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## Key Role of the Lewis Base Position in Asymmetric Bifunctional Catalysis: Design and Evaluation of a New Ligand for Chiral Polymetallic Catalysts

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Our group is involved in developing new asymmetric catalysts based on the concept of bifunctional catalysis.<sup>1</sup> Specifically, we recently clarified the three-dimensional crystal structures of asymmetric catalysts, useful in various cyanation reactions, containing rare earth metals and chiral ligands derived from D-glucose (1 and 2).<sup>2</sup> This previous study demonstrated that the active asymmetric catalyst is a polymetallic complex, and that the higher-order structure of the complex has profound effects on the function (enantioselectivity and activity) of the asymmetric catalyst. In this communication, we report that a subtle change of the chiral ligand structure is amplified in the higher-order structure of the polymetallic complex, resulting in a dramatic difference in the function of the asymmetric catalyst.

On the basis of previous crystal structures derived from ligands 1 and 2,<sup>2</sup> a catalytically active polymetallic complex was constructed through self-assembly of the modular unit depicted as 5 (Figure 1). In module 5, the chiral ligand acts as a tetradentate ligand with each ligand bridging two metals by forming a 7-, 5-, and 5-membered fused chelation ring system. Our hypothesis for the design of a new asymmetric polymetallic catalyst was that its higher-order structure will be more stable when assembled from more stable modules. Thus, we designed new ligands 6 and 7 with a truncated linker between the scaffolding cyclohexane ring and the Lewis base phosphine oxide. In this case, module 8 contains a 6-, 5-, 5-membered fused ring system.

Synthesis of the designed ligands was simple and high yielding using the catalytic hydrolytic dynamic kinetic resolution of allylcarbonate<sup>3</sup> as the initial key step (Scheme 1).<sup>4</sup> The thus-obtained enantiomerically enriched allylic alcohol 10 was subjected to hydrogen-bonding-directed epoxidation, producing cis-epoxy alcohol 11 with excellent stereoselectivity (24:1). After introduction of the catechol moiety through the Mitsunobu reaction, site-selective epoxide opening with LiPPh2 proceeded concomitantly with methyl ether cleavage at the phenolic oxygen. Enantiomerically pure 7 was obtained after one recrystallization.

To identify the utility of new ligands 6 and 7, we focused on the enantioselective ring-opening reaction of meso-aziridines with TMSCN. We previously reported the first example of this reaction type using a polymetallic Gd catalyst (2:3 or 4:5+oxo complex of Gd and **3**) generated from  $Gd(O^{i}Pr)_{3}$  and **3** in a 1:2 ratio.<sup>5</sup> Although the substrate generality was broad, the catalyst activity and enantioselectivity were not completely satisfactory (see Table 1, entry 3 for a typical result). Because this type of reaction is useful for the synthesis of enantiomerically enriched  $\beta$ -amino acids-

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Figure 1. Chiral ligands (1-4, 6, and 7) and schematic depiction of the modular unit structures (5 and 8) in polymetallic complexes.



important chiral building blocks for  $\beta$ -peptides and foldamers<sup>6</sup>—a more efficient asymmetric catalyst was desirable.

We began our studies by applying the previously optimized conditions (Table 1, entry 3) to a ring-opening reaction of aziridine 13a using ligand 7. As a result, amido nitrile 14a was obtained with 52% ee (99% yield in 15 h at room temperature). Through optimization of the reaction conditions, we identified several important deviations from the previously observed tendency: (1) Addition of a catalytic amount of TFA produced detrimental effects using 7. (2) Reaction in THF produced higher enantioselectivity than in propionitrile. (3) The enantioselectivity was consistently high (>95% ee) regardless of the Gd/ligand ratio (from 1:1 to 1:4) in the catalyst preparation.7 These dependencies are in sharp contrast to the previous results using ligand 3, in which the enantioselectivity was strongly dependent on the Gd/ligand ratio. (4) Although 7 contains the same chirality as 3, the product produced by the catalysts derived from these ligands had reversed enantioselectivity.

