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Assembly State of Catalytic Modules as Chiral Switches in Asymmetric Strecker Amino Acid Synthesis

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The functions of biomacromolecules are intimately related to their three-dimensional structures, which are constructed through hierarchically assembling individual modules. The fact that the higher-order structures of biomacromolecules are determined by noncovalent bond interactions is responsible for the flexibility of life. This feature at a molecular level, however, is also thought to be the cause of several diseases, especially neurodegenerative diseases such as Creutzfeldt−Jacob disease and Alzheimer's disease.[1] Proteins with multiple, thermodynamically stable, higher-order structures of local energy minima could exhibit either normal or aberrant functions, depending on the higher-order structure, despite the fact that the primary structures are the same.

Inspired by functional biomacromolecules, many artificial materials have been recently developed using a modular approach.[2] Our work focuses on developing enzyme-like artificial bifunctional asymmetric catalysts that can promote novel carbon−carbon bond-forming reactions via dual activation of substrates and reagents at defined positions using a catalyst.[3] We previously reported that a catalyst prepared from Gd(O-*i*-Pr)$_3$ and a D-glucose-derived ligand **2** in a 1:2 ratio (Gd-**2**) promoted the cyanation of ketoimines **4** with high enantioselectivity.[4,5] This reaction has made it possible to access a wide range of enantiomerically enriched α,α-disubstituted amino acids, versatile chiral building blocks for biologically active compounds.

On the basis of preliminary structural studies of the catalyst using ESI-MS, both a 2:3 complex of Gd and the ligand and a 4:5+oxo complex were found to be present in a catalyst solution, from which the 2:3 complex was proposed to be the active catalyst.[6] The two Gd metals in the asymmetric catalyst should cooperate as a Lewis acid and a nucleophile activator, respectively.[3] This information led to the recent finding that a new catalyst preparation method using Gd(HMDS)$_3$ (HMDS = hexamethyldisilazane) and **2** in a 2:3 ratio (Gd*-**2**) resulted in the formation of the 2:3 complex as the sole catalytically active species, which improved enantioselectivity and catalyst activity.[6] Here, we present the three-dimensional structural characterization of two catalyst complexes, one (crystal **A**) producing the opposite enantiomer with excellent selectivity compared to that obtained by the catalyst prepared in situ, and the other (crystal **B**) containing a 2:3 complex as a subunit and thus reflecting the optimized Gd catalyst in solution. Analogous to common phenomena in biological system, higher-order structural differences in an artificial asymmetric catalyst led to a dramatic change in its function.

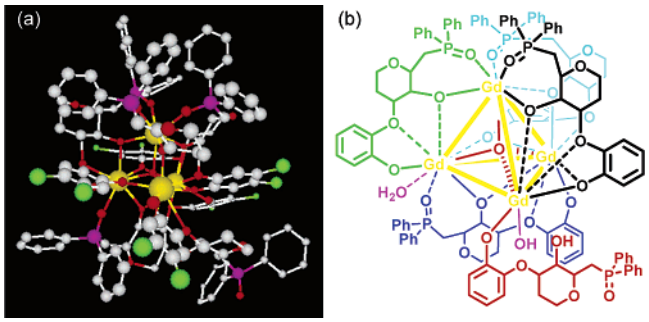

Figure 1. X-ray structure of crystal **A** (a) and its chemical structure (b). Stereochemistry of the ligands and chloride atoms on the catechol moieties are omitted in (b) for clarity.

Although Gd*-**2** produced optimum results in the enantioselective Strecker reaction, we screened various crystallization conditions to obtain single crystals of the catalytically active species, combining several related chiral ligands (e.g. **1**−**3**) and rare earth metal sources. Colorless, air-stable prisms were obtained from a propionitrile−hexane (2:1) solution of the complex prepared from Gd(O-*i*-Pr)$_3$ and ligand **3** in a 2:3 ratio (crystal **A**: 80% yield). X-ray crystallographic analysis revealed that crystal **A** was a 4:5 complex of Gd and **3** with a μ-oxo atom surrounded by four Gd atoms (Figure 1).[7] The tetranuclear structure was maintained in a solution state,[8] and the sole peak observed by ESI-MS corresponded to crystal **A**. Thus, crystal **A** was distinct from catalysts prepared in situ, such as Gd*-**2**, containing Gd and the chiral ligand in a 2:3 ratio. The difference in the assembly state of the chiral modules dramatically affected the catalytic function. When crystal **A** was used as a catalyst in the Strecker reaction of ketoimines, enantioselectivity was completely reversed compared to the catalyst prepared in situ (Table 1, entries 4, 10, 13, 15, and 17). The reaction rate was approximately 5−50 times slower than that using the catalyst prepared in situ.[9] The enantioswitching was not attributed to the chiral ligand **3**, because the in situ prepared Gd-**3** gave the "normal" (*S*)-products (Table 1, entries 3, 9, 12, and 16). Thus, the "aberrant" (*R*)-product formation using crystal **A** was attributed to the change in the assembly mode of the chiral modules through the crystallization process.

