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Synthesis of chiral dendrimers with a hydrocarbon backbone and application to the catalytic enantioselective addition of dialkylzincs to aldehydes

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Abstract

Chiral dendrimers with three or six β-amino alcohols on hyperbranched hydrocarbon chain-ends were synthesized. These macromolecules can act as chiral catalysts for the enantioselective addition of dialkylzincs to aldehydes. The corresponding secondary alcohols are obtained in high enantiomeric excess (up to 86% e.e.). © 2000 Elsevier Science Ltd. All rights reserved.

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Dendrimers and related hyperbranched macromolecules are well-defined polymers.[1–3] The functional groups at the chain-ends of the dendritic backbone determine their properties. These characteristics also make them attractive in the design of asymmetric catalysts. Chiral functionalities on the chain-ends of the dendritic backbone are positioned on the surface. Chiral environment of these functionalities are approximately the same, while these of chiral functionalities on the other polymers are not.[4] However, dendrimers that have been modified by chiral functionalities at the terminal position have rarely been used in asymmetric synthesis.[5,6] We previously reported that chiral starburst (PAMAM) dendrimers promote the enantioselective alkylation of *N*-diphenylphosphinylimines.[7] However, according to the increase in the size of PAMAM-based dendrimers, the enantioselectivity of alkylation decreased, presumably due to unfavorable intramolecular interactions between chiral functionalities caused by the relatively flexible backbones. Moreover, excess alkylating reagent is needed because of coordination of the alkylating reagent with the hetero atoms on the backbone. A similar observation has also been reported by another group.[5b]

We report here the synthesis of dendritic chiral catalysts **1a** (G1) and **1b** (G2), which have rigid hydrocarbon backbones with no hetero atoms, and their use as chiral catalysts in the enantioselective addition of dialkylzincs to aldehydes (Fig. 1).

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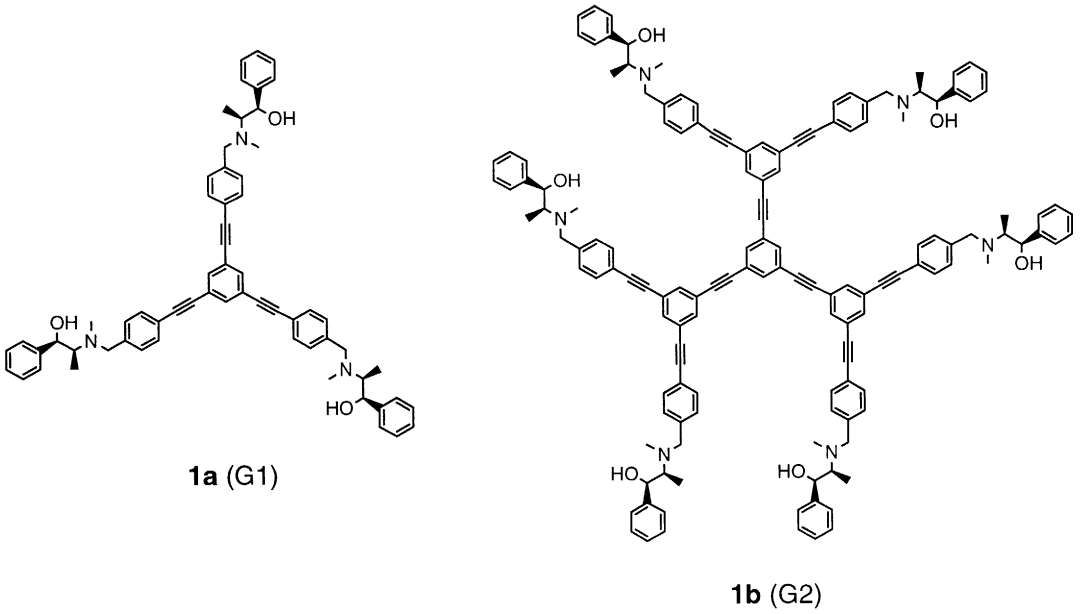
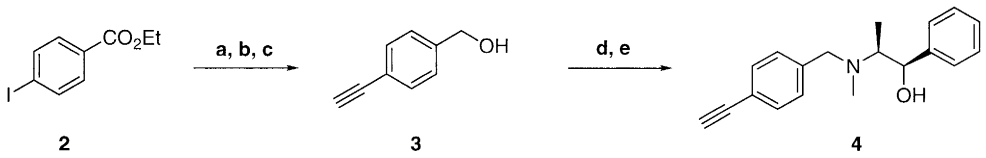


