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Polymer-Supported BisBINOL Ligands for the Immobilization of Multicomponent Asymmetric Catalysts

Tetuya Sekiguti, Yoshimasa Iizuka, Shinobu Takizawa, Doss Jayaprakash, Takayoshi Arai, and Hiroaki Sasai*

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

sasai@sanken.osaka-u.ac.jp

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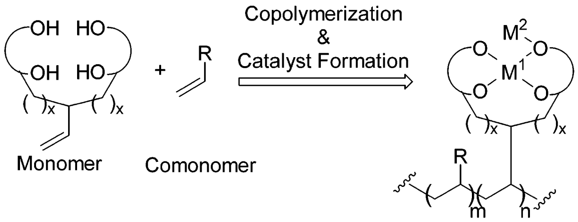
ABSTRACT



Polymer-supported bisBINOL ligands were successfully utilized for the immobilization of multicomponent asymmetric catalysts. The polymer-supported Al-Li-bis(binaphthoxide) (ALB) catalyst was more effective than the dendrimer-supported ALB in the Michael reaction of 2-cyclohexen-1-one with dibenzyl malonate affording the adduct in 91% yield with 96% ee. The polymer was also effective for the immobilization of a μ-oxodititanium complex that promoted carbonyl-ene reaction of ethyl glyoxalate with α-methyl styrene to provide the adduct with up to 98% ee.

Synergistic cooperation between two or more functional groups and/or metals plays an important role in realizing high reactivity and stereoselectivity in many enzymatic reactions. Highly organized multicomponent asymmetric catalysts have recently been designed that utilize this synergistic cooperation strategy for enantioselective reactions.[1,2] In this regard, we have reported a series of multicomponent asymmetric catalysts that consist of two or three molecules of BINOL and two kinds of metals for a range of asymmetric transformations.[3] Immobilization of these catalysts onto recoverable supports would expand their potential in terms of economic and operational benefits. However, such an attempt would require organization of the corresponding ligands on these supports in a manner observed in the parent homogeneous catalysts. The conventional approach using polystyrene resin resulted in less efficient catalysts due to the random orientation of ligands on the polymer affording the product in 27% yield with 0% ee. Dendrimers with well-defined macromolecular structures would construct a precisely controlled catalyst structure on their periphery.[4] Recently, we have developed dendrimer-supported BINOL ligands (Figure 1) for the immobilization of catalysts such as Al-Li-bis(binaphthoxide) complex (ALB) and Ga-Na-bis(binaphthoxide) complex (GaSB).[5] The dendrimer-supported catalysts were found to promote the asymmetric Michael

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(1) (a) Mikami, K.; Korenaga, T.; Terada, M.; Ohkuma, T.; Pham, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 495−497. (b) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180−8186. (c) Furuno, H.; Hanamoto, T.; Sugimoto, Y.; Inanaga, J. *Org. Lett.* **2000**, *2*, 49−52. (d) Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083−4084.

(2) For recent reviews, see: (a) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236−1256. (b) Rowlands, G. J. *Tetrahedron* **2001**, *57*, 1865−1882. (c) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187−2209.

(3) (a) Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 104−106. (b) Arai, T.; Yamada, Y. M. A.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *Chem. Eur. J.* **1996**, *2*, 1368−1372. (c) Arai, T.; Sasai, H.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 441−442.

