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Novel Chiral Dendritic Diphosphine Ligands for Rh(I)-Catalyzed Asymmetric Hydrogenation: Remarkable Structural Effects on Catalytic Properties

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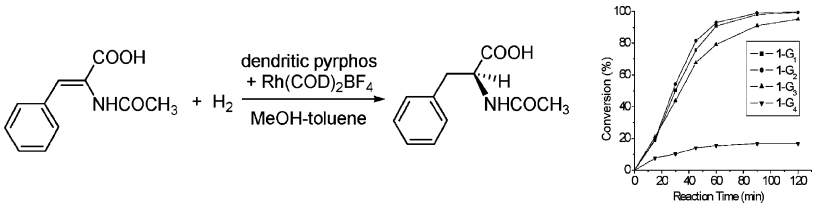
ABSTRACT



A series of dendritic ligands with a chiral diphosphine located at the focal point have been synthesized through coupling of pyrphos 2 with Fréchet-type polyether dendron 3. The relationship between the primary structure of the dendrimer and its catalytic properties was established in the Rh-catalyzed asymmetric hydrogenation of α-acetamido cinnamic acid 4. A remarkable structural effect on catalytic activity was observed.

The use of organometallic dendrimers in homogeneous catalysis is an important frontier of research in recent years.[1] Because of the well-defined molecular architecture of dendrimers, it is possible to fine tune their catalytic properties through the systematic adjustment of their structure, size, shape, and solubility. A number of organometallic dendrimers with catalytic sites at the core or at the periphery have been reported. However, only a few dendrimer catalysts have shown properties different from those of small molecule analogues. The "dendritic effects" range from total inhibition of the catalytic reaction to improvements in reactivity and stereoselectivity.[2−4] These novel effects, induced by the dendritic framework, obviously depend on the location of the functional group within the structure. In the case of the core-functionalized dendrimers, it is expected that the steric shielding or blocking effect of the specific microenvironment created by the dendritic structure could modulate the catalytic

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(1) For comprehensive reviews on dendritic organometallic catalysts, see: (a) Oosterom, G. E.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1828. (b) Astruc, D.; Chardac, F. *Chem. Rev.* **2001**, *101*, 2991. (c) van Heerbeek, R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Chem. Rev.* **2002**, *102*, 3717. (d) Fan, Q. H.; Li, Y. M.; Chan, A. S. C. *Chem. Rev.* **2002**, *102*, 3385.

(2) For examples of dendrimer catalysts with decreased activity, see: (a) Kleij, A. W.; Gossage, R. A.; Jastrzebski, J. T. B. H.; Boersma, J.; van Koten, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 176. (b) Kleij, A. W.; Gossage, R. A.; Gebbink, R. J. M. K.; Brinkmann, N.; Reijerse, Ed J.; Kragl, U.; Lutz, M.; Spek, A. L.; van Koten, G. *J. Am. Chem. Soc.*, **2000**, *122*, 12112. (c) Engel, G. D.; Gade, L. H. *Chem. Eur. J.* **2002**, *8*, 4319.

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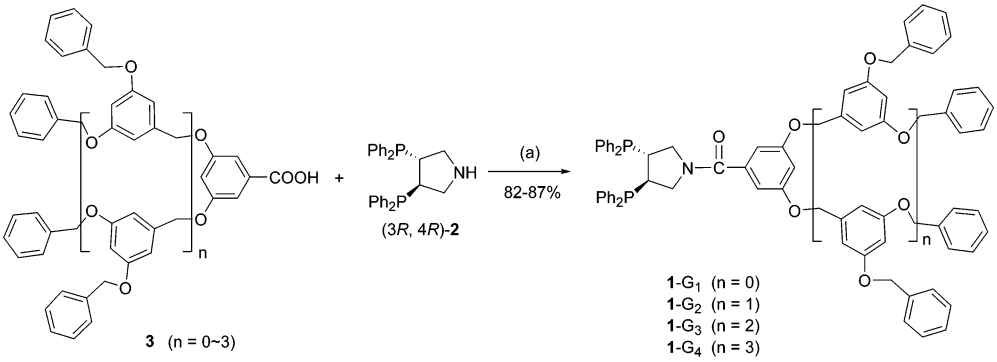
Scheme 1. Synthesis of Dendritic Pyrphos Ligands **1**-G_n[a]



[a] Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, rt, 10 h.

behaviors of the core. However, it is still unclear how the primary structure of the dendrimer biases its conformation and consequently influences its catalytic properties. Here we report a systematical study on the relationship between dendrimer structure and catalytic property by choosing 3,4-bis(diphenylphosphino)pyrrolidine (pyrphos, (3*R*,4*R*)-**2**) as a model ligand. This study demonstrated that the structure and conformation of the dendrimer significantly influenced its catalytic activity.

