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Linking Structural Dynamics and Functional Diversity in Asymmetric Catalysis

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Abstract: Proteins, the functional molecules in biological systems, are sophisticated chemical devices that have evolved over billions of years. Their function is intimately related to their three-dimensional structure and elegantly regulated by conformational changes through allosteric regulators and a number of reversible or unidirectional post-translational modifications. This functional diversification in response to external stimuli allows for an orderly and timely progression of intra- and extracellular events. In contrast, enantioselective catalysts generally exhibit limited conformational flexibility and thereby exert a single specific function. Exploiting the features of conformationally flexible asymmetric ligands and the variable coordination patterns of rare earth metals, we demonstrate dynamic structural and functional changes of a catalyst in asymmetric catalysis, leading to two distinct reaction outcomes in a single flask.

Introduction

Enantioselective catalysis has established its unwavering position in producing enantioenriched molecules with maximum efficiency.[1] In general, conformationally rigid ligands are preferred for metal-based catalysts because they provide a robust asymmetric architecture for the transition state of a specific reaction of interest.[2] Rigid and multidentate ligands are favorable to afford metal complexes with high association constants, thereby providing stable catalysts to prevent catalyst deactivation/decomposition during the reaction. Some recent progress has been made in using conformationally flexible organocatalysts for enantioselective transformations.[1c] Enantioselective catalysts are generally designed to exert a single function under one set of conditions in one reaction flask. The same catalyst can sometimes give rise to different products under an alternative set of conditions;[3] however, it is rare for a single metal-based or organocatalyst to be able to promote multiple highly enantioselective transformations within the same flask in response to an external signal.[4−7]

Proteins, on the other hand, are capable of carrying out multiple functions (including highly enantioselective transformations) in response to external signals (Figure 1a). Their polypeptide-based structure displays a distinct three-dimensional architecture through noncovalent interactions, while a reasonable degree of conformational freedom remains to allow modification of its three-dimensional shape in response to specific signals such as the noncovalent binding of allosteric regulators, or covalent modification of structure-determining functionalities (e.g., acetylation/phosphorylation of H-bond donors and ionizable groups, cleavage of peptide domains). A particularly intriguing feature of functional proteins and enzymes is the

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(2) In contrast, various kinds of conformationally flexible organocatalysts have been developed, see ref 1c and references cited therein. For an example on the importance of catalyst flexibility in metal-based enantioselective catalysis, see: Malcolmson, S. J.; Meek, S. J.; Elizabeth, S. S.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2008**, *456*, 933.

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10.1021/ja900084k CCC: $40.75

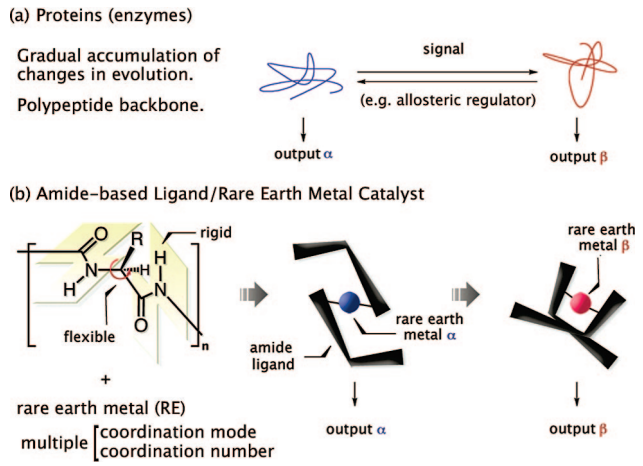
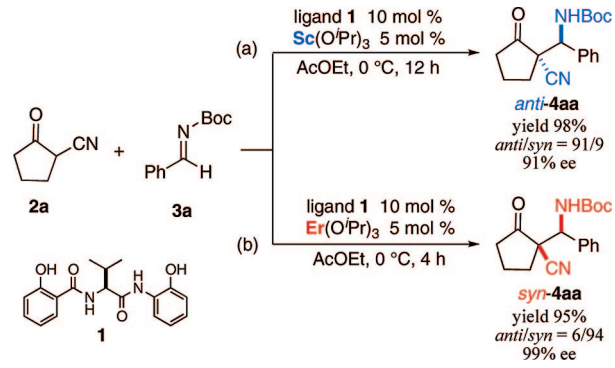


