

# Asymmetric Catalysis with Bis(hydroxyphenyl)diamides/ Rare-Earth Metal Complexes

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amides · asymmetric catalysis · atom economy ·  
heterobimetallic · rare earths

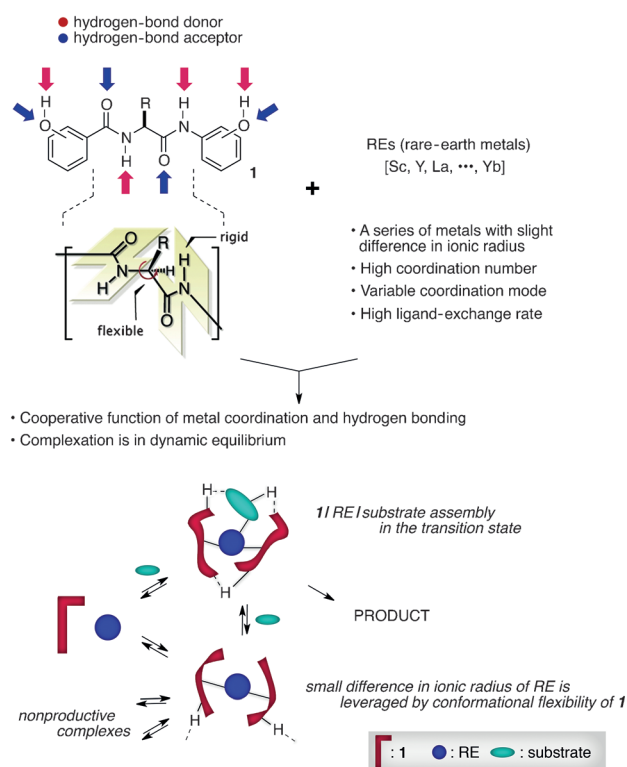
**A** series of asymmetric catalysts composed of conformationally flexible amide-based chiral ligands and rare-earth metals was developed for proton-transfer catalysis. These ligands derived from amino acids provide an intriguing chiral platform for the formation of asymmetric catalysts upon complexation with rare-earth metals. The scope of this arsenal of catalysts was further broadened by the development of heterobimetallic catalytic systems. The cooperative function of hydrogen bonding and metal coordination resulted in intriguing substrate specificity and stereocontrol, and the dynamic nature of the catalysts led to a switch of their function. Herein, we summarize our recent exploration of this class of catalysts.

## 1. Introduction

Enantioselective catalysis has established its unwavering position in producing enantioenriched molecules with maximum efficiency.<sup>[1]</sup> At the beginning of the development, asymmetric metal complexes, composed of chiral ligands and metal cations, emerged as asymmetric catalysts. Metal-based asymmetric catalysis constitutes a huge research field, and the scope is still rapidly expanding, along with the radical extension of organocatalysis.<sup>[2]</sup> In general, conformationally rigid ligands are preferentially designed and employed in the formation of metal-based catalysts, probably because they provide a robust asymmetric architecture for the transition state of the reaction of interest.<sup>[3,4]</sup> Designing a catalyst with limited conformational freedom is more viable in both an intuitive and a computational way, facilitating a ligand-discovery/optimization process. Moreover, rigid and multi-dentate ligands are favorable to afford metal complexes with a high association constant, thereby providing stable catalysts to prevent catalyst deactivation/decomposition during the reaction.

During the past years, we have explored a different type of catalyst design, namely, the combination of conformationally flexible amide-based ligands **1** with rare-earth metals (REs; Figure 1).<sup>[5–7]</sup> Ligands **1** are readily

prepared from amino acids through straightforward and cost-effective procedures.<sup>[8]</sup> Two phenol groups of **1** coordi-



**Figure 1.** Design principle of amide-based ligand **1**/RE catalyst.

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nate to metal cations in a monodentate fashion, and complexation with metal cations is weak and in dynamic equilibrium. In contrast to a dogma of metal-based catalysis, in which a specific metal complex is formed before the reaction is run, and this preformed rigid complex is the catalytically active species, **1**/metal catalysts elicit their function through assembly in the transition state; **1** and metal cations do not form any distinct metal complexes, but instead associate with substrates by metal coordination and multiple hydrogen-bond interactions.<sup>[8]</sup> We focused on the use of REs as a partner of **1**, because we assumed that a slight difference in the ionic radius of REs can be leveraged by the conformational flexibility of **1**, thus allowing the production of a series of catalysts that exhibit similar catalytic function, but are produced with largely different asymmetric environments.<sup>[9]</sup> The cooperative function of specific metal coordination and hydrogen-bond interaction resulted in high substrate specificity,<sup>[10]</sup> giving high stereoselectivity with highly coordinative substrates, the catalytic enantioselective transformation of which is difficult otherwise (Figure 2). The dynamic equilibrium of **1** and REs resulted in the functional switching of the catalyst.<sup>[11]</sup> The scope of the catalytic system was expanded by employing other metal cations to create heterobimetallic catalytic systems.<sup>[12–14]</sup> Some of the catalysts were employed in the enantioselective synthesis of therapeutics, highlighting their

