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Highly enantioselective addition of diethylzinc to *N*-diphenylphosphinylimines using dendritic chiral ligands with hydrocarbon backbones

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Abstract

Chiral dendrimers bearing three or six chiral β-amino alcohols on the hyperbranched hydrocarbon chain-ends act as efficient chiral ligands for the enantioselective addition of diethylzinc to *N*-diphenylphosphinylimines to afford enantiomerically enriched *N*-diphenylphosphinylamines with up to 94% e.e.

Dendrimer, an orderly hyperbranched macromolecule, is defined as one of the polymers with a certain molecular weight and a molecular architecture. Its characteristics are usually determined by the functional groups at the chain-ends.[1–3] When the well-designed chiral functionalities are loaded on the chain-ends of the dendritic backbone, those functionalities are positioned on the surface and the resulting chiral dendrimer is expected to act as a chiral ligand in asymmetric synthesis. Dendritic chiral ligands are prominent in their features among other polymeric chiral ligands[4] such as: (1) all of the chiral sites are placed on the surface of a dendrimer; and (2) individual chiral environments of these functionalities are approximately the same, while those of the chiral functionalities on other polymers are not. However, dendrimers modified by chiral functionalities at the terminal positions have rarely been utilized in asymmetric synthesis.[5–7] Our recent report shows that the dendrimers loaded with chiral amino alcohols on hydrocarbon backbones can be used as effective chiral ligands in the enantioselective alkylation of aldehydes.[8]

Meanwhile, the enantioselective alkylation of imines represents one of the challenges in asymmetric synthesis.[9] Compared with the asymmetric addition of dialkylzincs to aldehydes,[10] an enantioselective addition of dialkylzincs to imines has rarely been examined. We previously reported the enantioselective alkylation of *N*-diphenylphosphinylimines in the presence of chiral

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β-amino alcohols which provides a direct and convenient method for the formation of enantiomerically enriched secondary *N*-diphenylphosphinylamines.[11,12] Subsequent removal of the diphenylphosphinyl group by acid hydrolysis affords enantiomerically enriched secondary amines.[13]

We report here a highly enantioselective addition of diethylzinc (Et_2Zn) to *N*-diphenylphosphinylimines in the presence of dendritic chiral ligands possessing hydrocarbon backbones. Each of chiral ligands **1a** and **1b** bears three chiral sites on the *para*- and *meta*-positions to the backbone, respectively, and a second-generation chiral ligand **2** possesses six chiral β-amino alcohols on the phenylacetylene chain-end (Fig. 1).

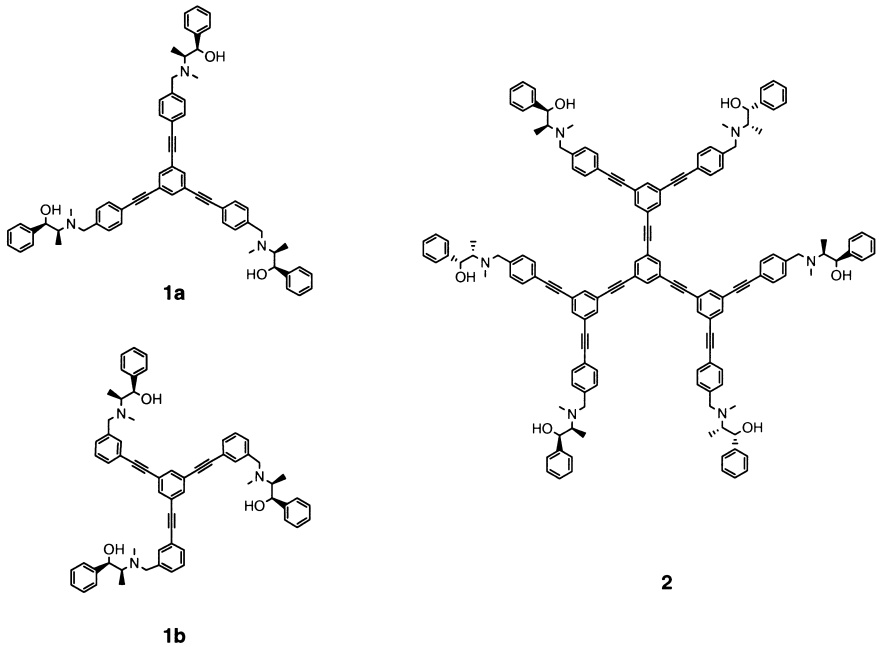
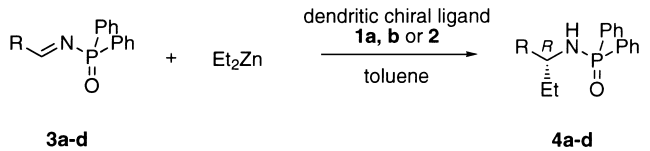


Figure 1.