Figure 1. Structural dynamics and functional diversity in (a) a biomacromolecule and (b) an enantioselective catalyst.

seamless linking of structural dynamics and their functional diversity, namely that their structural change leads to turning on/off their function or acquiring another function, enabling the regulation of timely intra- and extracellular events to progress with elegant synergy.[8] The logic of functional molecules that exploit structural dynamics in biological systems inspired us to explore the timely functional change of an enantioselective catalyst in which the functional switching property is encoded by its structural dynamics. Molecular dynamics is currently of intense interest in the field of molecular machines,[9] but its significance does not receive much attention in enantioselective catalysis. Herein, we report our attempt to link structural dynamics and functional switching in an artificial catalyst, through which we demonstrate diastereoselectivity switching in a single flask.

We hypothesized that a catalyst comprising small amide-based ligands derived from α-amino acids and rare earth metals (REs) would constitute a catalytic system well suited for our purpose to achieve protein-like multifunctionality through flexible structural dynamics,[10] because (1) amide-based ligands possess reasonable rigidity (planar amide) and conformational flexibility (α-carbon), and (2) REs have multiple coordination modes and coordination numbers, depending on the peripheral chemical environments (Figure 1b).[11] In this combination, the possibility of multiple ligand coordination modes together with variable

Scheme 1. *anti*- and *syn*-Selective Catalytic Asymmetric Mannich-Type Reaction of α-Cyanocyclopentanone **2a** and *N*-Boc Imine **3a** with the **1**/RE Catalyst



coordination patterns to REs would allow the formation of alternative structures capable of exerting different catalytic functions. By exploiting these chemical properties, we envisioned the development of a catalytic system that allowed for timely functional modifications.

Results and Discussion

Asymmetric Mannich-Type Reaction with 1/RE Catalyst. Previously, we reported that a **1**/Sc catalyst, prepared by mixing amide-based ligand **1**[12] and $Sc(O^iPr)_3$ in a ratio of 2:1, allowed for a catalytic asymmetric *anti*-selective Mannich-type reaction of 2-cyanocyclopentanone (**2a**) and *N*-Boc imine **3a** to afford *anti*-**4aa** with high enantiomeric excess (Scheme 1a).[13,14] The protocol enabled the construction of a chiral quaternary carbon via intermolecular asymmetric catalysis, which remains a formidable task in modern organic synthesis,[15] and was

(5) A review on asymmetric activation and deactivation, see: Mikami, K.; Aikawa, K. *New Frontiers in Asymmetric Catalysis*; Mikami, K., Lautens, M., Eds.; Wiley: New York, 2007; pp 221−257.
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(12) Ligand **1** was prepared from L-valine in a four-step chromatography free procedure. For the utility of **1**, see: (a) Mashiko, T.; Hara, K.; Tanaka, D.; Fujiwara, Y.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 11342. (b) Nitabaru, T.; Kumagai, N.; Shibasaki, M. *Tetrahedron Lett.* **2008**, *49*, 272. (c) Mashiko, T.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 2725.
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(14) For reviews on α-cyanocarboanions, see: (a) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React.* **1984**, *31*, 1. (b) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1. (c) Fleming, F. F.; Iyer, P. S. *Synthesis* **2006**, 893.
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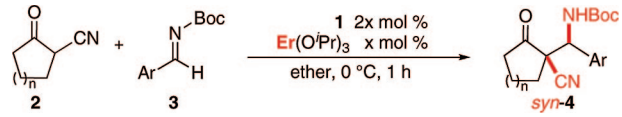
Table 1. *syn*-Selective Catalytic Asymmetric Mannich-Type Reaction with the **1**/Er Catalyst