practical utility. Because of the hydrogen-bond array of **1**, solvent-dependent heterochiral aggregation of **1** was uncovered, and the aggregation of **1** bearing a chromophore could be regulated by photoirradiation.<sup>[15,16]</sup> Herein, we describe our exploration of **1**/RE catalysts.

## 2. Asymmetric Catalysis with Highly Coordinative Substrates

### 2.1. Catalytic Asymmetric Amination

Our investigation began with a specific project targeting the efficient enantioselective synthesis of AS-3201 (Ranirestat, **2**), a pharmaceutical candidate of a novel aldose reductase inhibitor for diabetic neuropathy, developed by Daiinippon Sumitomo Pharma (Scheme 1).<sup>[17]</sup> The challenge of constructing the tetrasubstituted stereogenic center embedded in the spirosuccinimide ring system, and the prospect of clinical trials led us to devise a practical enantioselective synthetic route for **2**. The enantioselective installation of the nitrogen atom appeared to be the most straightforward way to access key intermediate **3**.<sup>[18–22]</sup> Therefore, we commenced our study with a catalytic asymmetric amination of succinimide derivative **4**. Unexpectedly, this reaction turned out not to be

a simple task. Nitrogen-containing substructures commonly occur in a wide variety of biologically active chiral compounds and therapeutics, and several catalytic systems have been established for this specific transformation using azodicarboxylate **5** as an electrophilic aminating agent. However, **4** was not a suitable substrate in asymmetric amination using literature-known metal-based catalysts and organocatalysts; in all synthetic attempts, we obtained product **3** in less than 20 % *ee*.<sup>[8,23]</sup> We attributed this unproductive result to the highly coordinative nature of succinimide derivative **4**, which bears multiple coordination sites for both metal coordination and hydrogen bonding, displays multiple coordination patterns, and compromises the stereochemical course of the reaction. Investigations of the substrate scope in asymmetric catalysis gener-

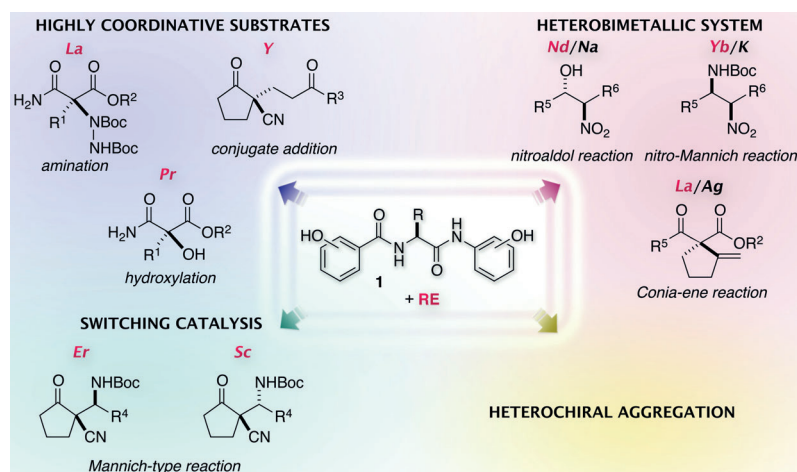
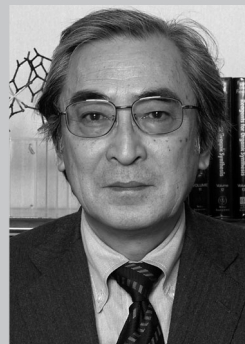


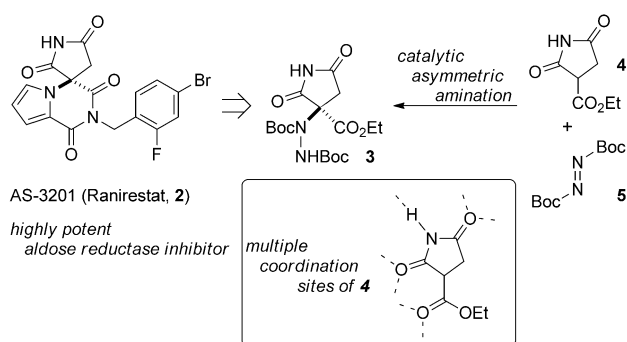
Figure 2. Applications of amide-based ligand **1**/RE catalysts.