10.1021/ol034797l CCC: $25.00

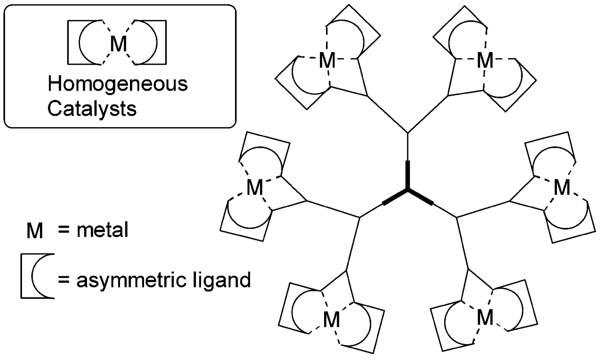
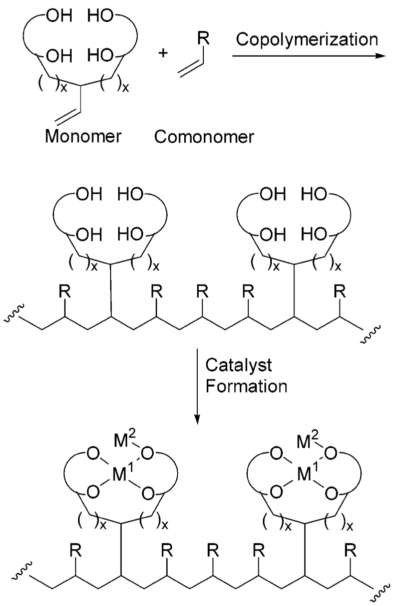


Figure 1. Dendrimer-supported multicomponent asymmetric catalyst.

reaction of 2-cyclohexen-1-one with dibenzyl malonate. While the Michael adduct was obtained with good selectivity, the chemical yields were moderate. In addition, the synthesis of the dendrimers involves multiple steps and often results in low yields, thereby limiting their potential in dendrimer-supported catalysts. In this regard, dendronized polymers,[6] which combine the advantages of dendrimers and linear polymers, appear to be promising alternatives. Polymerization of a dendron with a comonomer would readily afford polymeric ligands (Scheme 1) that could be used for the efficient construction of asymmetric catalysts.[7] Herein, we report the immobilization of multicomponent asymmetric catalysts using polymers containing bisBINOL ligands that closely resemble dendronized polymers.

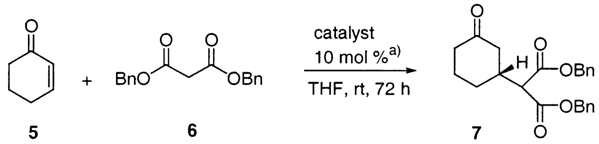
As shown in Scheme 2, monomer **2** consisting of bis-BINOL moiety was synthesized from **1**[5] by coupling with acryloyl chloride followed by cleavage of the protecting groups. Copolymerization of **2** with 1 equiv of methyl methacrylate (MMA) in the presence of AIBN afforded the polymer-supported bisBINOL ligand **3a**, which was precipitated from MeOH (Mw = 84 000, PDI = 10 by GPC analysis).

Scheme 1. Representative Preparation of Polymer Containing BisBINOL Ligand



The polymer-supported ALB catalyst **4a** was obtained as a white precipitate by the addition of AlMe$_3$ and *t*-BuLi to polymer **3a** in THF.[8] The catalyst **4a** promoted asymmetric Michael reaction of 2-cyclohexen-1-one (**5**) with dibenzyl malonate (**6**), affording the Michael adduct **7** in 36% yield with 96% ee (Table 1, entry 1).[9] A possible reason for the low yield could be overcrowding of the catalytic sites resulting in diminished reaction rates. To enable site separation between the catalysts, momomer **2** was polymerized with 3 equiv of MMA to obtain polymer **3b** (Mw = 16 000, PDI = 2.1 by GPC analysis). As expected the catalyst **4b**,

Table 1. Asymmetric Michael Reaction Catalyzed by Polymer-Supported ALB



entry	catalyst	yield (%)	ee (%)
1	**4a**	36	96
2	**4b**	91	93
3	dendrimer-supported catalyst	77	90

[a] As a monomeric catalyst.

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(4) (a) Sato, I.; Shibata, T.; Ohtake, K.; Kodaka, R.; Hirokawa, Y.; Shirai, N.; Soai, K. *Tetrahedron Lett*. **2000**, *41*, 3123−3126. (b) Schneider, R.; Köllner, C.; Weber, I.; Togni, A. *Chem. Commun*. **1999**, 2415−2416. (c) Seebach, D.; Marti, R. E.; Hintermann, T. *Helv. Chim. Acta* **1996**, *79*, 1710−1740. (d) Van Heerbeek, R.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M.; Reek, J. N. H. *Chem. Rev*. **2002**, *102*, 3717−3756. (e) Astruc, D.; Chardac, F. *Chem. Rev*. **2001**, *101*, 2991−3023. (f) Reek, J. N. H.; De Groot, D.; Oosterom, G. E.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M. *Rev. Mol. Biotechnol*. **2002**, *90*, 159−181.