		cyanoketone **2**		imine **3**					
entry	*x*	*n*		Ar		product	yield[a] (%)	*anti*/*syn*	ee (*syn*) (%)
1	2	1	**2a**	Ph	**3a**	**4aa**	92	6/94	95
2[b]	1	1	**2a**	Ph	**3a**	**4aa**	99	15/85	98
3[c]	5	2	**2b**	Ph	**3a**	**4ba**	97	13/87	97
4[c]	5	3	**2c**	Ph	**3a**	**4ca**	79	30/70	94
5	2	1	**2a**	2-MeC_6H_4	**3b**	**4ab**	99	5/95	99
6	2	1	**2a**	4-MeC_6H_4	**3c**	**4ac**	86	5/95	97
7[d]	2	1	**2a**	2-naphthyl	**3d**	**4ad**	96	7/93	92
8	2	1	**2a**	2-ClC_6H_4	**3e**	**4ae**	99	4/96	99
9	2	1	**2a**	4-ClC_6H_4	**3f**	**4af**	95	5/95	91
10	2	1	**2a**	2-FC_6H_4	**3g**	**4ag**	91	7/93	99
11	2	1	**2a**	2-MeOC_6H_4	**3h**	**4ah**	99	4/96	99
12	2	1	**2a**	4-MeOC_6H_4	**3i**	**4ai**	82	4/96	92
13	2	1	**2a**	2-furyl	**3j**	**4aj**	99	7/93	84
14	2	1	**2a**	3-thienyl	**3k**	**4ak**	99	4/96	96

[a] Isolated yield. [b] Reaction time was 3 h. [c] Reaction time was 20 h. [d] Dichloromethane was used as solvent.

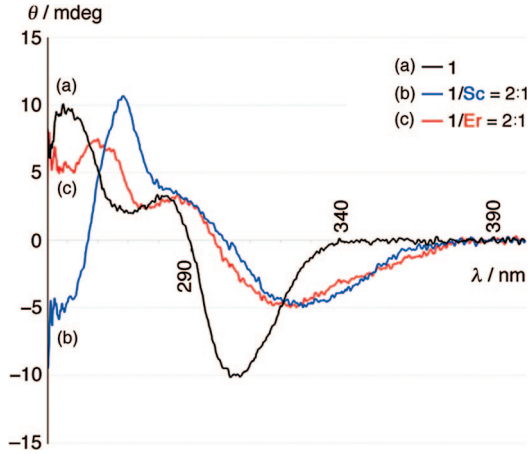


Figure 2. CD spectra of (a) ligand **1**, (b) the **1**/Sc = 2:1 catalyst, and (c) the **1**/Er = 2:1 catalyst in ethyl acetate.

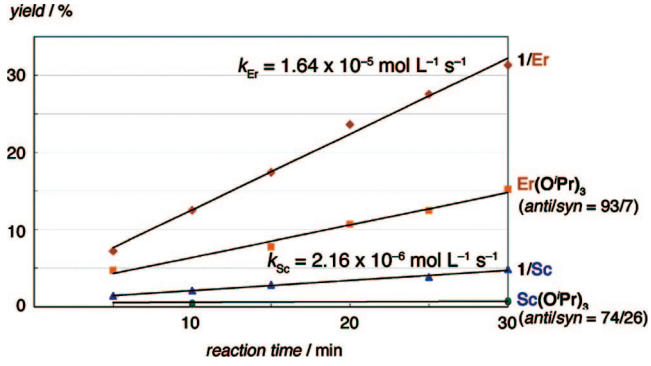


Figure 3. Initial rate kinetics of the reaction of **2a** and **3a** with four different catalysts, **1**/Er, **1**/Sc, Er(O^{i}Pr)$_3$, and Sc(O^{i}Pr)$_3$. The catalyst loading was 5 mol % each (based on RE). The reactions were conducted at −30 °C for accurate measurement. k_{Er} and k_{Sc} were the observed rate constants for the **1**/Er catalyst and **1**/Sc catalyst, respectively.

complementary to other *syn*-selective Mannich-type reactions.[16,17] Particularly noteworthy is that the **1**/Sc catalyst did not form a distinct structure on the basis of ^{1}H NMR analysis, likely because several complexation patterns would be possible due to the structural flexibility and the monodentate coordination