Naoya Kumagai was born in 1978 and raised in Ibaraki, Japan. After he received his Ph.D. in Pharmaceutical Sciences at the University of Tokyo in 2005 under the supervision of Prof. Masakatsu Shibasaki, he pursued a postdoctoral study in the laboratory of Prof. Stuart L. Schreiber at Harvard University in 2005–2006. He moved back to Prof. Shibasaki's group at the University of Tokyo as an assistant professor in 2006. He is currently a senior researcher at the Institute of Microbial Chemistry, Tokyo. His research interest is the development of new methodologies in asymmetric catalysis and their application to bioinspired dynamic processes.

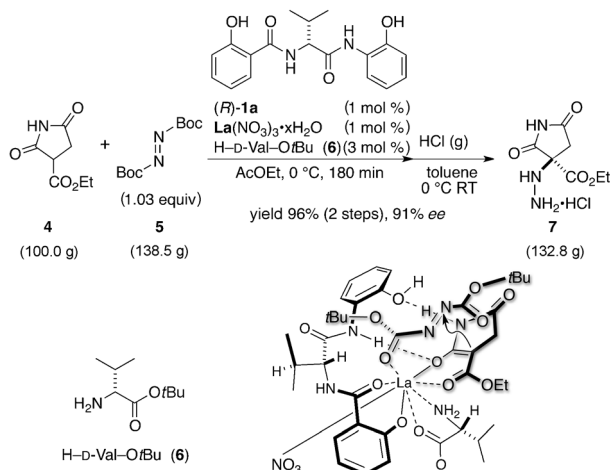


Masakatsu Shibasaki received his Ph.D. from the University of Tokyo in 1974 with Professor Shun-ichi Yamada before his post-doctoral studies with Professor E. J. Corey (Harvard University). In 1977, he joined Teikyo University as an associate professor. In 1983, he moved to Sagami Chemical Research Center as a group leader, and in 1986 took up a professorship at Hokkaido University, before returning to the University of Tokyo as a professor in 1991. Currently, he is a director of the Institute of Microbial Chemistry (Tokyo). His research interests include asymmetric catalysis and medicinal chemistry of biologically significant compounds.



**Scheme 1.** Retrosynthetic analysis of AS-3201 (Ranirestat, **2**) based on the catalytic asymmetric amination of succinimide derivative **4** and azodicarboxylate **5**.

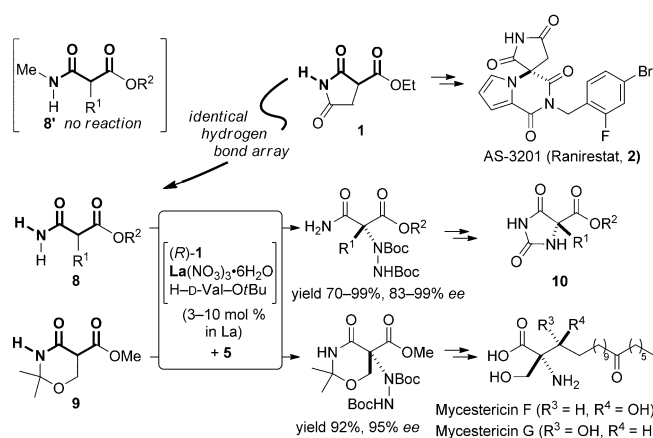
ally involve relatively simple substrates (little functionality, little steric demand, etc.) and **4** could be an outlier in the general criteria of suitable substrates in asymmetric catalysis. We therefore turned our attention to devising a new catalytic system that can produce a high level of enantioselectivity using this class of highly coordinative substrate. We assumed that a metal-based catalyst that exhibits cooperative function of metal coordination and hydrogen bonding would be beneficial to achieve high enantioselectivity. It was considered important that the metal complex should not be a rigid entity, but rather should be flexible and coordinatively dynamic, which would result in the metal, chiral ligand, and substrate forming a transition-state complex through metal coordination and hydrogen bonding.<sup>[24]</sup> We designed diamide ligand (*R*)-**1a**, which bears two phenol groups and multiple donor and acceptor sites for hydrogen bonds.<sup>[23]</sup> As for metal cations, we chose REs, because a high ligand-exchange rate,<sup>[25]</sup> a high coordination number, and multiple coordination modes appear to be suitable properties for our specific purpose (see Figure 1).<sup>[9]</sup> A series of REs with slightly different ionic radii are available, and their small differences can be leveraged by the conformational flexibility of **1a** to generate various transition-state architectures with largely different chiroptical properties. On the basis of catalytic efficiency, enantioselectivity, and cost, we eventually developed ternary mixtures of the amide-based ligand (*R*)-**1a**,  $\text{La}(\text{NO}_3)_3 \cdot x\text{H}_2\text{O}$  ( $x = 3-5$ ) and *H*-D-Val-*O*tBu (**6**) as the best catalysts for the asymmetric amination of **4** (Scheme 2).<sup>[8,26,27]</sup> (*R*)-**1a** is readily prepared from D-Val through a chromatography-free process; the reaction was conducted with as little as 1 mol % catalyst loading and afforded the corresponding hydrazine-HCl salt **7** in 91 % *ee* after acidic removal of the Boc groups. *H*-D-Val-*O*tBu (**6**), a primary amine base, not only functions as a Brønsted base, but also participates in the complexation, as evidenced by the fact that the structure of the additional amine has a significant impact on enantioselectivity.<sup>[8,26]</sup> Mechanistic studies suggest that the three components of the catalyst are in dynamic equilibrium and the dissociated state is dominant, and that they assemble with substrate **4** and azodicarboxylate **5** through metal coordination and hydrogen bonding to promote the reaction in a highly enantioselective manner. The large negative activation en-