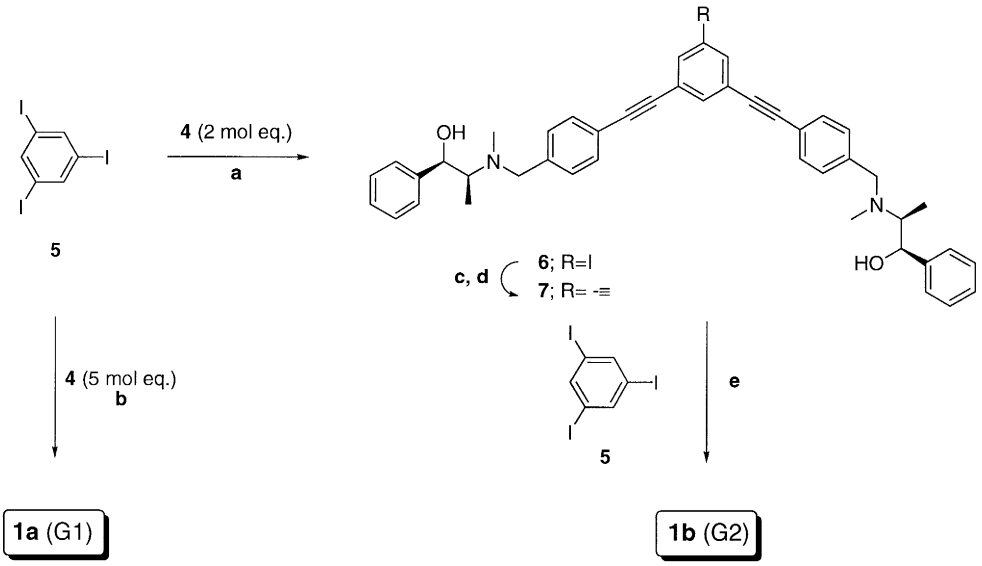
Fig. 1.

Chiral dendrimers **1a** (G1) and **1b** (G2) were synthesized as follows. Hagihara–Sonogashira coupling reaction[8] of ethyl 4-iodobenzoate (**2**) with ethynyltrimethylsilane, subsequent reduction of the ester, and removal of a trimethylsilyl group afforded 4-ethynylbenzyl alcohol **3** (Scheme 1). Mesylation of **3** and treatment with (1*R*,2*S*)-ephedrine and potassium carbonate gave the chiral amino alcohol **4**. As shown in Scheme 2, when 1,3,5-triiodobenzene (**5**) was treated with two molar equivalents of **4**, a bis-coupled product **6** was obtained as a major product. When compound **5** was treated with excess **4**, **1a** (G1)[9] bearing three ephedrine moieties was synthesized in 66% yield. On the other hand, compound **6** was further converted to the terminal alkyne **7** by coupling with ethynyltrimethylsilane and subsequent removal of the trimethylsilyl group. The coupling reaction of **7** with **5** produced **1b** (G2),[10] which bears six catalytic sites derived from ephedrine, in 88% yield based on **5**.



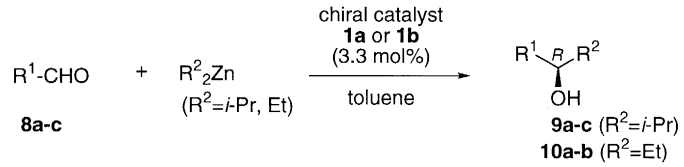
Scheme 1. Reagents and conditions: (a) HC≡C–$SiMe_3$, cat. $Pd(PPh_3)_4$, cat. CuI, Et_3N, THF, reflux; (b) $LiAlH_4$, ether; (c) Bu_4NF, THF, overall 83% (three steps); (d) MsCl, Et_3N, CH_2Cl_2; (e) (1*R*,2*S*)-ephedrine·HCl, K_2CO_3 CH_3CN, reflux, overall 76% (two steps)