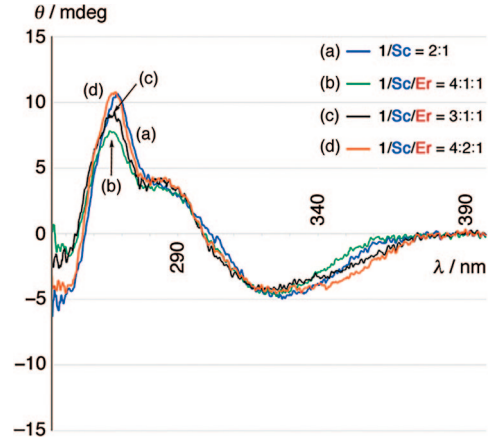
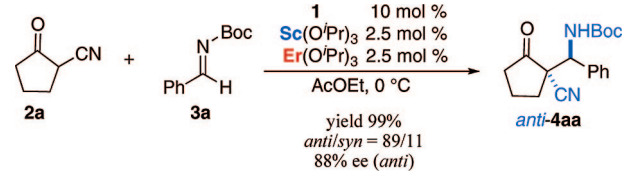


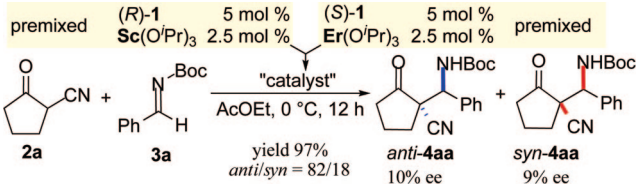
Figure 4. CD spectra of the **1**/Sc/Er solution in ethyl acetate with a variable **1**/Sc/Er ratio. (a) **1**/Sc = 2:1; (b) **1**/Sc/Er = 4:1:1; (c) **1**/Sc/Er = 3:1:1; (d) **1**/Sc/Er = 4:2:1.

Scheme 2. Catalytic Asymmetric Mannich-Type Reaction of **2a** and **3a** Using **1**/Sc/Er = 4:1:1 Solution as a Catalyst



mode of the two phenol moieties of **1**. The high stereoselectivity would be rationalized by assuming a well-organized association at the transition state from a nonordered reaction mixture ensemble. The nondefined structure of the **1**/Sc catalyst might indicate that the catalytic system of the **1**/RE retains the potential to provide a catalyst with a different structural motif in different reaction ensembles. This assumption prompted us to explore the possibility of structural/functional modifications of the catalyst using this reaction system. In our search for other **1**/RE catalysts, we found that a **1**/Er catalyst, prepared from **1** and Er(O^{i}Pr)$_3$ in a ratio of 2:1, displayed remarkable diastereoselectivity reversal compared to the **1**/Sc catalyst to give *syn*-**4aa** with 99% ee under otherwise identical reaction conditions

Scheme 3. Catalytic Asymmetric Mannich-Type Reaction of **2a** and **3a** Using a Catalyst Prepared by Mixing a Premixed (*R*)-**1**/Sc Solution and a (*S*)-**1**/Er Solution



(Scheme 1b).[3,18,19] Determination of the absolute configuration of *syn*-**4aa** by X-ray crystallography revealed that enantioselection of the enolate derived from **2a** was inverted. The reversal of diastereoselectivity was uniformly observed with a broad range of substrates (Table 1). Particularly noteworthy is that enhanced catalytic activity was observed with the **1**/Er catalyst, allowing the reaction to reach completion after 1 h of stirring at 0 °C with 2 mol % of catalyst loading. A comparable level of stereoselectivity was attained with as little as 1 mol % of catalyst loading with an extended reaction time (entry 2). Detrimental effects on the reaction time were detected in the reaction with 6- and 7-membered α-cyanoketones **2b** and **2c**, and lower diastereoselectivity was observed (entries 3,4). Generally, a high *syn*-selectivity (*anti*/*syn* = 7/93−4/96) and enantioselectivity (91−99% ee) were observed in the reaction with a wide range of aromatic *N*-Boc imines **3**, including those with heteroaromatic functionality (entries 5−12, 14). Lower enantioselectivity was observed with imine with a 2-furyl substituent (entry 13).