**Scheme 2.** Catalytic asymmetric amination of **4** followed by the removal of Boc groups. An assembled transition state is proposed.

ergy derived from an Eyring plot is consistent with this mechanism.<sup>[28]</sup>

As expected, the present catalytic system is effective for substrates that have a specific hydrogen-bond array. The 1,3-dicarbonyl group and *trans*-amide hydrogen atom were found to be crucial for catalysis. Primary amide **8** and lactam **9** shared an identical hydrogen-bond array and their catalytic amination proceeded smoothly with high enantioselectivity (Scheme 3). *N*-Nonprotected  $\alpha$ -alkoxycarbonyl amides **8**,



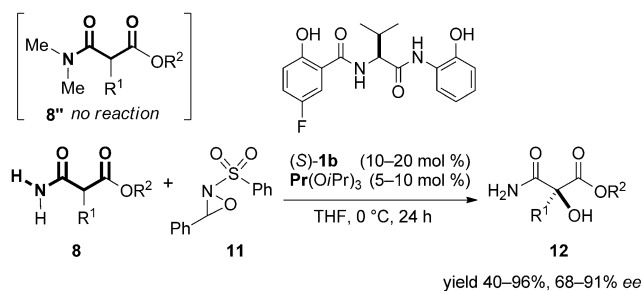
**Scheme 3.** Catalytic asymmetric amination of **8** and **9** having identical hydrogen-bond arrays.

which have never been utilized in asymmetric catalysis,<sup>[29,30]</sup> were expected to display multiple coordination modes. Analogous substrates that lack the *trans*-amide hydrogen atom (**8'**) failed in the reaction under otherwise identical conditions, indicating that hydrogen-bond interaction involving this hydrogen atom plays a crucial role in the formation of transition-state assembly. The synthetic utility of the present catalytic system is highlighted by the transformation of these amination products to AS-3201 (Ranirestat, **2**),<sup>[8,23,26]</sup> enantiomerically enriched hydantoin derivatives **10**,<sup>[8]</sup>

tericins.<sup>[31]</sup> The high potency and prospective demand for AS-3201 (**2**) are of particular importance, and several alternative enantioselective synthetic routes have been reported.<sup>[32]</sup> Our synthetic route is now under investigation for the industrial production of **2** in the United States and Japan.

## 2.2. Catalytic Asymmetric Hydroxylation

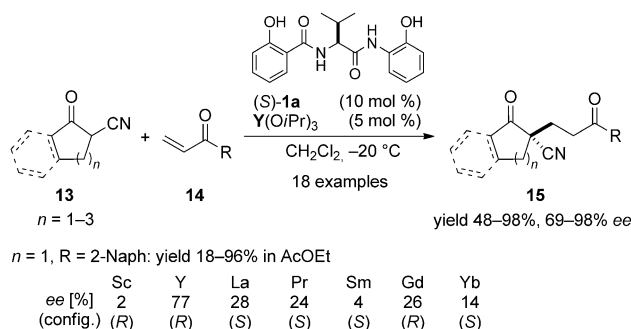
The **1**/RE catalytic system proved effective in promoting the enantioselective addition reactions of the enolate generated from nonprotected  $\alpha$ -alkoxycarbonyl amides **8** bearing a *trans*-amide hydrogen atom. Our next focus was the enantioselective installation of an oxygen functionality to this particular class of substrates. Davis oxaziridine **11** was chosen as electrophile and REs were screened for the one that gave the most favorable transition-state assembly.<sup>[33–35]</sup> Pr emerged as the best RE in terms of enantioselectivity, and the fluoro-substituted ligand (*S*)-**1b** outperformed (*S*)-**1a**, presumably because of a slight modification of the transition-state architecture as a result of steric repulsion and/or electronic perturbation on hydrogen-bond interaction (Scheme 4).<sup>[36]</sup> As expected, a related substrate that lacks the *trans*-amide hydrogen atom (**8'**) was not recognized in this catalytic system.