Further efforts to obtain single crystals relevant to the catalyst prepared in situ led to the isolation of a second crystal type. Colorless, air-stable prisms (crystal **B**) grew from a THF solution of La(O-*i*-Pr)$_3$ and ligand **1** mixed in a 2:3 ratio (47% yield). The X-ray diffraction study revealed the structure to be a unique *pseudo*

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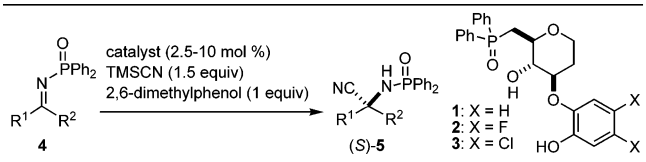
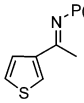
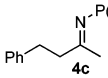
Table 1. Catalytic Enantioselective Strecker Reaction of Ketoimines



entry	substrate	catalyst[a]	time (h)	yield (%)	ee[b] (%)	config.
1		Gd-**1** (2.5 mol %)	0.5	99	99	(*S*)
2		Gd*-**2** (2.5 mol %)	0.1	99	99	(*S*)
3		Gd-**3** (5 mol %)	0.5	99	98	(*S*)
4		crystal **A** (Gd: 7 mol %)	2	99	91	(*R*)
5		crystal **B** (La: 8 mol %)	15	99	26	(*S*)
6	**4a**	La-**1** (5 mol %)	2	99	16	(*S*)
7		La-**2** (5 mol %)	2	99	47	(*S*)
8		Gd-**2** (2.5 mol %)	2	98	97	(*S*)[c]
9		Gd-**3** (5 mol %)	0.5	99	88	(*S*)[c]
10		crystal **A** (Gd: 7 mol %)	1	93	96	(*R*)[c]
11	**4b**	crystal **B** (La: 8 mol %)	6	99	27	(*S*)[c]
12		Gd-**3** (5 mol %)	2	99	87	(*S*)
13	 **4c**	crystal **A** (Gd: 7 mol %)	2	95	87	(*R*)
14		Gd-**2** (2.5 mol %)	2.5	91	80	(*S*)
15	 **4d**	crystal **A** (Gd:7 mol %)	12	99	82	(*R*)
16		Gd-**3** (10 mol %)	2	92	74	(*S*)
17	 **4e**	crystal **A** (Gd:7 mol %)	14	99	98	(*R*)

[a] In entry 2, the catalyst was prepared from Gd(HMDS)$_3$ and ligand **2** in a 2:3 ratio. In other entries, the catalyst was prepared from a lanthanide (either Gd or La) isopropoxide. [b] Determined by chiral HPLC. [c] Absolute configuration was determined as shown. In other entries, the absolute configuration was temporarily assigned.

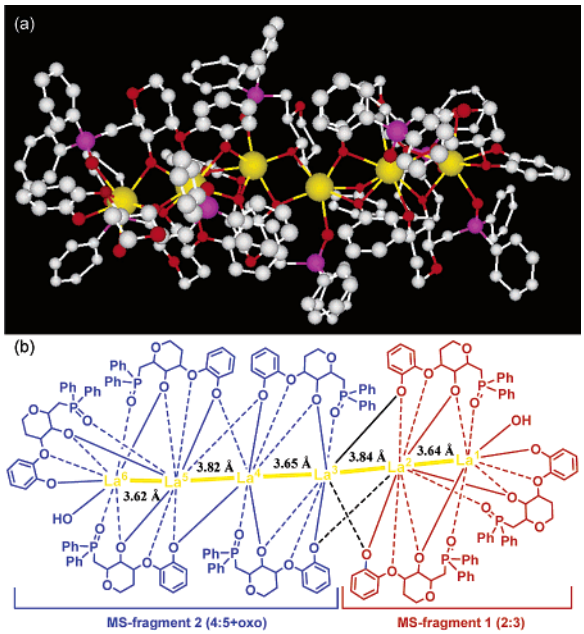


Figure 2. X-ray structure of crystal **B** (a) and its chemical structure (b).