CD and Kinetic Analyses of the 1/Sc and 1/Er Catalyst. Of prime importance in the present catalytic system is the origin of diastereoswitching. The paramagnetic nature of Er hampered a detailed NMR analysis of the **1**/Er catalyst. Circular dichroism (CD) spectra of **1**/Sc and **1**/Er catalyst provided insight into the differences in the assembly states of each catalytic system. The CD spectrum of **1** at the UV−vis region in ethyl acetate is shown in Figure 2. Clear differences in the spectral pattern were observed between the CD spectra of **1**, and the **1**/Sc = 2:1 and **1**/Er = 2:1 solution, suggesting that a chiroptically different **1**/RE assembly developed in each solution (Figure 2). Due to the exquisite combination of factors; (1) structural flexibility of the chiral ligand **1**; (2) high coordination number of RE; and (3) availability of various coordination patterns of RE, **1** provided chiroptically different asymmetric catalysts in response to the properties of the RE, consequently affording *anti* and *syn* products with high enantioselectivity under otherwise identical reaction conditions. An initial rate kinetics study revealed clear ligand acceleration in both Sc and Er cases (Figure 3).[20] Also worth noting is that **1**/Er exhibited higher catalytic activity than the Sc counterparts. This can be attributed to the different three-dimensional architectures of these catalysts.[21] A significant deviation from linearity between the enantiopurity of **1** and that of the product in both the Sc and Er cases suggested the involvement of multiple molecules of **1** around the metal center at the transition state.[22]

The Catalyst in the Presence of Both Sc and Er. With a suitable catalytic system of **1**/RE in hand, in which **1** displayed different assembly patterns in response to different REs, we envisioned in situ structural/functional modifications in the course of the catalytic asymmetric Mannich-type reaction. An attempted reaction of **2a** and **3a** with the **1**/Sc/Er = 4:1:1 catalyst afforded the *anti*-product **4aa** preferentially (*anti*/*syn* = 89/11) in 88% ee (Scheme 2), comparable to that obtained with the **1**/Sc catalyst (Scheme 1a). If both **1**/Sc (**1**/Sc = 2:1) and **1**/Er (**1**/Er = 2:1) catalysts were formed in a comparable quantity and promoted the reaction independently, the consequence should have been a *syn*-selective reaction because the initial rate kinetics experiment revealed that the reaction rate with the **1**/Er (rate constant $k_{Er} = 1.64 \times 10^{-5}$ mol L^{-1} s^{-1}) catalyst was 7.6-fold faster than that of the **1**/Sc catalyst ($k_{Sc} = 2.16 \times 10^{-6}$ mol L^{-1} s^{-1}) (Figure 3). At this point, there were two possibilities: (1) a **1**/Sc/Er heteropolymetallic complex was formed and promoted the *anti*-selective reaction with enantioselectivity similar to that obtained with **1**/Sc; or (2) a **1**/Sc catalyst was preferentially formed over the **1**/Er catalyst, affording a similar reaction output to that of the **1**/Sc catalyst. The CD spectra of the **1**/Sc/Er = 4:1:1, 3:1:1, and 4:2:1 solutions would represent the formation of the aggregate, which had chiroptical properties similar to those of the original *anti*-selective catalyst **1**/Sc = 2:1 (Figure 4). In particular, the CD spectral pattern of **1**/Sc/Er = 4:2:1 showed a nearly perfect match with that of **1**/Sc = 2:1, suggesting that most Er^{3+} would be excluded from the coordination site of **1** due to a competitive coordination of Sc^{3+} to **1**. The formation of the **1**/Sc/Er heteropolymetallic aggregate showing a similar CD pattern would be less likely. The lability of **1** in the present catalytic system was examined in the following attempted reaction. When separate solutions of preformed (*R*)-**1**/Sc = 2:1 and (*S*)-**1**/Er = 2:1 solution were mixed together and the resulting solution was

