Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 805–808

TETRAHEDRON: *ASYMMETRY*

Highly enantioselective addition of dialkylzincs to aldehydes using dendritic chiral catalysts with flexible carbosilane backbones

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Received 2 April 2002; accepted 25 April 2002

Abstract—Chiral dendrimers bearing four or twelve chiral β-amino alcohols on the hyperbranched flexible carbosilane chain-ends act as efficient chiral catalysts for the enantioselective addition of dialkylzinc to aldehydes to afford enantiomerically enriched *sec*-alcohols with up to 93% e.e.

Dendrimers, orderly hyperbranched macromolecules, are defined as polymers with a particular molecular weight and molecular architecture. Synthetic applications of functionalized dendrimers are of current interest.[1] All of the dendritic branches are capable of adding chiral functionalities to their chain-ends, and the resulting chiral dendrimers work as dendritic chiral ligands in asymmetric synthesis.[2,3] Every chiral site at the periphery would work effectively with approximately the same effect and efficiency. It would therefore have superior characteristics to other polymer-bound chiral ligands.[4] We have recently found that those dendrimers that possess several chiral amino alcohols on the rigidly constructed poly(phenylethyne) framework act as effective chiral catalysts and ligands in the enantioselective addition of dialkylzincs to aldehydes and *N*-diphenylphosphinylimines, respectively.[5,6] On these chiral dendrimers, each catalytic site is designed to be located at a separate position and to work independently.

Here we report the synthesis of chiral dimer **1** as well as of dendrimers **2** and **3** (Fig. 1), bearing two, four and twelve chiral β-amino alcohols, respectively, on the flexible carbosilane chain-ends,[7] and their effective application to the enantioselective addition of dialkylzincs to aldehydes. Rationalities of the design are: (1) carbosilane skeletons are free from coordination of organometallics; (2) interaction between chiral sites is possible because of the flexible structure. The syntheses of ephedrine moieties **7a**, **7b** and chiral dimer **1** are shown in Scheme 1. After the amino group of (1*R*,2*S*)-ephedrine **5** was reacted with 4-bromobenzyl bromide **4**, the alcohol was protected as its *tert*-butyldimethylsilyl (TBDMS) ether to give **7a** (99%) or as its trimethylsilyl (TMS) ether to give **7b** (98%). Addition of 2 mol. equiv. of lithiated **7a** to the 1,6-di(chlorodimethylsilyl)ethane, followed by cleavage of the silyl ether using tetrabutylammonium fluoride, resulted in chiral dimer **1**. Similarly, chiral dendrimers **2** and **3** were synthesized by using tetra(chlorosilane) **8** or dodeca(chlorosilane) **10**, which were prepared according to the procedure of van der Made and van Leeuwen (Scheme 2).[7c] Treatment of tetra(chlorosilane) **8** with 4.0 mol. equiv. of lithiated **7a** gave **9** in 90% yield. Cleavage of the four silyl ether of **9** afforded the desired dendrimer **2**. The functionalization of dodeca(chlorosilane) **10** with 12 ephedrine moieties was conducted by using the TMS ether of (1*R*,2*S*)-*N*-(4-bromobenzyl)ephedrine **7b**. Addition of lithiated **7b** and consequent cleavage of the TMS ether on silica gel produced chiral dendrimer **3** with twelve ephedrine moieties in 45% yield. The ^{1}H and ^{13}C NMR spectra and MALDI-TOF MS analysis clearly show the structure of **3**.

Enantioselective addition of dialkylzincs to aldehydes[8] was examined in the presence of a catalytic amount of