Chiral diphosphines are the most widely used ligands in the asymmetric catalytic hydrogenation of C=C and C=O bonds.[5] Chiral dendritic diphosphines have been reported by Brunner et al.,[6] Togni et al.,[7] Gade et al.,[2c,4e] and ourselves.[3b,8] However, most of the ligands studied do not contain the necessary functionalities for the convenient attachment to dendrimers. Pyrphos,[9] which was easily synthesized from natural tartaric acid, contains a functional amino group to which organic or inorganic supports may be directly attached. Rhodium pyrphos and its derivatives have been studied for the asymmetric hydrogenation of dehydroamino acid with up to 99% ee. To recycle these expensive and oxygen-sensitive catalysts, the complexes have been immobilized on the Merrifield resin, silica gel, and TentaGel.[10,11] However, most of these immobilized catalysts have shown lower catalytic activity and/or enantioselectivity compared to that of the corresponding homogeneous catalyst. Recently, we have reported a soluble poly(ethylene glycol)-supported pyrphos, which showed highly catalytic efficiency due to the homogeneous state during reaction.[12] To make better-defined immobilized catalysts for the study of the structure−property relationships, we have now synthesized a number of Fréchet-type dendrimers in which one pyrphos unit was located at the focal point. To the best of our knowledge, the attachment of this diphosphine ligand at the focal point of a dendrimer has not been reported to date.

The synthesis of new dendritic chiral pyrphos ligands is outlined in Scheme 1. Polyether dendrons **3** with carboxyl groups located at the focal point were synthesized by using the convergent method reported by Fréchet and co-workers;[13] **2** was synthesized according to the procedures reported by Nagel and co-workers.[10] A polyether dendrimer was chosen to ensure catalyst stability under the reaction conditions. The condensation reaction of **2** with **3** in the presence of 1,3-dicyclohexylcarbodiimine (DCC) and 4-(dimethylamino)-pyridine (DMAP) in dichloromethane at room temperature gave chiral dendrimer ligands **1**-G_n ($n = 0-3$) in high yield. These ligands were purified by flash column chromatography and were characterized by ^1H, ^{13}C, and ^{31}P NMR spectroscopy, elemental analyses, and/or HRMS and MALDI-TOF mass spectrometry. All results are consistent with the compounds synthesized.

To investigate the efficiency of **1**-G_n in asymmetric catalysis, the rhodium-catalyzed asymmetric hydrogenation of α-acetamido cinnamic acid (**4**) was chosen to be the model reaction. The dendritic Rh catalysts were prepared in situ via the reaction of **1**-G_n with $[Rh(COD)_2]BF_4$ in dichloromethane at room temperature for 30 min. All dendritic Rh-**1** complexes were tested, and the preliminary results are summarized in Table 1.

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(7) (a) Köllner, C.; Pugin, B.; Togni, A. *J. Am. Chem. Soc.* **1998**, *120*, 10274. (b) Schneider, R.; Köllner, C.; Weber, I.; Togni, A. *Chem. Commun.* **1999**, 2415.

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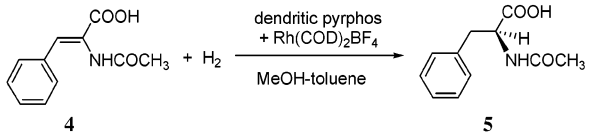
(10) For immobilized Pyrphos-containing catalysts, see: (a) Nagel, U. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 435. (b) Nagel, U.; Kinzel, E. *J. Chem. Soc. Chem. Commun.* **1986**, 1098. (c) Nagel, U.; Leipold, J. *Chem. Ber.* **1996**, *129*, 815.

(11) During our study, fixation of pyrphos to the periphery of poly(propyleneimine) and PAMAM dendrimers was reported by Gade, L. H. et al.; see refs 2c and 4e.

(12) Fan, Q. H.; Deng, G. J.; Lin, C. C.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 1241.

(13) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638.

Table 1. Asymmetric Hydrogenation of **4** with Dendritic Pyrphos-Rh(I) Catalysts[a]



4 **5**

entry	ligand	sub/cat	time (h)	conv[b] (%)	ee[c] (%)
1	**1**-G_1	200	2	100	98.3
2	**1**-G_2	200	2	100	98.7
3	**1**-G_3	200	4	25	95.3
4	**1**-G_2	200	2	100	97.7
5[d]	**1**-G_1	800	1	91 (96)[e]	96.8 (96.8)[e]
6[d]	**1**-G_2	800	1	93 (86)[e]	96.9 (95.1)[e]
7[d]	**1**-G_3	800	1	79 (59)[e]	96.9 (94.6)[e]
8[d]	**1**-G_4	800	6	20	97.0
9	**1**-G_3	100	0.5	94	97.5
10[f]	**1**-G_3	100	0.5	81	97.7
11[g]	**1**-G_3	100	0.5	55	97.7