**Scheme 4.** Catalytic asymmetric hydroxylation of **8** with Davis oxaziridine **11** promoted by (*S*)-**1b**/Pr catalyst.

## 2.3. Catalytic Asymmetric Conjugate Addition

$\alpha$ -Cyanoketones **13** are another class of substrates to which the **1**/RE catalytic system is applicable. Aiming for the enantioselective formation of all-carbon quaternary centers,<sup>[37]</sup> we attempted the catalytic asymmetric conjugate addition of **13** and vinyl ketones **14**.<sup>[38,39]</sup> In a specific substrate combination of 2-cyanocyclopentanone **13a** and 2-naphthyl vinyl ketone **14a**, REs were screened to provide divergent enantioselectivity in terms of both the degree of enantioselectivity and absolute configuration (Scheme 5).<sup>[40]</sup> No clear correlation between the ionic radius of the RE and the observed enantioselectivity was detected, and a chiroptically different transition-state assembly was formed. This observation was further supported by the differential pattern of circular dichroism (CD) spectra of (*S*)-**1a**/RE solution. The reaction using (*S*)-**1a**/Y catalyst in  $\text{CH}_2\text{Cl}_2$  was optimal and afforded the desired product **15** with a quaternary stereocenter in up to 98% *ee*.

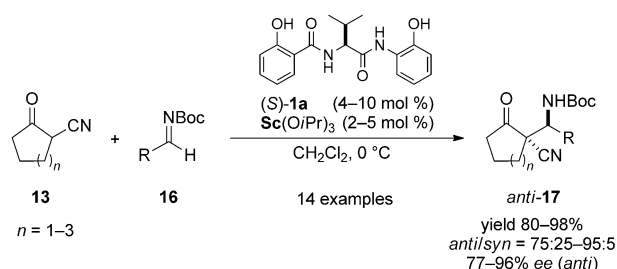


**Scheme 5.** Catalytic asymmetric conjugate addition of  $\alpha$ -cyanoketone **13** promoted by (*S*)-**1a**/Y catalyst.

## 3. Switching of the Catalyst Function

### 3.1. Catalytic Asymmetric Mannich-type Reaction

The catalytic asymmetric Mannich-type reaction of  $\alpha$ -substituted  $\beta$ -ketoesters has attracted growing attention as a valuable transformation to produce consecutive tetra- and trisubstituted stereogenic centers.<sup>[41,42]</sup> The reaction using  $\alpha$ -cyanoketones **13** affords the analogous products bearing (protected) amine, carbonyl, and nitrile functionalities, which would be beneficial to diverse functional-group transformations. The (*S*)-**1a**/Sc catalyst emerged as an effective catalyst in the Mannich-type reaction of **13** and N-Boc-protected imines **16**, affording *anti* product **17** with high enantioselectivity (Scheme 6).<sup>[43]</sup>  $^1\text{H}$  NMR analysis provided no evidence

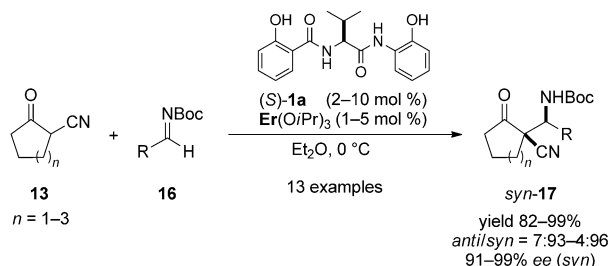


**Scheme 6.** Catalytic asymmetric *anti*-selective Mannich-type reaction of  $\alpha$ -cyanoketone **13** and N-Boc-protected imines **16** promoted by (*S*)-**1a**/Sc catalyst.

of the formation of any distinct complex.  $\text{Sc}(\text{O}i\text{Pr})_3$ , (*S*)-**1a**, and substrate mixtures are in dynamic equilibrium and can assemble to form the transition-state complex through metal coordination and hydrogen bonding.<sup>[44]</sup> Indeed, there is no need for the precomplexation of  $\text{Sc}(\text{O}i\text{Pr})_3$  and (*S*)-**1a**. An identical reaction outcome was observed with a one-shot procedure, in which all the catalyst components and substrates were added at the same time.

