b] The enantiomeric excess was determined by HPLC on a chiral stationary phase (Chiralpak OD column, hexane/propan-2-ol 97:3); *R*-isomer, t_R 27.22 min and *S*-isomer, t_R 44.71 min.

4.4. Recovery of the dendritic chiral polymer

The recovered dendritic chiral polymer thus obtained after the diethylzinc addition reaction through the column chromatography was precipitated from its THF solution in a 4:1 mixture of methanol 2 M HCl followed by stirring for 4 h. The polymer was then reprecipitated again from its THF solution to methanol and after being freeze dried from its absolute benzene solution for 24 h, the recycled dendritic chiral polymer was used again in the enantioselective addition of diethylzinc to imines.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.08.093.

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