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(17) For selected examples of catalytic asymmetric Mannich reactions with 1,3-dicarbonyl compounds generating quaternary carbon stereocenters, see: (a) Marigo, M.; Kjærsgaard, A.; Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem. Eur. J.* **2003**, *9*, 2359. (b) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1525. (c) Ting, A.; Lou, S.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 2003. (d) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191. (e) Yamaoka, Y.; Miyabe, H.; Yoshizumi, Y.; Takemoto, Y. *Synthesis* **2007**, 2571. (f) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170. For selected examples of catalytic asymmetric Mannich reactions with 1,3-dicarbonyl compounds generating tertiary stereocenters, see: (g) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (h) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256. (i) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048. (j) Sasamoto, N.; Dubs, C.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2006**, *128*, 14010.

(18) A general review on enantioselectivity reversal using a single chiral source, see: Tanaka, T.; Hayashi, M. *Synthesis* **2008**, 3361, and references therein.

(19) A notable example of an asymmetric catalyst exhibiting sharp enantioswitching, depending on the assembly state of the catalyst, see: Kato, N.; Mita, T.; Kanai, M.; Therrien, B.; Kawano, M.; Yamaguchi, K.; Danjo, H.; Sei, Y.; Sato, A.; Furusho, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6768.

(20) The rate acceleration suggested the involvement of hydrogen-bonding to promote the reaction and enhance the stereodiscrimination at the transition state. The hydrogen-bonding in peptide-based catalysts is well-documented, see: (a) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496. (b) Sculimbrene, B. R.; Morgan, A. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 11653. (c) Jakobsche, C. E.; Peris, G.; Miller, S. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6707, and references therein.

(21) We cannot exclude the possibility that a higher ligand exchange rate of Er would contribute to enhanced catalyst turnover.

(22) See Supporting Information for details.