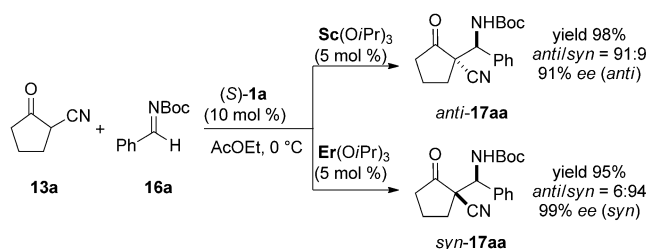
A particularly intriguing feature of the present catalytic system is that a slight change in the ionic radius of RE produces a distinct transition-state architecture with largely different chiroptical properties. In the Mannich-type reaction, the (*S*)-**1a**/Er catalyst exhibited high catalytic activity and the *syn* products **17** were preferentially obtained with high

enantioselectivity (Scheme 7).<sup>[11]</sup> Although optimization of the reaction conditions identified CH<sub>2</sub>Cl<sub>2</sub> and diethyl ether as the best solvents for the *anti*-selective reaction with (*S*)-**1a**/Sc and the *syn*-selective reaction with (*S*)-**1a**/Er, respectively



**Scheme 7.** Catalytic asymmetric *syn*-selective Mannich-type reaction of  $\alpha$ -cyanoketone **13** and N-Boc-protected imines **16** promoted by (*S*)-**1a**/Er catalyst.

(Scheme 6 and 7), ethyl acetate was a suitable solvent for these reactions and diastereoselectivity was changed only by changing the RE (Scheme 8). CD spectra of (*S*)-**1a**/Sc and (*S*)-**1a**/Er in AcOEt solution displayed distinct patterns, suggesting that chiroptically different assemblies were produced.<sup>[45–47]</sup>

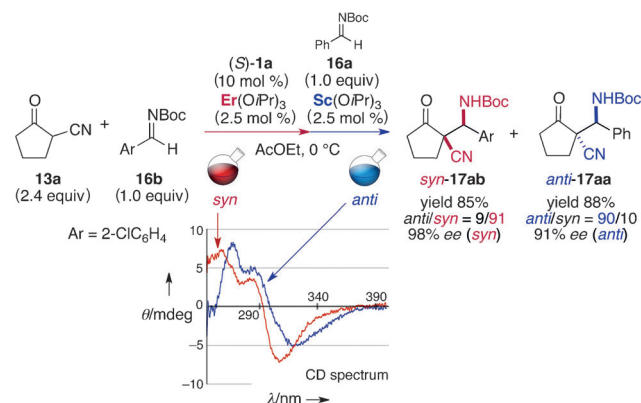


**Scheme 8.** Diastereo-switching in a Mannich-type reaction promoted by (*S*)-**1a**/RE catalyst.

### 3.2. In Situ Switching of the Catalyst Function

In general, asymmetric catalysts are designed to exert a single catalytic function under a single set of reaction conditions in one reaction flask. Although there are a few examples in which a catalyst can afford different reaction outputs under an alternative set of conditions, it is rare for a single metal-based catalyst or organocatalyst to be capable of promoting multiple, highly enantioselective transformations within a single reaction medium in response to an external trigger.<sup>[48,49]</sup> A characteristic feature of functional biomacromolecules is the seamless link of their structural dynamics and their functional diversity. This intriguing example in biosystems inspired us to explore the functional change of an asymmetric catalyst in which the property of functional switching is encoded by its conformation and complexation dynamics. Molecular dynamics is currently attracting great interest in the field of molecular assemblies and molecular machines,<sup>[50]</sup> but its significance in asymmetric catalysis does not receive as much attention as it deserves. We

directed our attention to the functional change of the asymmetric catalyst during the course of the reaction in a single reaction medium,<sup>[49]</sup> and the Mannich-type reaction promoted by the (*S*)-**1a**/RE catalyst described in Section 3.1 appeared to be a suitable system. Control experiments<sup>[11]</sup> indicated that 1) the (*S*)-**1a**/RE complexes are in dynamic equilibrium, 2) a catalyst mixture containing both Sc(OiPr)<sub>3</sub> and Er(OiPr)<sub>3</sub> ((*S*)-**1a**/Sc/Er = 4/1/1) promoted an *anti*-selective reaction similar to the (*S*)-**1a**/Sc catalyst itself, and 3) the pattern in the CD spectrum of the (*S*)-**1a**/Sc/Er catalyst is nearly identical to that of the (*S*)-**1a**/Sc catalyst. These data exploited to delineate an in situ functional switching of the asymmetric catalyst (Scheme 9).<sup>[11]</sup> Initially, the *syn*-selective



**Scheme 9.** In situ functional switching of the asymmetric catalyst in a Mannich-type reaction promoted by (*S*)-**1a**/RE catalyst.