[a] Hydrogenations were carried out in 0.032 M solution of **4** (20 mg) under the following reaction conditions: solvent = MeOH (entries 1−3), MeOH/toluene (2:1, v/v, entries 4−11); reaction temperature = 20 °C; H_2 pressure = 60 atm. [b] Based on GC or ^{1}H NMR analysis. [c] ee values of **5** were determined by chiral GC with a 25 m × 0.25 mm Chrompack Chirasil-L-Val column. The absolute configuration of **5** is *S*. [d] 200 mg of substrate and 30 mL of solvent were used. [e] Data in the brackets were obtained by using the backfolded dendrimers Rh(**6**-G_n) described below as catalysts. [f] Recycled catalyst from entry 9 was used. [g] Recycled catalyst from entry 10 was used.

According to our previous study,[12] methanol was initially chosen as the solvent for this reaction. High enantioselectivities (up to 98.7%) for the first and second generation dendrimer catalysts were observed (entries 1 and 2), which were higher than those from the use of the soluble polymer-supported catalyst (95.5% ee). This confirmed the value of Rh(**1**) catalysts with a well-defined dendritic wedge. However, the third generation catalyst gave lower enantioselectivity and significantly decreased conversion (entry 3). The profound "generation effect" was due to the insolubility of the third generation catalyst in methanol. Therefore, a binary solvent system (MeOH−toluene) was chosen to be the reaction medium in order to sustain homogeneous reaction conditions for all generation catalysts. In comparison with those in methanol, slightly lower enantioselectivity was obtained (entry 4). High enantioselectivities for these dendrimer catalysts were further observed under low catalyst loading (entries 5−8). In contrast to the dendrimer BINAP previously studied,[3b] the rate of the reaction decreased when higher generation catalysts were used (entries 5−8). To further demonstrated the "size effect", we determined the time course curves of this reaction with different generation catalysts (Figure 1). To our surprise, the dendrimer catalyst almost lost its activity when going from generation 3 to generation 4. In general, core-centered single-site catalysts show a gradual decrease of reactivity with increasing dendrimer generation due to steric shielding. We originally thought that the dramatic change in activity of the fourth generation dendrimer might be caused by the different coordination modes of **1**-G_4 with rhodium. Therefore, the

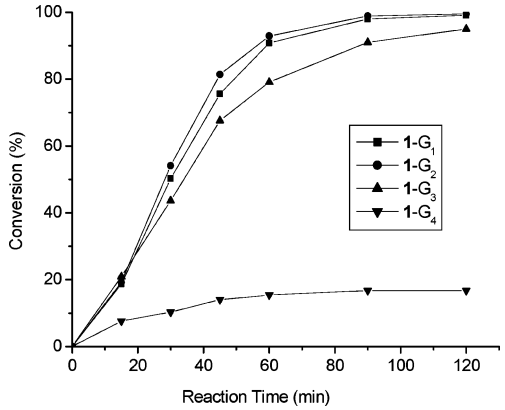


Figure 1. Time course curves of the hydrogenation of **4** for different generation catalysts Rh(**1**-G_n)

^{31}P NMR spectroscopy of **1**-G_1 and **1**-G_4 with [Rh(COD)$_2$]-BF_4 were examined, respectively. The chemical shifts of these two catalysts were very similar [Rh(1-G_1) δ = 34.8, 33.3 (dd, $^1J_{P-Rh}$ = 150.2 Hz, $^2J_{P'-Rh}$ = 149.1 Hz, J_{P-P} = 28.4 Hz) ppm; Rh(1-G_4) δ = 34.8, 33.2 (dd, $^1J_{P-Rh}$ = 149.9 Hz, $^2J_{P'-Rh}$ = 148.6 Hz, J_{P-P} = 28.8 Hz) ppm]. These results, together with the similar enantioselectivity resulting from these two catalysts, indicated that the sterically demanding dendritic wedge could not influence the coordination of rhodium with the phosphorus atoms at the core of the dendrimer. It has been reported that a transition in shape of the Fréchet-type dendrimer from an extended to a more globular structure occurred on going from generation 3 to generation 4.[14] The sudden loss of the activity of the fourth generation dendritic catalyst might be thus attributed to the change in dendrimer conformation, i.e., from an extended to a more globular structure as the steric requirements of the dendritic branches increase. Therefore, the globular structure of the dendrimer resulted in encapsulation of the active species by the dendrimer, which consequently influenced the diffusion of the substrates into the catalytically active core of the dendrimer. On the other hand, the dramatic change in activity, which correlated with a transition of the dendrimer conformation, might also provide a possibility of probing the dendrimer microstructure and overall shape by using asymmetric hydrogenation reaction.

