



A dendrimer-supported heterobimetallic asymmetric catalyst

Takayoshi Arai,^a Tetuya Sekiguti,^a Yoshimasa Iizuka,^a Shinobu Takizawa,^a Shigeru Sakamoto,^b Kentaro Yamaguchi^b and Hiroaki Sasai^{a,*}

^aThe Institute of Scientific and Industrial Research (ISIR), Osaka University, Mihogaoka, Ibaraki, Osaka 567-0047, Japan

^bChemical Analysis Center, Chiba University, Yayoicho, Inage-ku, Chiba 263-8522, Japan

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Abstract—Plural ligands consisting of catalysts such as AlLibis(binaphthoxide) complex (ALB) and GaNabis(binaphthoxide) complex (GaSB) are effectively introduced onto the periphery of a dendrimer. The resulting dendrimer-supported heterobimetallic catalysts promoted the asymmetric Michael reaction of 2-cyclohexenone with dibenzyl malonate to give the adduct with up to 97% ee. © 2002 Elsevier Science Ltd. All rights reserved.

Dendrimers are defined as a class of polymers with hyper-branched chains, typically having a spherical structure, and possessing a central core with a number of branching dendron units attached. Because the structure, size, shape and solubility of the dendrimers are tunable, these polymers have attracted considerable attention as a new class of well-defined nanometer-scale material.¹ Among the large number of various applications, the development of dendrimer-supported catalysts is one attractive area of research into dendritic materials.² Using the nanometer-scale branching dendrimer scaffold, these well-defined dendrimers could combine the advantages of homogeneous and heterogeneous catalysis. Despite the potential of these systems, positive reports on dendritic effects in catalysis have been rather limited.³ Recently, Jacobsen et al. reported on an example in which two catalytic sites at the terminal positions of a dendrimer assisted the ring-opening reaction of epoxides.⁴ We have also assumed that a dendritic framework would be useful for enforcing and controlling cooperative interactions between two ligands attached to the periphery of the dendrimer, as represented in Fig. 1.

Starting from BINOL as a chiral ligand we have developed heterobimetallic catalysts such as LaNa₃tris-(binaphthoxide) complex (LSB) and AlLibis(binaphthoxide) complex (ALB), which promote asymmetric reactions with synergistic cooperations of metals in the catalysts to give the products with high regio- and stereoselectivities.⁵ In heterobimetallic catalysts, two or

three molecules of BINOLs construct one catalyst through a self-assembly process. For heterobimetallic catalysts, the conventional method of catalyst immobilization using a sterically disordered polymer backbone (e.g. polystyrene resin) was resulted in the inefficient construction of polymer-supported catalyst due to the random orientation of the ligands. In the case of dendrimers, the highly defined branches can serve as an ideal structure for arranging two BINOL molecules to the suitable positions in the construction of an efficient heterobimetallic multifunctional catalytic site.⁶ Herein, we report on the first synthesis of dendritic heterobimetallic multifunctional asymmetric catalysts, and their application as catalysts in asymmetric Michael reactions. The substitution at the 6-position of BINOL was not expected to affect the asymmetric environment generated by the BINOL derived catalyst. The length of the alkyl side chain as a spacer was determined based on computational calculations.⁷ Molecular dynamics simulation of the dendrimer-supported ALB catalyst