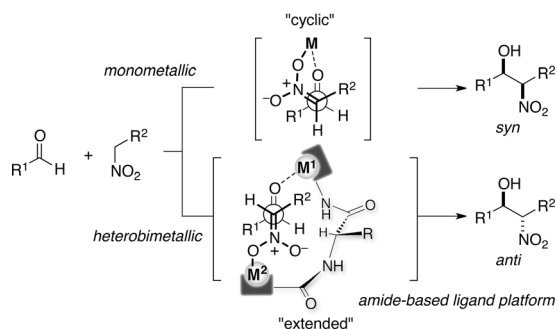
Mannich-type reaction of **13a** and **16b** was conducted with the (*S*)-**1a**/Er catalyst to afford *syn*-**17ab**. After the consumption of **16b**, Sc(OiPr)<sub>3</sub> was added to switch the function to the *anti*-selective (*S*)-**1a**/Sc catalyst, and another imine **16a** was added to run the *anti*-selective reaction. CD spectra were measured before and after the addition of Sc(OiPr)<sub>3</sub>, and a clear change in the spectral pattern was detected, promoting the subsequent reaction with **16a** in an *anti*-selective manner. The diastereo- and enantioselectivity of the products **17ab** and **17aa** were as high as those of the normal batch reactions and the functional change of the asymmetric catalyst during the course of the reaction was confirmed.

## 4. Heterobimetallic Catalysis

### 4.1. anti-Selective Catalytic Asymmetric Nitroaldol Reaction

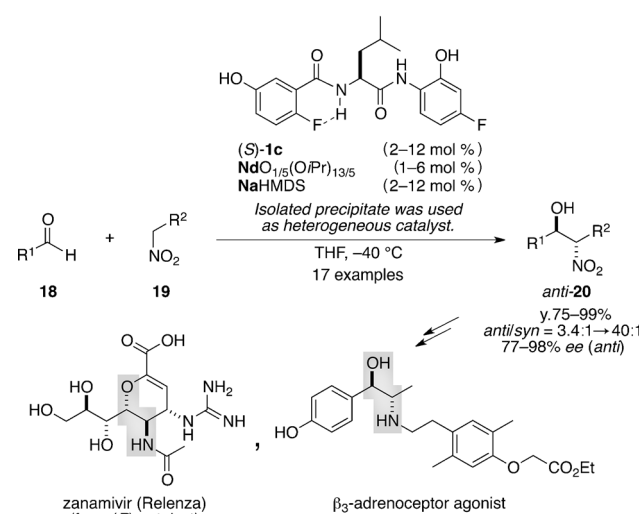
The main focus of the previous sections was the development of a **1**/RE catalyst comprising a single RE source. The obvious expansion of the scope of the **1**/RE catalytic system involved the additional use of other metal sources to produce a heterobimetallic catalyst. We developed an Nd/Na heterobimetallic catalyst in our specific research program on an *anti*-selective catalytic asymmetric nitroaldol (Henry) reaction.<sup>[12,51]</sup> In contrast to the numerous reports on the catalytic asymmetric nitroaldol reaction using nitromethane,<sup>[52,53]</sup> more advanced diastereoselective versions using other nitroalkanes

suffered from limited scope;<sup>[54]</sup> the first successful example of an *anti*-selective reaction has been reported in 2007.<sup>[55–57]</sup> We hypothesized that the amide-based ligand **1** could serve as a suitable platform to accommodate two distinct metals and that each of the metal sites would function cooperatively. We assumed that the formation of an “extended” transition state would override its “cyclic” counterpart by structural modification of the amide-based ligand, thus delivering *anti* products preferentially (Figure 3). A newly designed amide-based



**Figure 3.** “Extended” transition state based on the heterobimetallic catalyst with the amide-based ligand platform for *anti* selectivity.

ligand **1c**, in which one phenol group is shifted from the *ortho* to the *meta* position and two fluorine substituents are introduced, exhibited favorable performance in combination with  $[\text{Nd}_5\text{O}(\text{O}i\text{Pr})_{13}]$  and NaHMDS (Scheme 10).<sup>[12,58]</sup> The fluorine substituent on the *m*-hydroxybenzamide part is critical for high stereoselectivity. It can be assumed that the intramolecular C–F...H–N hydrogen bond restricts the rotation along the C–C bond between the aromatic ring and the amide carbonyl moiety,<sup>[59]</sup> thus favoring the conformation suitable for the extended transition state. Intriguingly, mixing (*S*)-**1c**,  $[\text{Nd}_5\text{O}(\text{O}i\text{Pr})_{13}]$ , and NaHMDS in THF led to the formation of a precipitate, which was characterized by X-ray fluorescence (XRF) and inductively coupled plasma atomic