To further demonstrate the effect of encapsulation on the catalytic activity, we designed a number of backfolded dendrimers **6**-G_n by modifying the branching pattern of Fréchet-type dendritic wedges. It was expected that primary structure elements that create backfolded linkages within the dendrimer should increase the degree of steric congestion around the active core, thus leading to more effective encapsulation. To our knowledge, no experiment on probing the effect of this type of dendritic structure on the properties of a catalytically active core has been reported. The synthetic approach to **6**-G_n was similar to the synthesis of **1**-G_n except

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for using the backfolded wedges with a carboxyl acid at the focal point instead of **3**.[15] The reaction yields, however, were lower than those of **1**-G_n as a result of the increased steric effect of the backfolded wedges. The attempt to obtain the fourth generation dendrimer was not successful because we could not synthesize the corresponding backfolded dendritic carboxyl acid wedges. The purity and structure of all dendrimers were determined by standard spectroscopic and elemental analyses as described above.

With these dendrimer ligands on hand, we probed their catalytic efficiency in the Rh-catalyzed asymmetric hydrogenation of **4**. The experimental data are summarized in Table 1. Although the first generation dendrimer **6**-G_1 behaved similarly to **1**-G_1 (entry 5 in Table 1), the size of the dendrimer with higher generations, as expected, influenced the reactivity of these catalysts more significantly as compared to **1**-G_n (entries 6 and 7 in Table 1). As seen from Figure 2, this effect was most pronounced when going from

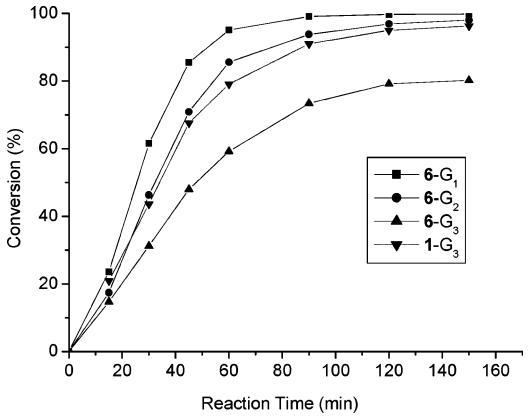
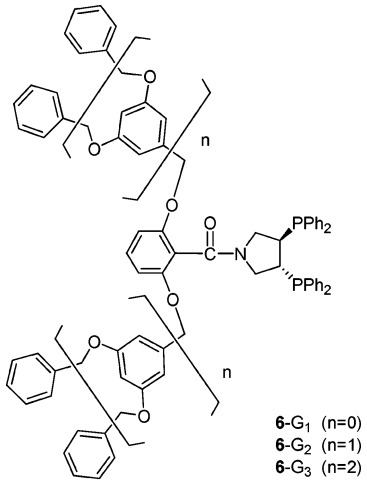


Figure 2. Time course curves of the hydrogenation of **4** for different generation catalysts Rh(**6**-G_n)

generation 2 to generation 3. This behavior was consistent with the more effective encapsulation of the active core by the backfolded dendrimer. Furthermore, unlike **1**-G_n, the enantioselectivity decreased along with the use of higher generation catalysts. This was probably due to a smaller, more compact structure around the active center resulting from the sterically demanding backfolded dendritic wedge, which influenced the dissymmetric arrangement of the four-phenyl rings of the diphenylphosphino groups of pyrphos.

In addition, we have also studied the possibility of the separation and recycling of the dendrimer catalyst using a solvent precipitation method. The third generation dendrimer was chosen for this study. Upon the completion of the



Backfolded dendrimers

reaction, most of the reaction solvent was removed under reduced pressure. Methanol was then added to this mixture, and the catalyst was precipitated and recovered via filtration. The recovered catalyst was reused for two cycles with similar enantioselectivity, albeit decreased activity (entries 9−11). The methanol layer, which contained the reduced product, was used by adding more substrate to it. No hydrogenation was observed when the reaction was carried out under otherwise identical conditions. However, when this reaction was carried out for 24 h, some of the newly added substrate was found to be reduced, indicating that a small amount of the catalyst remained dissolved in methanol.

In conclusion, we have developed a new class of dendritic catalysts with a chiral diphosphine located at the focal point of the dendrimer. The relationship between the primary structure of the dendrimer and its catalytic properties was established in asymmetric hydrogenation reaction. In the case of **1**-G_n, a dramatic change in catalytic activity was observed on going from generation 3 to generation 4, which might correlate with a transition in shape of the dendritic macromolecule from an extended to a more globular structure. We expect that this finding could give a clue to more sophisticated catalyst designs of dendrimers for highly selective organic syntheses.

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Supporting Information Available: Synthesis method; characterization information; ^{1}H, ^{13}C, and ^{31}P NMR spectra for all ligands; and general procedures for the catalytic hydrogenation. This material is available free of charge via the Internet at http://pubs.acs.org.

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