(1)

N-Diphenylphosphinylimines were treated with Et_2Zn in the presence of dendritic chiral ligands **1a**,[8] **1b**,[14] and **2**[8] (Eq. (1)). All the reactions were carried out in toluene at room temperature. The results are summarized in Table 1. In the presence of *para*-substituted chiral ligand **1a** (0.34 mol equiv.), *N*-diphenylphosphinylimine **3a** was ethylated to give *N*-diphenylphosphinylamine (*R*)-**4a** with 89% e.e. (Entry 1).[15] Enantioselective alkylations of *N*-diphenylphosphinylimines **3b** and **3c** in the presence of chiral ligand **1a** gave the corresponding chiral (*R*)-amines **4b** and **4c** with 94 and 89% e.e., respectively (Entries 2 and 3). *N*-Diphenylphosphinylimine

3d with heteroaromatic ring was also ethylated to afford enantiomerically enriched (*R*)-**4d** (Entry 4). On the other hand, *meta*-substituted chiral dendrimer **1b** drove asymmetric ethylation of *N*-diphenylphosphinylimines with 73 to 85% e.e. (Entries 5–7). The enantioselectivity of chiral ligand **1a** was higher than that of **1b**. This is probably due to the fact that the environments of active sites of **1a** have enough space to work as a chiral ligand, while active sites of **1b** are too close to the backbone chains. Highly enantioselective ethylation also proceeded using dendritic chiral ligand **2** bearing six amino alcohols. In the presence of 0.17 mol equiv. of **2**, imine **3a** was converted to (*R*)-amine **4a** with 87% e.e. in good yield (Entry 8). The reaction was complete within 20 h. The rate of the reaction was almost the same as in the cases using 0.34 mol equiv. of dendritic ligand **1a** (Entry 1) or 1.0 mol equiv. of *N*-benzylephedrine.[15] The ligand **2** could be recovered (80%) by purification on silica gel TLC (Entry 8) and could be reused without a considerable change in the enantioselectivity (81% e.e.). Similarly, enantioselective addition of Et_2Zn to imines **3b** and **3c** gave amines **4b** and **4c** in 90 and 85% e.e., respectively (Entries 9 and 10).

Table 1
Enantioselective alkylation of various *N*-diphenylphosphinylimines **3a–d** using dendritic chiral ligands **1a**,**b** and **2**

	Imine **3**		Chiral ligand		(*R*)-Amine **4**[b]		
Entry[a]	R			Mol. Equiv.		Yield / %	E.e. / %
1	phenyl	**3a**	**1a**	0.34	**4a**	73	89
2	*p*-tolyl	**3b**			**4b**	77	94
3	2-naphthyl	**3c**			**4c**	80	89
4	2-furyl	**3d**			**4d**	77	71
5	phenyl	**3a**	**1b**	0.34	**4a**	62	85
6	*p*-tolyl	**3b**			**4b**	70	83
7	2-naphthyl	**3c**			**4c**	84	73
8	phenyl	**3a**	**2**	0.17	**4a**	77	87
9	*p*-tolyl	**3b**			**4b**	79	90
10	2-naphthyl	**3c**			**4c**	74	85

[a] Reactions were run in toluene for 20-27 h at room temperature using 3.0 molar equiv. of diethylzinc.
[b] Isolated yields. E.e. was determined by HPLC analysis using a chiral stationary phase. For the absolute configuration, see Ref. 11a.

Typical experimental procedure is as follows (Table 1, Entry 9): To a solution of *N*-diphenylphosphinylimine **3b** (63.9 mg, 0.20 mmol) and dendritic chiral ligand **2** (68.2 mg, 0.033 mmol) in toluene (4 ml) was added a 1 M toluene solution of Et_2Zn (0.6 ml, 0.6 mmol) at 0°C under an argon atmosphere. After the mixture was stirred at room temperature for 20 h, saturated aq. ammonium chloride (5 ml) was added. The mixture was filtered using Celite, and the filtrate was extracted with dichloromethane. The combined organic layer was dried over anhydrous sodium sulfate and evaporated. Purification of the residue by silica gel TLC (developing solvent, hexane:ethyl acetate:methanol = 5:4:1) gave *N*-diphenylphosphinylamine (*R*)-**4b** (51.1 mg, 79%). Enantiomeric excess was determined as 90% by HPLC analysis using a chiral stationary phase (Chiralcel OD).

In conclusion, chiral dendrimers bearing three or six β-amino alcohols on the hyperbranched hydrocarbon chain-ends work as efficient chiral ligands for the enantioselective addition of diethylzinc to *N*-diphenylphosphinylimines. The corresponding *N*-diphenylphosphinylamines are obtained with up to 94% e.e.

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14. Dendritic chiral ligand **1b** was synthesized by the Sonogashira coupling [cat. $PdCl_2(PPh_3)_2$ cat. CuI, *i*-Pr_2NH, 50°C] between (1*R*,2*S*)-*N*-(3-ethynylbenzyl)ephedrine and 1,3,5-tribromobenzene; $[\alpha]_D^{24}$ +30.0 (*c* 1.0, CH_3OH).
15. The enantioselective addition of diethylzinc to imine **3a** in the presence of 1.0 mol equiv. of (1*R*,2*S*)-*N*-benzylephedrine for 24 h gave the corresponding (*R*)-amine **4a** with 92% e.e. in the yield of 91%. It should be noted that, in the reaction using chiral ligand **2**, a lesser amount of chiral ligand **2** (0.17 mol equiv.) was utilized (Table 1, Entry 8).