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PII: S0957-4166(02)00203-3

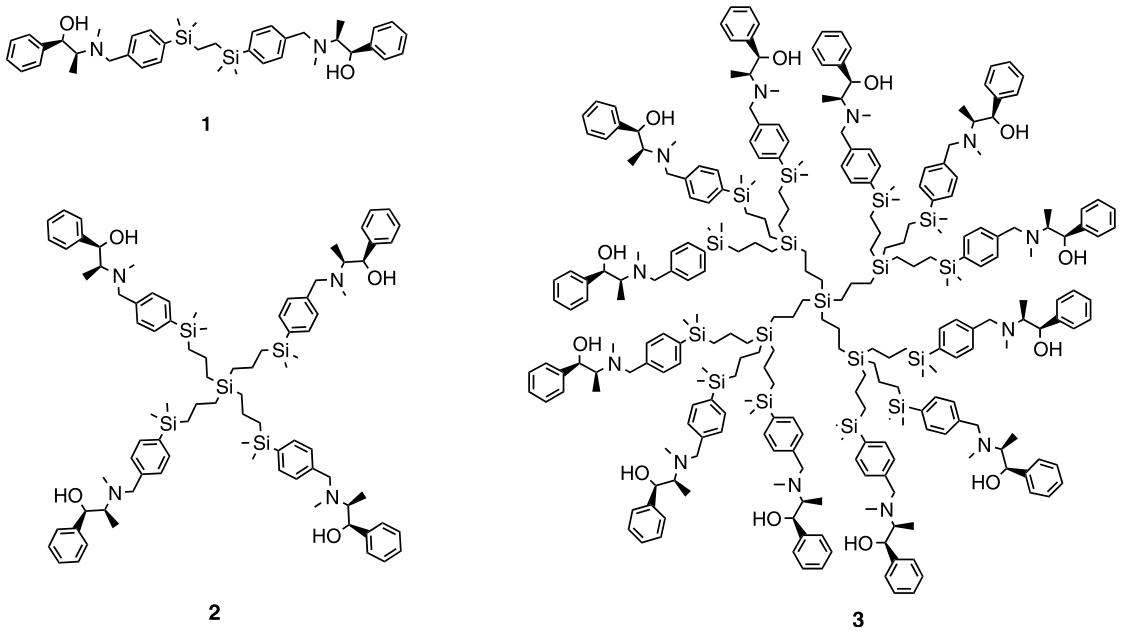
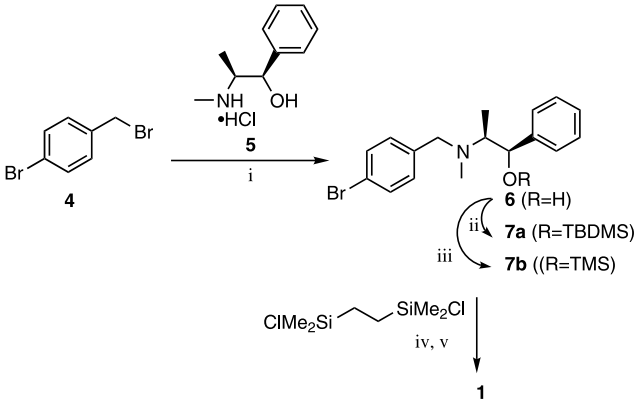


Figure 1.



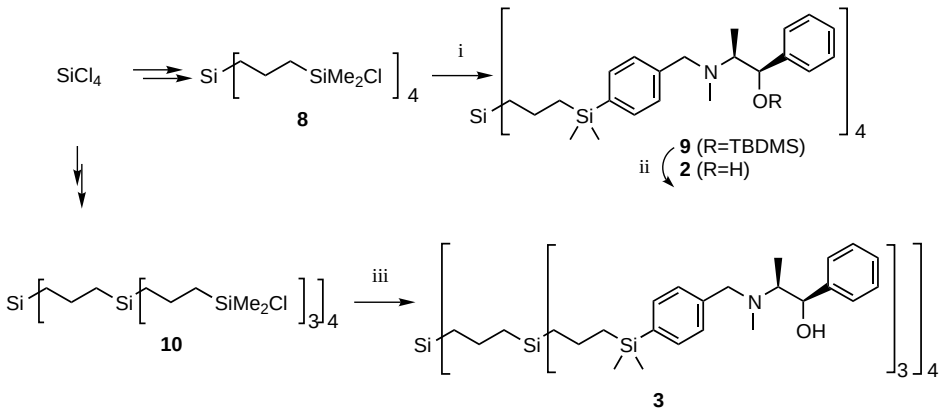
Scheme 1. *Reagents and conditions*: (i) **4** (1.0 mol. equiv.), K_2CO_3, CH_3CN, reflux, 87%; (ii) *t*-$BuMe_2SiCl$, imidazole, DMF, 99%; (iii) Me_3SiCl, Et_3N, THF, 98%; (iv) **7a** (2.0 mol. equiv.), BuLi, THF, −100°C, 65%; (v) Bu_4NF, THF, rt, 83%.

chiral dimer **1** or dendrimers **2** or **3** (Table 1). When chiral dendrimer **2** (5 mol%) was used as the chiral catalyst, addition of diethylzinc (Et_2Zn) to benzaldehyde **11a** gave (*R*)-1-phenylpropanol **12a** with 82% e.e. in 80% yield (Table 1, entry 1). Enantioselective addition of diisopropylzinc (*i*-Pr_2Zn) was also catalyzed by chiral dendrimer **2** to give (*R*)-2-methyl-1-phenylpropanol **12b** with 82% e.e. (entry 2). 2-Naphthaldehyde **11b** and 1-naphthaldehyde **11c** were converted to the corresponding *sec*-alcohols in 88 and 86% e.e., respectively (entries 3 and 4). Addition to 3-phenylpropanal **11f** proceeded in a highly enantioselective manner to give the (*R*)-alcohol **12f** with 93% e.e. (entry 6). The higher generation chiral dendrimer was also found to serve as an effective chiral catalyst.[9] Addition of *i*-Pr_2Zn to **11a** using 1.7 mol% of chiral dendrimer **3** afforded alcohol **12b** with 83% e.e. (entry 7). The reaction with the recovered catalyst gave alcohol **12b** with 85% e.e. (entry 8). An increase in the amount of catalyst **3** (5 mol%) gave **12b** with a similar 86% e.e. (entry 9). Enantioselective addition to 2-naphthaldehyde **11b** and 1-naphthaldehyde **11c** in the presence of **3** proceeded to give corresponding alcohols with 84 and 87% e.e., respectively (entries 10 and 11). Finally, enantioselective addition of *i*-Pr_2Zn to 3-phenylpropanal **11e** using chiral dendrimer **3** gave **12f** with 93% e.e. (entry 13).