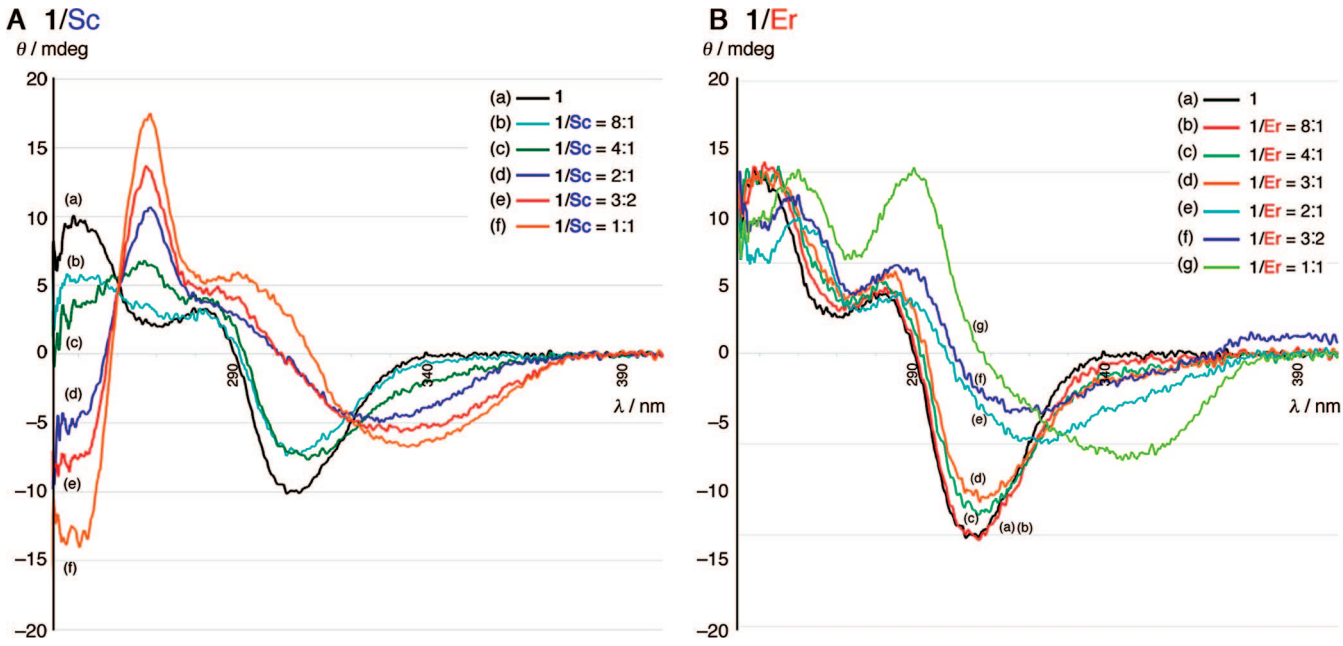
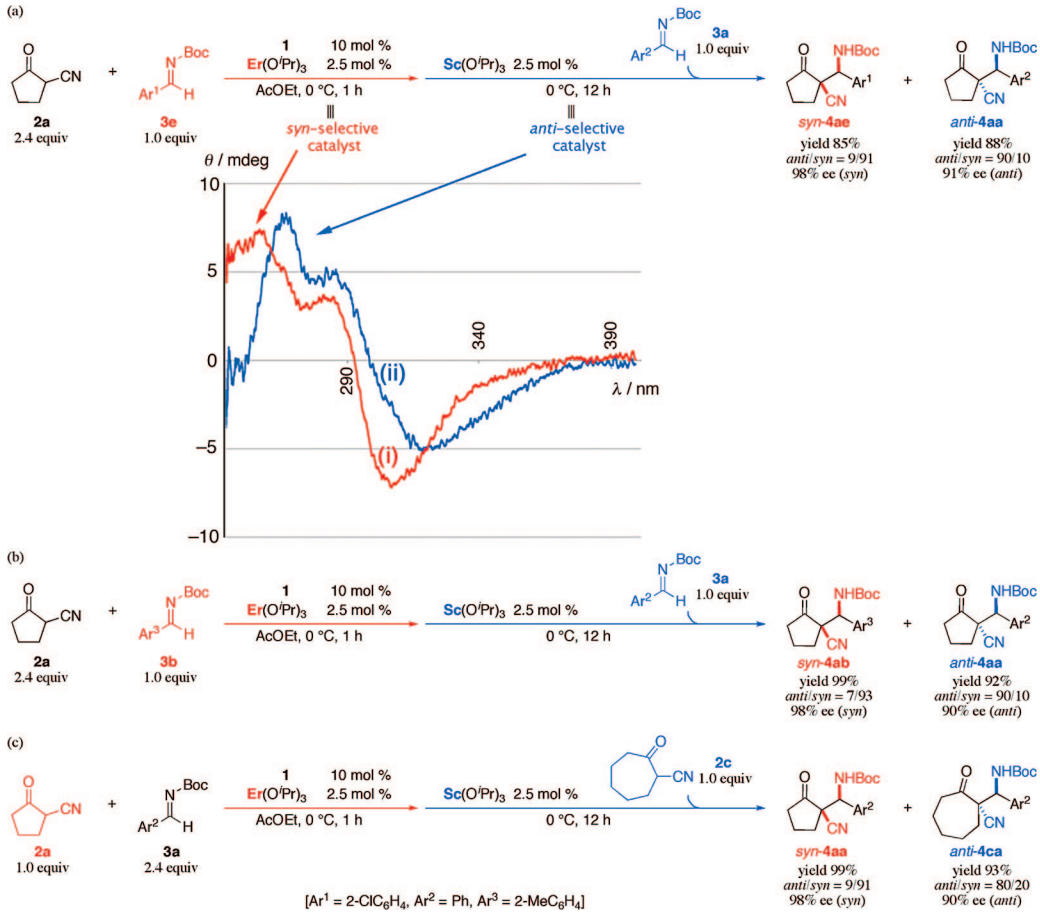


Figure 5. CD spectra of the **1**/Sc and **1**/Er catalyst solution with variable **1**/RE ratio.