C_2-symmetric 6:8 complex of La and **1** (Figure 2a).[7] Six La atoms were arrayed in line as a backbone ornamented with eight chiral ligands. This is the longest linear homopolymetallic lanthanide array in one molecule (maximum distance = 2.75 nm) among the enantiomerically pure lanthanide complexes reported to date.[10] This structure was maintained in solution, based on the fact that the parent peak corresponding to crystal **B** was observed by ESI-QFT-MS.[7] In addition, two major fragment peaks corresponding to metal: ligand = 2:3 and 4:5+oxo complexes were observed (Figure 2b). Crystal **B** (8 mol % La) promoted the catalytic, enantioselective Strecker reaction of **2a**, giving the product with 26% ee (Table 1, entry 5). Configuration of the major product was the same (*S*) as when using a catalyst prepared in situ (e.g., Gd*-**2**). Crystal **B** produced a similar level of enantioselectivity as when using a catalyst prepared in situ from La(O-*i*-Pr)$_3$ and **1** (La-**1**: entry 6). Therefore, crystal **B** represents one of the structures of the lanthanum catalyst in solution.

Although crystallization of the 2:3 Gd complex that gives optimal enantioselectivity in the Strecker reaction has not been successful, the ESI-MS fragment patterns of crystal **B** provides insight into the relevance of crystal **B** to the optimized Gd catalyst in solution.[11] The observed fragments (2:3 and 4:5+oxo) can be viewed as building domains of the whole polymetallic assembly. The X-ray structure of crystal **B** supports this consideration: the distance between La^2 and La^3 atoms (or La^4 and La^5 atoms) was significantly longer than that between La^1 and La^2 (or La^5 and La^6) (Figure 2b). Thus, the 6:8 complex (crystal **B**) is likely to be constructed via assembly of the 2:3 subunit (shaded red in Figure 2b) and the 4:5+oxo subunit (shaded blue). We previously reported that there is a correlation between the enantioselectivity and population of the 2:3 Gd complex in ESI-MS analysis.[6] Together, this previous observation along with the present structural information suggests that the terminal 2:3 subunits of crystal **B** correspond to the optimized active catalyst (Gd*-**2**) of the enantioselective Strecker reaction.

These results demonstrate, for the first time with three-dimensional structural elucidation, that function (enantioselectivity) of an artificial asymmetric catalyst is tunable, depending on the assembly mode of the chiral modules. This finding will accelerate the development of on-demand artificial asymmetric catalysts with switchable functions, via controlling the higher-order modular assembly.

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Supporting Information Available: Experimental procedures, X-ray diffraction data, and ESI-MS charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) For example, see: Kato, T.; Mizoshita, N.; Kishimoto, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 38.
(3) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, 1491.
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(5) Catalytic enantioselective Strecker reaction of ketoimines reported from other groups, see: (a) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867. (b) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012. (c) Chavarot, M.; Byrne, J. J.; Chavant, P. Y.; Vallée, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1147.
(6) See Supporting Information (SI) for details. For advantages in using Gd*-**2** to Gd-**2**, see: (a) Fukuda, N.; Sasaki, K.; Sastry, T. V. R. S.; Kanai, M.; Shibasaki, M. *J. Org. Chem.* **2006**, *71*, 1220. (b) Suzuki, M.; Kato, N.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 2527.
(7) For detailed X-ray and MS data, see SI.
(8) Studies to elucidate the complex structures in solution using NMR did not give any useful information even when nonparamagnetic metals such as Y or La were used (no significant signals were observed).
(9) Due to this significant difference in catalyst activity between the 2:3 complex and the 4:5+oxo complex, the Strecker products were obtained with high enantioselectivity in (*S*)-configuration even using Gd-**1**, **2**, or **3** prepared from Gd(O-*i*-Pr)$_3$, which contain both the 2:3 and 4:5+oxo complexes (Table 1).
(10) For reviews, see (a) Buünzli, J. G.; Piguet, C. *Chem. Rev.* **2002**, *102*, 1897. (b) Aspinall, H. C. *Chem. Rev.* **2002**, *102*, 1807.
(11) The lower enantioselectivity of crystal **B** than that of Gd-**1** or **2** might be due to differences in the metal character and not to the basic structure of the catalytically active subunit. Very similar ESI-QFT-MS fragment patterns were observed from crystal **B**, Gd-**1**, and Gd-**2**. See SI.

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