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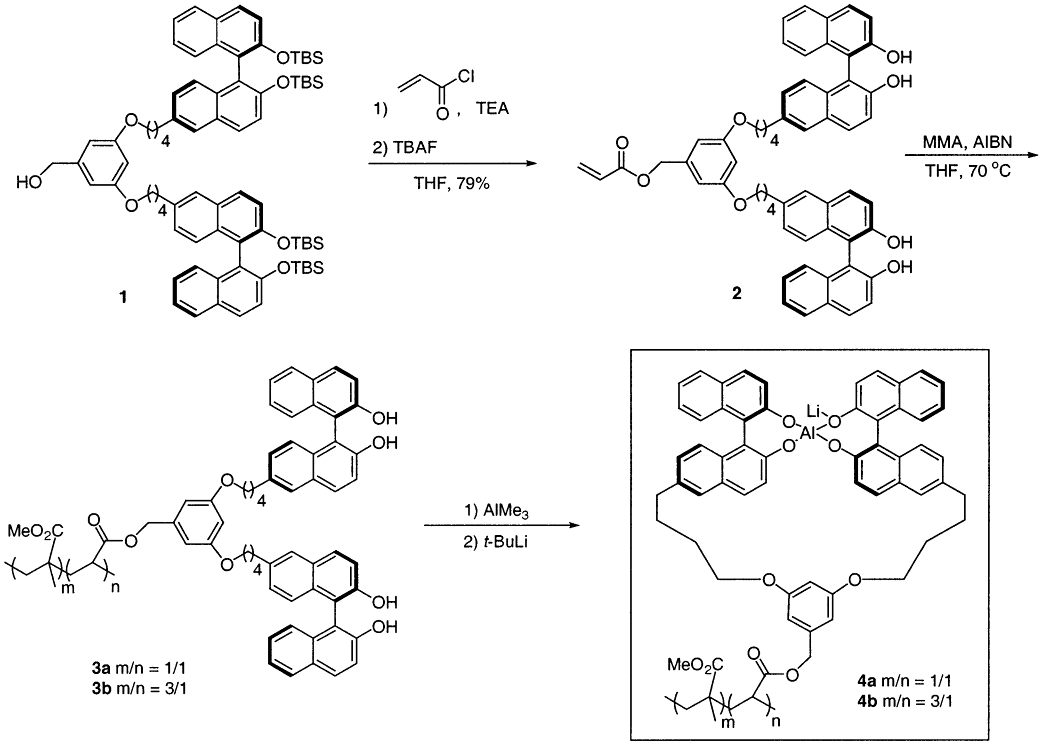
(6) (a) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev*. **2001**, *101*, 3819−3867. (b) Hecht, S.; Fréchet, J. M. J. *Angew. Chem., Int. Ed*. **2001**, *40*, 74−91. (c) Schlüter, A. D.; Rabe, J. P. *Angew. Chem., Int. Ed*. **2000**, *39*, 864−883. (d) Yin, R.; Zhu, Y.; Tomalia, D. A.; Ibuki, H. *J. Am. Chem. Soc*. **1998**, *120*, 2678−2679. (e) Percec, V.; Ahn, C.-H.; Ungar, G.; Yeardley, D. J. P.; Möller, M.; Sheiko, S. S. *Nature* **1998**, *391*, 161−164. (f) Frey, H. *Angew. Chem., Int. Ed*. **1998**, *37*, 2193−2197. (g) Schlüter, A. D. Dendrimers with Polymeric Core: Towards Nanocylinders. In *Topics in Current Chemistry*; Vögtle, F., Ed.; Springer: Berlin, 1998; Vol. 197: Dendrimers, pp 165−191.

(7) Dendronized polymers as chiral ligands: (a) Hu, Q.-S.; Sun, C.; Monaghan, C. E. *Tetrahedron Lett*. **2002**, *43*, 927−930. (b) Sellner, H.; Rheiner, P. B.; Seebach, D. *Helv. Chim. Acta* **2002**, *85*, 352−387.