Scheme 4. Dynamic Structural and Functional Change of the **1**/RE Catalyst



used as catalyst (**1**/Sc/Er = 4:1:1), nearly racemic *anti*-**4aa** was obtained, indicating that the association between **1**-Sc and **1**-Er was not kinetically stable and **1** was involved in a dynamic exchange with Sc^{3+} and Er^{3+} (Scheme 3). The CD spectra of the **1**/Sc solution with variable ratios showed monotonic transitions as the amount of Sc^{3+} increased (Figure 5A). On the other hand, that of **1**/Er showed an apparent biphasic transition and negligible change at a low Er concentration (Figure 5B), suggesting that the association of **1**/Er was weaker than that of **1**/Sc. These results suggest that **1**/Sc aggregation is

preferentially formed in **1**/Sc/Er = 4:1:1 to exhibit a reaction outcome similar to that of the **1**/Sc = 2:1 catalyst, enabling a unidirectional catalyst modification.

Timely Structural Change and Functional Modification of the 1/RE catalyst. We next explored the possibility that a dynamic functional change of the enantioselective catalyst occurred in the course of the reaction. We designed the reaction system as follows; (1) a Mannich-type reaction of **2a** (2.4 equiv) and **3e** (1.0 equiv) was conducted with the **1**/Er = 4:1 catalyst (**1**: 10 mol %, $Er(O^iPr)_3$ 2.5 mol %) to form *syn*-**4ae**; (2) then $Sc(O^iPr)_3$ (2.5 mol %) was added to modify the catalyst structure, and another imine **3a** (1.0 equiv) was introduced to afford *anti*-**4aa**. The catalyst switched gears and engaged in an *anti*-selective reaction to afford *anti*-**4aa** with high diastereo- and enantioselectivity (Scheme 4a). In this process, the structure of the catalyst was changed in response to the property of the RE, affording both *syn* and *anti* products in a single flask.[23] Structural changes of the catalyst upon the addition of $Sc(O^iPr)_3$ were traced by CD analysis of the reaction mixture as illustrated ((i) before the addition of $Sc(O^iPr)_3$, (ii) after the addition of $Sc(O^iPr)_3$). Other combinations of substrates, **2a** and **3b** for a *syn*-selective reaction and **2a** and **3a** for an *anti*-selective reaction, were also examined, and similar levels of functional switches of the catalyst were observed (Scheme 4b). The process was also operative in the reaction of two different α-cyanoketones, i.e., the first *syn*-selective reaction of **2a** (1.0 equiv) and **3a** (2.4 equiv) with the **1**/Er = 4:1 catalyst, and the following addition of **2c** (1.0 equiv) after the structural change with $Sc(O^iPr)_3$ afforded *syn*-**4aa** and *anti*-**4ca** (Scheme 4c). These results are indicative of a timely functional change of the artificial asymmetric catalyst through dynamic structural modifications.

(23) The reaction with the opposite order of metal source addition did not show functional changes as expected from the results of the previous section. Details are shown in Supporting Information.

Conclusion

We revealed that the ligand **1** provides enantioselective catalysts with different chiroptical properties upon complexation with $Sc(O^iPr)_3$ or $Er(O^iPr)_3$, allowing for either an *anti*- or *syn*-selective catalytic asymmetric Mannich-type reaction of α-cyanoketones **2** and *N*-Boc imines **3**. The structural dynamics and functional diversity of the present catalytic system culminated in timely functional switching over the course of the reaction. Although three-dimensional conformational change in response to external stimuli is intimately linked to functional diversity in biomacromolecular systems and ubiquitously utilized as a means of regulation, such a process has been underutilized in the field of asymmetric catalysis. The present catalytic system is an important contribution to chemistry in which multifunctionality is encoded in the intrinsic structural dynamics of the catalyst, ultimately leading to the construction of an artificial system in which dozens of multifunctional catalysts endowed with timely regulable processes work in a synergistic manner like a cellular system prototype. The development of enantioselective catalysts that enable reversible functional switching will be the focus of future investigations.

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Supporting Information Available: Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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