The enantioselective addition of dialkylzincs to aldehydes[11] was examined using dendrimers **1a** (G1) and **1b** (G2) as chiral catalysts (Eq. (1)). The results are summarized in Table 1. In the presence of chiral dendrimer **1a** (G1) (3.3 mol%), benzaldehyde (**8a**) was isopropylated with *i*-Pr_2Zn to give (*R*)-2-methyl-1-phenylpropan-1-ol (**9a**) in high e.e. (86% e.e.) (entry 1). Furthermore, enantioselective isopropylation of benzaldehyde and 2-naphthaldehyde catalyzed by higher-generation dendrimer **1b** (G2) yielded **9a** and **9b** in 80 and 86% e.e., respectively (entries 7 and 8). Unlike our previous chiral PAMAM dendrimers, chiral dendrimers **1a** (G1) and **1b** (G2) do not require excess dialkylzincs. The catalysts **1a** (G1) and **1b** (G2) themselves are soluble in toluene, and were recovered and reused without any loss of



Scheme 2. Reagents and conditions: (a) **4** (2 mol equiv.), cat. $Pd(PPh_3)_4$, cat. CuI, Et_3N, THF, reflux, 49%; (b) **4** (5 mol equiv.), cat. $Pd(PPh_3)_4$, cat. CuI, Et_3N, DMF, 66%; (c) HC≡C–$SiMe_3$, cat. $Pd(PPh_3)_4$, cat. CuI, Et_3N, DMF, 69%; (d) Bu_4NF, THF, 83%; (e) **7** (5 mol equiv.), cat. $Pd(PPh_3)_4$, cat. CuI, Et_3N, DMF, 88% based on **5**

enantioselectivity (entries 2 and 3).[12] Thus, the rigid backbones of **1a** (G1) and **1b** (G2) are effective at impairing an unfavorable intramolecular interaction between the catalytic sites.



(1)

Table 1
Enantioselective alkylation of various aldehydes using chiral catalysts **1a** (G1) and **1b** (G2)

Entry[a]	Aldehyde **8**		R^2	Chiral catalyst	(*R*)-Alcohol[b]		
	R^1					Yield / %	E.e. / %
1	phenyl	**8a**	*i*-Pr	**1a** (G1)	**9a**	63	86
2			Et	**1a** (G1)	**10a**	61	78
3			Et	**1a** (G1)[c]	**10a**	64	77
4	2-naphthyl	**8b**	*i*-Pr	**1a** (G1)	**9b**	59	84
5[d]			Et	**1a** (G1)	**10b**	50	86
6	*p*-tolyl	**8c**	*i*-Pr	**1a** (G1)	**9c**	67	77
7	phenyl	**8a**	*i*-Pr	**1b** (G2)	**9a**	70	80
8	2-naphthyl	**8b**	*i*-Pr	**1b** (G2)	**9b**	32	86

[a] Reaction was performed in toluene. 2.2 molar equiv. of dialkylzinc was added to a solution of aldehyde and 3.3 mol% of chiral catalyst and the mixture was stirred at room temperature for 15-96 h.
[b] E.e. was determined by HPLC analysis using chiral column. Configuration of **9b** and **9c** are tentatively assigned based on that of **9a** (ref. 13).
[c] Recovered catalyst was used.
[d] 4.1 molar equiv. of diethylzinc.

In summary, chiral dendrimers **1a** (G1) and **1b** (G2) with rigid hydrocarbon backbones are useful catalysts for the enantioselective addition of dialkylzincs. Application of these chiral dendrimers to other asymmetric syntheses is in progress.

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10. Data of **1b** (G2): $[\alpha]_D^{25}$ −34.1 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.01 (18H, d, *J*=6.8 Hz), 2.21 (18H, s), 2.60 (6H, br s), 2.91 (6H, qd, *J*=6.8, 5.0 Hz), 3.63 (12H, s), 4.86 (6H, d, *J*=5.1 Hz), 7.2–7.7 (66H, m); ^{13}C NMR (125 MHz, CD_2Cl_2) ppm 9.8, 38.7, 59.1, 64.1, 74.4, 87.6, 88.6, 89.5, 90.9, 121.5, 123.9, 124.2, 124.7, 126.6, 127.4, 128.3, 129.1, 132.0, 134.3, 134.8, 141.1, 143.4; IR (KBr) 3429, 2210 cm^{-1}; HR MS (FAB$^+$) found *m/z* 2041.029, calcd for $C_{144}H_{132}N_6O_6$: 2041.021.
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