(8) Typical Procedure for the Preparation of a Polymer-Supported ALB Catalyst: Polymer **3a** (18.2 mg, 0.04 mmol as a BINOL unit) was dissolved in 0.4 mL of THF after drying at 45 °C in vacuo for 2 h. To the solution were added AlMe$_3$ (0.98M, 20.4 μL, 0.02 mmol) and *t*-BuLi (1.49M, 13.5 μL, 0.02 mmol) at −78 °C. A white precipitate, obtained when the solution was warmed to room temperature, was directly used as an immobilized ALB catalyst.

Scheme 2. Synthesis of Polymer-Supported BisBINOL Ligand and Preparation of Supported ALB Catalyst

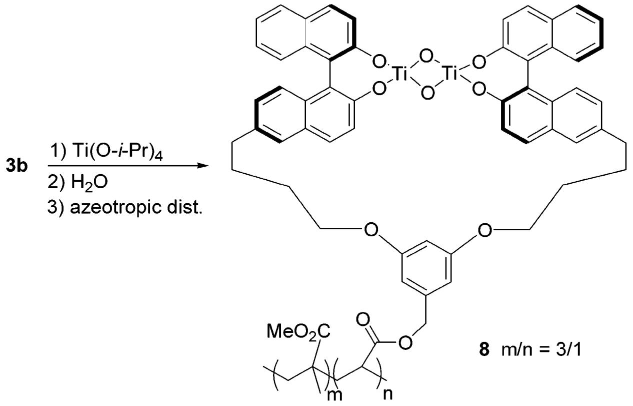


prepared from polymer **3b**, afforded the Michael adduct in 91% yield with 93% ee (entry 2). The polymers enable easy site separation, thereby resulting in enhanced reactivity. While a similar effect could account for lower yields in the case of dendrimer-supported catalysts (entry 3),[5] site separation on the periphery with higher generation dendrimers is rather difficult. Thus, by virtue of a simpler synthetic route, the new polymer-supported catalysts promise to be advantageous over dendrimer-supported counterparts. After the completion of the reaction, the polymer **3b** was quantitatively recovered by precipitation from MeOH.

To demonstrate the generality of the use of polymer-supported bisBINOL ligands for the construction of immobilized multicomponent asymmetric catalysts, the study was extended to μ-oxodititanium catalysts. Nakai et al. reported that bimetallic titanium BINOL complex promoted the asymmetric carbonyl-ene reaction of methyl glyoxylate (**9**) with α-methyl styrene (**10**) in high yield with excellent enantioselectivity.[10] The polymer-supported Ti complex was prepared as shown in Scheme 3.

To a solution of **3b** (27 mg, 0.06 mmol as BINOL unit) in CH_2Cl_2 (1.5 mL) was added 1 equiv of Ti(O-*i*-Pr)$_4$ (18 μL, 0.06 mmol) at 0 °C. After the mixture was stirred for 6 h at room temperature, a mixed solution of toluene (0.7 mL), CH_2Cl_2 (7 mL), and H_2O (0.06 mmol, 1.1 μL) was added. The solution was stirred for 18 h, and the solvents were removed azeotropically at 80 °C under reduced pressure. The reddish brown complex **8** thus obtained promoted the carbonyl-ene reaction of **9** with **10** in Et_2O to give the adduct **11** in 53% yield with 95% ee after 72 h (Table 2, entry 1). Addition of 4 Å molecular sieves (MS) (100 mg/mmol of **10**) dramatically improved the catalytic activity (entry 2). The enantioselectivities obtained with this system are higher than those reported with soluble linear polymers and highlight