In conclusion, chiral dendrimers bearing four or twelve β-amino alcohols on the carbosilane chain-ends work as efficient chiral catalysts for the enantioselective addition of dialkylzincs to aldehydes. Flexibility of the skeleton of the dendritic chiral catalyst enables the high enantioselectivity. These results constitute the guidelines for designing of dendritic chiral catalyst in organometallic chemistry.

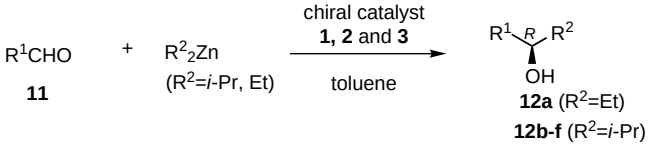
Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan and by Japan Space Forum.



Scheme 2. *Reagents and conditions*: (i) **7a** (4.0 mol. equiv.), BuLi, −100°C, 90% based on **8**; (ii) Bu_4NF, THF, 21%; (iii) **7b** (24 mol. equiv.), BuLi, −100°C to rt; SiO_2, CH_2Cl_2, two steps 45% based on **10**.

Table 1. Highly enantioselective addition of dialkylzincs to aldehydes using chiral dendrimers **2**, **3** or chiral dimer **1**



Entry[a]	Aldehyde **11**		Chiral catalyst (mol%)		(*R*)-Alcohol **12**		
	R^1			R^2		Yield (%)[b]	E.e. (%)[c]
1	Phenyl	**11a**	**2** (5.0)	Et	**12a**	80	82
2	Phenyl	**11a**	**2** (5.0)	*i*-Pr	**12b**	80	82
3	2-Naphthyl	**11b**	**2** (5.0)	*i*-Pr	**12c**	75	88
4	1-Naphthyl	**11c**	**2** (5.0)	*i*-Pr	**12d**	42	86
5	4-$CH_3OC_6H_4$	**11d**	**2** (5.0)	*i*-Pr	**12e**	80	85
6	$PhCH_2CH_2$	**11e**	**2** (5.0)	*i*-Pr	**12f**	56	93
7	Phenyl	**11a**	**3** (1.7)	*i*-Pr	**12b**	83	83
8[d]	Phenyl	**11a**	**3** (1.7)	*i*-Pr	**12b**	79	85
9	Phenyl	**11a**	**3** (5.0)	*i*-Pr	**12b**	84	86
10	2-Naphthyl	**11b**	**3** (1.7)	*i*-Pr	**12c**	77	84
11	1-Naphthyl	**11c**	**3** (1.7)	*i*-Pr	**12d**	42	87
12	4-$CH_3OC_6H_4$	**11d**	**3** (1.7)	*i*-Pr	**12e**	79	83
13	$PhCH_2CH_2$	**11e**	**3** (1.7)	*i*-Pr	**12f**	55	93
14	Phenyl	**11a**	**1** (5.0)	Et	**12a**	80	74
15	Phenyl	**11a**	**1** (5.0)	*i*-Pr	**12b**	77	79
16	1-Naphthyl	**11c**	**1** (5.0)	*i*-Pr	**12d**	42	88

[a] Reactions were run in toluene for 48 h at 0°C using 2.2 molar equiv. of dialkylzinc.
[b] Isolated yields.
[c] Determined by HPLC analysis using a chiral stationary phase. For the absolute configuration, see Ref. 10.
[d] Recovered catalyst was used.

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9. **Typical experimental procedure of enantioselective addition of dialkylzincs to aldehydes** (Table 1, entry 8). To a toluene (0.5 ml) solution of dendritic chiral catalyst **3** (15.3 mg, 0.0034 mmol, recovered by TLC purification) was added a 1 M toluene solution of *i*-Pr_2Zn (0.44 ml, 0.44 mmol) under an argon atmosphere. After the mixture was stirred for 20 min at 0°C, toluene solution of benzaldehyde (21.2 mg, 0.20 mmol) was added to the mixture. The reaction mixture was stirred at 0°C for 48 h, and quenched by adding 3 ml of satd aq. sodium hydrogen carbonate. 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, dichloromethane) gave (*R*)-2-methyl-1-phenylpropanol **12b** (23.6 mg, 79%). Enantiomeric excess (e.e.) was determined as 85% by HPLC analysis using a chiral stationary phase (Chiralcel OD).
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