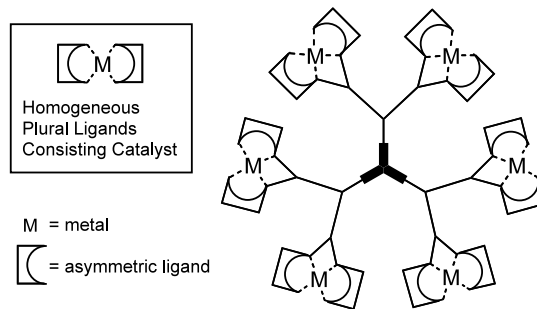
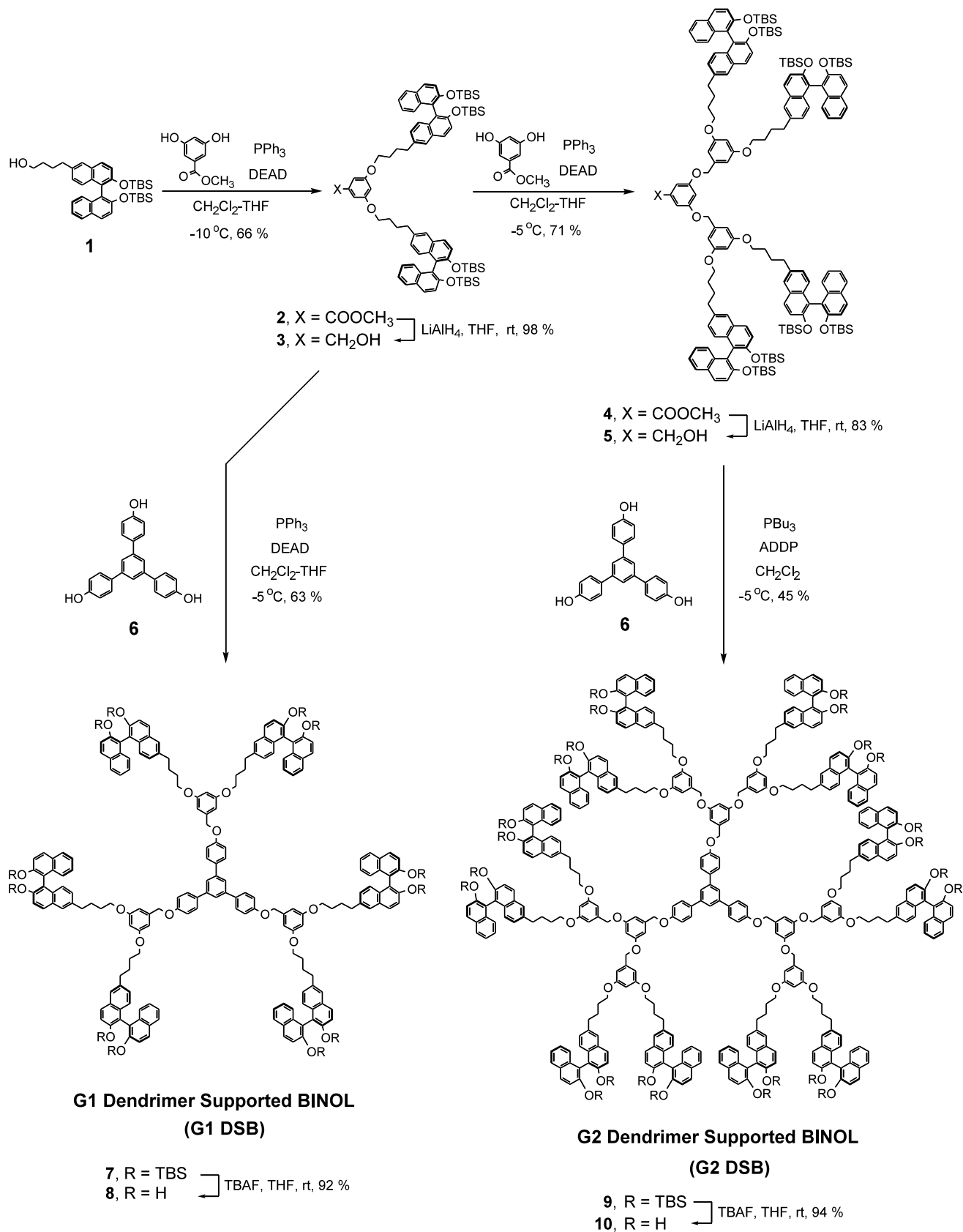


Figure 1. Efficient construction of plural ligands consisting catalyst on the periphery of the dendrimer.

* Corresponding author. Tel.: +81-6-6879-8465; fax: +81-6-6879-8469; e-mail: sasai@sanken.osaka-u.ac.jp



Scheme 1. Synthesis of dendrimer supported BINOL.

with various spacer lengths suggested a C₄ to C₆ alkyl side chain would be optimal for the formation of ALB on the dendrimer periphery. Since a longer spacer may result in the unwanted formation of the ALB type catalyst in an inter-dendron manner, the synthesis of the terminal dendron **2** was initiated using **1**,⁸ which has a C₄ alkyl chain. As shown in Scheme 1, two molecules of BINOL derivative **1** were incorporated with methyl 3,5-dihydroxybenzoate using the Mitsunobu coupling reaction⁹ to give the dendrimer terminal unit **2** in 66% yield, which was reduced with LiAlH₄ to afford compound **3** in 98% yield. The resulting benzyl alcohol **3** was combined with core unit **6**¹⁰ under Mitsunobu conditions to give the chiral generation 1 (G1) dendrimer **7** in 63% yield, which contains six BINOL units at the terminal positions. Subsequent deprotection of **7** using TBAF afforded the corresponding G1 dendrimer ligand **8**¹¹ (G1 DSB) in 92% yield. The G1 DSB was characterized by spectroscopic analyses including coldspray ionization (CSI) mass spectrometry¹² by the observation of an ion peak [M+Na]⁺ at *m/z* = 2786 (Fig. 2). Similarly, as shown in Scheme 1, the second generation dendrimer **10**¹³ (G2 DSB), which consists of 12 BINOL units at its terminal positions, was prepared using the improved Mitsunobu reagent.¹⁴ The molecular weight of G2 dendrimer **10** (G2 DSB) up to 5538 was also confirmed by CSI mass spectrometry by the detection of the peaks corresponding to [M+Na]⁺ (*m/z* = 5561) and [M+2Na]²⁺ (*m/z* = 2792).