Scheme 3. Preparation of Polymer-Supported Ti Complex



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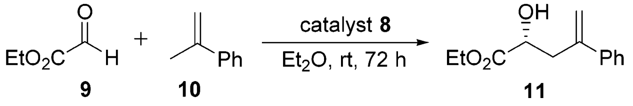
[9] Typical Procedure for Asymmetric Michael Reaction. To the polymer-supported ALB catalyst **4** (0.02 mol as a single catalytic site) in THF (0.4 mL) were added **5** (25 μL, 0.22 mmol) and **6** (50 μL, 0.20 mmol) at room temperature. After completion of the reaction, the reaction was quenched with aqueous 1 N HCl at room temperature, and the mixture was then extracted with AcOEt. The combined organic extracts were neutralized with saturated aqueous $NaHCO_3$, washed with brine, dried over Na_2SO_4, and concentrated. Separation of crude Michael product from polymer **3** was accomplished by precipitation of the residue from hexane. After concentration of the resulting supernatant, purification by flash chromatography (SiO_2, acetone/hexane = 1/10) gave **7**. The enantiomeric purity of **7** was determined by chiral HPLC analysis (Daicel CHIRALPAK AS, *i*-PrOH/hexane = 1/4, 1.0 mL/min, 254 nm).

[10] Kitamoto, D.; Imma, H.; Nakai, T. *Tetrahedron Lett.* **1995**, *36*, 1861−1864.

Table 2. Application and Reuse of Polymer-Supported Ti Catalyst in Asymmetric Carbonyl-Ene Reaction



entry	mol % catalyst	4 Å MS	yield (%)	ee (%)
1	10	−	53	95
2	10	+	quant	96
3 (2nd use)	20	+	83	98
4 (3rd use)	20	+	74	92

the advantage of these polymers.[11] Encouraged by these results, we tried to reuse **8**.[12] The catalyst **8** was recovered by removing the clear supernatant with a syringe under an Ar atmosphere. The catalyst maintained high enantioselectivity even during the third use (entry 4). Although the ICP-AES analysis revealed that less than 2% of the immobilized titanium was lost by way of leaching after the first use, a 17% decrease in chemical yield was observed between the first and second use of the catalyst. The decrease in yield was unavoidable despite the addition of 4 Å MS to the reaction during the second use of the catalyst. A possible reason for the decrease in yield could be the conversion of the polymer-bound complex to a less active form with time.

In conclusion, we have demonstrated a brief preparation of polymer-supported bisBINOL ligands to immobilize multicomponent asymmetric catalysts such as ALB and μ-oxodititanium catalysts. Both immobilized catalysts promoted the target reactions with high enantioselectivities. This is the first example of the use of polymers containing bisBINOL ligands to immobilize multicomponent asymmetric catalysts. Further applications toward the immobilization of other catalysts are in progress.[13]

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Yamada, Y. M. A.; Ichinohe, M.; Takahashi, H.; Ikegami, S. *Tetrahedron Lett*. **2002**, *43*, 3431−3434.

(12) Typical Procedure for Reuse of Polymer-Supported μ-Oxodititanium Catalyst. To a mixture of activated 4 Å MS (dried in vacuo at 150 °C for 2 h) (30 mg) and the insoluble polymer-supported μ-oxodititanium catalyst (0.03 mmol as the single catalytic site) in Et_2O (2 mL) were added **9** as a 50% toluene solution (92 μL, 0.9 mmol) and **10** (39 μL, 0.3 mmol). After the mixture was stirred at room temperature for 72 h, the clear supernatant was removed via syringe. The catalyst was repeatedly washed with fresh Et_2O (1 mL × 2) under an Ar atmosphere. The combined Et_2O extract was concentrated and purified by flash column chromatography (SiO_2, AcOEt/hexane = 1/7) to give **11**. To the catalyst residue were added fresh Et_2O (2 mL), **9** (46 μL, 0.45 mmol), and **10** (20 μL, 0.15 mmol). The enantiomeric purity of **11** was determined by chiral HPLC analysis (Daicel CHIRALPAK AS, *i*-PrOH/hexane = 1/4, 1.0 mL/min, 254 nm).

(13) Recently, we have demonstrated a new and general concept for constructing multicomponent asymmetric catalysts using a “catalyst analogue”. In this method, after copolymerization of a catalyst analogue having olefinic moieties with a monomer (e.g., MMA), the resulting polymer was used to prepare an active catalyst by exchanging the connecting group in the catalyst analogue with a catalytically active group. Arai, T.; Sekiguti, T.; Otsuki, K.; Takizawa, S.; Sasai, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 2144−2147.