Under the optimized conditions, we next investigated the scope of this catalysis (Table 1). Excellent enantioselectivity was produced

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<sup>*a*</sup> Isolated yield. <sup>*b*</sup>Determined by chiral HPLC. <sup>*c*</sup> In the presence of 10 mol % of 2,6-dimethylphenol at room temperature. <sup>*d*</sup> Using a catalyst generated from 10 mol % of Gd( $O^{i}Pr$ )<sub>3</sub> and 20 mol % of **3** in the presence of 5 mol % of TFA and 1 equiv of 2,6-dimethylphenol in propionitrile at 0 °C. Product with the opposite configuration (*S*,*S*) was obtained. See ref 5. <sup>*e*</sup> Absolute configuration was determined as shown (*R*,*R*). <sup>*f*</sup> Reaction temperature = 60 °C.

from a range of aziridines using 2 mol % of the catalyst. When using **13a** as a substrate, catechol-containing ligand **6** produced better results than **7** (entry 2). Thus, significantly higher enantioselectivity and catalyst turnover<sup>8</sup> were generally produced using catalysts prepared from **6** or **7** than when using the previous D-glucose-derived ligand **3**.

Comparing the two asymmetric catalysts prepared from Dglucose-derived ligands (1-3) and the new ligands (6 and 7), the contrasting dependency of the enantioselectivity on the Gd/ligand ratio in catalyst preparation and the reverse enantioselectivity suggest that the modular assembly state in the polymetallic catalysts differs depending on the chiral ligands. This assumption was supported by ESI-QFT-MS observation; while the Gd/ligand = 2:3 and 4:5+oxo complexes were the main species when the catalyst was prepared from Gd(O'Pr)<sub>3</sub> and 1-3 in a 1:2 ratio,<sup>2</sup> the 5:6+oxo+OH complex [MW = 3474.3881 (M + H)<sup>+</sup>] was the sole species in a catalyst solution prepared from Gd(O'Pr)<sub>3</sub> and 7 in both 1:1.2 and 1:4 ratios.<sup>7</sup>

The dramatic change in the modular assembly state of the polymetallic complexes was not due to the absence of the oxygen atom in the scaffolding cyclohexane ring in **6** and **7**; using a catalyst prepared from  $Gd(O^{2}Pr)_{3}$  and a control ligand **4** in a 1:2 ratio (10 mol %), we obtained **14a** with the same absolute configuration to that produced by D-glucose-derived ligands and with 44% ee. Therefore, the higher-order structure change of the polymetallic complex and the resulting change in the function of the asymmetric catalyst are likely due to the one carbon difference in the relative position of the phosphine oxide and Gd.

Studies toward elucidation of the three-dimensional structure of the active catalyst derived from **7** led us to isolate colorless prisms



Figure 2. X-ray structure of 3:4+2OH complex (a) and its chemical depiction (b).

from a catalyst solution in propionitrile. Crystallographic analysis revealed that the crystal was a Gd/ligand = 3:4+2OH complex (Figure 2).<sup>7</sup> Using this crystal as a precatalyst (Gd = 12.5 mol %), product 14a was obtained with only 62% ee. On the basis of the ESI-MS observations, the composition of 3:4+2OH was maintained when the crystal was dissolved in solution. Thus, the crystal structure does not represent the actual catalyst of the aziridine opening reaction. The enantioselectivity, however, recovered to 94% ee when Gd(O<sup>i</sup>Pr)<sub>3</sub> was added to the crystal solution to adjust the Gd/ligand ratio to 5:6 and heated at 50 °C for 1 h before the reaction was conducted. Therefore, the assembly-state conversion from the 5:6+oxo+OH complex to the 3:4+2OH complex in the crystallization process is reversible under appropriate conditions. Importantly, the crystal structure in Figure 2 strongly supports our initial hypothesis that the module contains a stable fused tricyclic chelation structure, in which one ligand binds to two Gd metals.

In summary, we identified new chiral ligands (6 and 7) for asymmetric polymetallic catalysts. The catalysts demonstrated improved, *reversed* enantioselectivity as well as significantly higher activity in an asymmetric ring-opening reaction of *meso*-aziridines with TMSCN, compared to the previous D-glucose-derived catalysts. The functional difference between the two catalyst groups is attributable to a higher-order structure change caused by a subtle modification in the position of the Lewis base. Further studies to elucidate the active catalyst structure and extension of the current concept to other reactions are ongoing.

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**Supporting Information Available:** Catalyst preparation, spectra, and cyrstallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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- (7) See Supporting Information for details.
- (8) For example, the reaction of **13a** was completed at room temperature in 4 h and in 15 min using 10 mol % of catalyst derived from **3** and **7**, respectively.

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