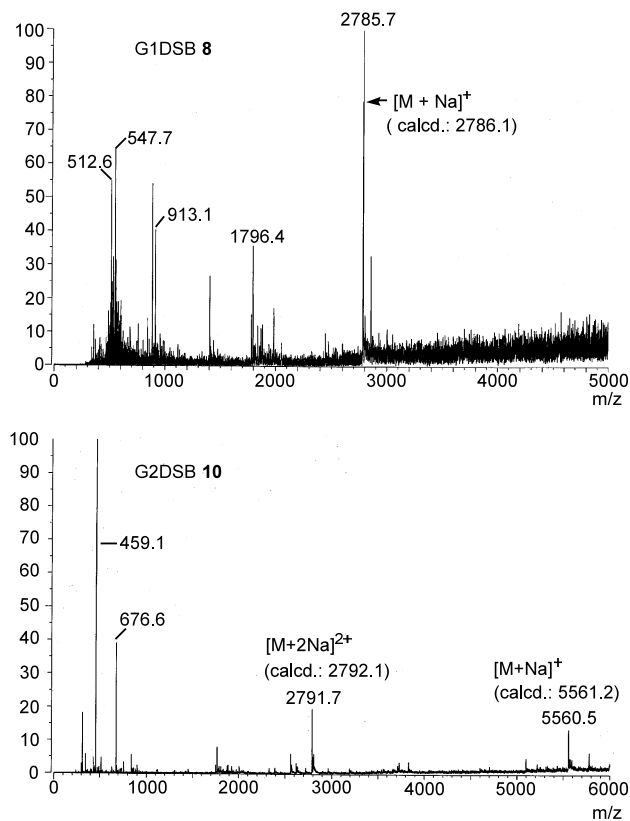


Figure 2. CSI mass spectra of **8** and **10**.

An insoluble catalyst of G1 dendritic ALB was formed by the treatment of G1 DSB **8** with AlMe₃ and *n*-BuLi. As expected, chiral dendritic ALB exhibited moderate catalytic activity in the asymmetric Michael reaction of 2-cyclohexenone **11** with dibenzyl malonate **12**. After 48 h, the Michael adduct **13** was obtained in 63% yield with 91% ee (Table 1, entry 1). In a similar procedure, G2 dendritic ALB gave **13** in 59% yield with 91% ee (Table 1, entry 4). Because the ALB derived from randomly introduced BINOLs on polystyrene resin gave **13** with almost racemic form, this is an apparent advantage of the use of dendrimers.^{15–17} The chiral dendritic BINOLs **8** and **10** were quantitatively recovered using silica gel column chromatography.¹⁸

Since G1 dendritic ALB was efficient as a solid catalyst, we examined the re-use of the catalyst in asymmetric Michael reactions. Because it has been reported that moisture sensitive aluminum Lewis acid catalysts are difficult to re-use, recovery of the dendritic ALB was carried out simply by removing the clear supernatant via syringe under a stream of argon. THF, **11**, and **12** were successively added to the residue to carry out the next Michael reaction. As shown in Table 1, the recycled catalyst gave comparable results with that of entry 1 (entries 2 and 3).¹⁹

These preliminary results prompted us to conduct further studies using the activated ALB (ALB-II).²⁰ Addition of an equivalent quantity of a basic reagent to the parent ALB catalyst enhances the catalytic activity while maintaining high enantiomeric excess of the Michael adducts. Although the dendritic ALB catalyzed reactions in the presence of 0.9 equiv.²¹ of *n*-BuLi or NaO-*t*-Bu reduced the enantiomeric excess values of **13**, the use of 0.3 equiv.²¹ of NaO-*t*-Bu gave the **13** in 79% yield with 89% ee (Table 1, entry 5).

Table 1. Asymmetric Michael reaction catalyzed by dendritic heterobimetallic catalysts

Entry	Dendritic catalyst	Time (h)	Yield (%)	Ee (%)
1	G1 Dendritic ALB	48	63	91
2	G1 Dendritic ALB (2nd use)	48	63	93
3	G1 Dendritic ALB (3rd use)	48	57	94
4	G2 Dendritic ALB	72	59	91
5	G1 Dendritic ALB II ^b	48	79	89
6	G1 Dendritic GaSB	22	40	92
7	G1 Dendritic GaSB II ^c	72	83	97

^aBased on a single catalytic site on the dendrimer.

^b0.3 equiv. of NaO-*t*-Bu to Al was added.

^c0.5 equiv. of NaO-*t*-Bu to Ga was added.

Furthermore, we examined another type of heterobimetallic multifunctional catalyst, which consisted of gallium, sodium and two BINOL moieties (GaNBis(bi-naphthoxide) complex) (GaSB).²⁰ A solution of **8** (G1 DSB) was treated with GaCl₃ and NaO-*t*-Bu to form G1 dendritic GaSB as an insoluble catalyst, which was shown to have moderate catalytic activity in the asymmetric Michael reactions. Moreover, the combined use of 0.5 equiv.²¹ of NaO-*t*-Bu and 10 mol% dendritic GaSB showed enhanced catalyst activity, affording the Michael adduct **13** in 83% yield with up to 97% ee (Table 1, entry 7).²²

In conclusion, dendrimer-supported heterobimetallic catalysts such as ALB and GaSB promoted the Michael reaction with excellent enantiomeric excess. These reactions are the first examples of the immobilization of a heterobimetallic multifunctional catalyst on the periphery of a dendrimer surface. Further applications toward the immobilization of other heterobimetallic catalysts, consisting of plural ligands, are the focus of our continuing efforts.

Acknowledgements

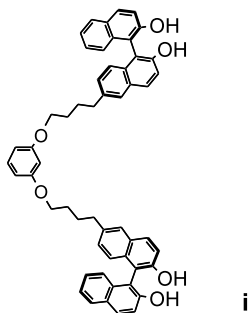
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11. Selected physical properties of G1 DSB **8**: IR (neat) 1091.6, 1220.9, 1359.7, 1419.5, 1635.5, 1705.0, 3510.0 cm⁻¹; ¹³C NMR (67.7 MHz, acetone-*D*₆): δ 28.58, 30.38, 30.66, 35.87, 67.96, 68.34, 101.12, 106.37, 114.55, 114.90, 115.92, 119.25, 123.44, 123.88, 125.29, 126.82, 127.32, 128.33, 128.64, 128.89, 129.72, 129.89, 129.93, 130.30, 133.69, 134.25, 137.35, 139.80, 140.33, 142.32, 153.68, 154.17, 159.14, 160.50, 161.14; [α]_D²⁵ -21.0 (c 0.240, CHCl₃); Mw on GPC analysis: 2600–2800.
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13. Selected physical properties of G2 DSB **10**: IR (neat) 819.7, 1126.4, 1145.6, 1458.1, 1508.2, 1596.9, 1701.1, 2923.9, 3410.0 cm⁻¹; ¹³C NMR (67.7 MHz, CDCl₃): δ 28.56, 30.54, 30.65, 35.87, 68.33, 70.37, 101.17, 106.41, 114.51, 114.88, 119.24, 123.45, 125.29, 125.90, 126.84, 127.31, 128.36, 128.64, 128.82, 129.53, 129.71, 129.87, 129.96, 130.31, 133.65, 135.22, 137.36, 140.17, 153.65, 154.15, 156.55, 160.69, 161.07; [α]_D²⁵ -30.9 (c 0.745, CHCl₃); Mw on GPC analysis: 5500–5700.
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15. Polystyrene-supported ALB was prepared by the reaction of Na-alkoxide of **1** with chloromethylated polystyrene (catalog No. 038-09524, Wako Pure Chemical Industries,

Ltd.), followed by the removal of the TBS group and catalyst formation with AlMe_3 and $n\text{-BuLi}$. The polymer supported ALB gave **13** in 27% yield with 0% ee after 72 h.

- Under high dilution conditions (0.03 M G1 dendritic ALB), the Michael adduct was obtained with 94% ee, which strongly suggests that the ALB complex forms on a single independent dendrimer molecule.
- The ALB catalyst derived from the peripheral dendron unit **i** gave **13** in 72% yield with 97% ee after 48 h.



- The recovered **8** was able to re-use as a ligand giving the Michael adduct in 63% yield with 91% ee.
- In the 4th use, **13** was obtained in 57% yield with 79% ee.
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- Equivalency to the single catalytic site.
- Typical procedure for asymmetric Michael reaction: To the insoluble dendritic heterobimetallic catalyst (0.1 equiv. as the single catalytic site) in THF (0.03 M) was added a solution of $\text{NaO-}t\text{-Bu}$ (0.03 equiv. to Al, 0.05 equiv. to Ga) in THF at 0°C. After stirring for 2 h at room temperature, **11** (0.031 mL, 0.317 mmol, 1.1 equiv.) and **12** (0.072 mL, 0.289 mmol, 1.0 equiv.) were added. After completion of the reaction, the reaction mixture was quenched with 1N HCl aq. at 0°C and then extracted with AcOEt. The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated to give an oily residue. Purification by flash chromatography (SiO_2 , acetone/hexane=1/10) gave **13**. The enantiomeric purity of the product was determined by chiral HPLC analysis (Daicel CHIRALPAK AS, *i*-PrOH/hexane=1/4, 1.0 mL/min, 254 nm).