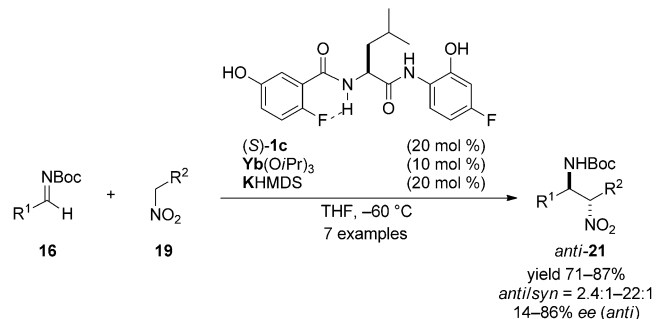


**Scheme 10.** *Anti*-selective catalytic asymmetric nitroaldol reaction promoted by the heterogeneous (*S*)-**1c**/Nd/Na heterobimetallic catalyst.

emission spectrometry (ICP-AES), and was composed of (*S*)-**1c**/Nd/Na in a ratio of approximately 2/1/2. This precipitate can be used as a heterogeneous and storable heterobimetallic catalyst.<sup>[60,61]</sup> Centrifugation and isolation of the precipitate allowed us to eliminate defective complexes that produced poor stereoselectivity. With 1–6 mol % catalyst loading, various aldehydes **18** and nitroalkanes **19** were transformed into the corresponding *anti*-1,2-nitroalkanols **20**.<sup>[12]</sup> *Anti*-1,2-Amino alcohols, a common structural motif in a number of biologically active compounds and therapeutics, can be accessed by facile reduction of the nitroaldol products produced by the present catalysis. The **1c**/Nd/Na heterobimetallic catalyst was implemented in the enantioselective synthesis of a  $\beta_3$ -adrenoceptor agonist and zanamivir (Relenza), a clinically used neuraminidase inhibitor.<sup>[12,62]</sup>

#### 4.2. *anti*-Selective Catalytic Asymmetric Nitro-Mannich Reaction

Changing the electrophile from aldehyde **18** to N-Boc-protected imine **16** for a catalytic asymmetric nitro-Mannich (aza-Henry) reaction required another combination of an RE and an alkali metal based on the (*S*)-**1c** platform.<sup>[63–65]</sup> The catalytic asymmetric nitro-Mannich reaction enables rapid access to enantioenriched 1,2-diamines, which led us to conduct a detailed study to identify a (*S*)-**1c**/Yb/K heterobimetallic catalyst (Scheme 11).<sup>[13]</sup> Unfortunately, the (*S*)-**1c**/Yb/K system did not afford a precipitate, and the stereoselectivity of the obtained product **21** was less satisfactory than that observed for the nitroaldol reaction with (*S*)-**1c**/Nd/Na.

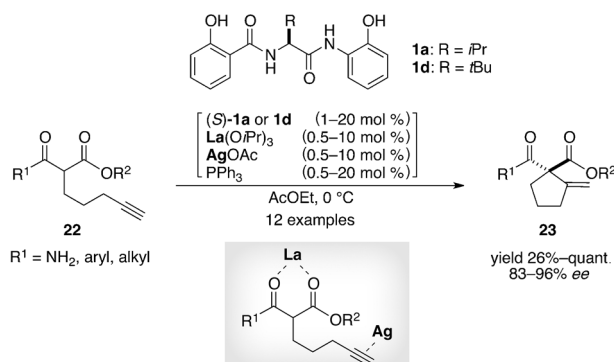


**Scheme 11.** *Anti*-selective catalytic asymmetric nitro-Mannich reaction promoted by the (*S*)-**1c**/Yb/K heterobimetallic catalyst.

#### 4.3. Catalytic Asymmetric Conia-ene Reaction

The development of a heterobimetallic catalytic system comprising two metal atoms that exhibit distinct chemical properties significantly expands the scope of bimetallic catalysis. We next turned our interest from an RE/alkali metal bimetallic system to an RE/ $\pi$ -acidic-metal bimetallic system, anticipating the cooperative activation of a 1,3-dicarbonyl pronucleophile and an alkyne electrophile. We targeted a catalytic asymmetric Conia-ene reaction with an RE/ $\pi$ -acidic-metal bimetallic system.<sup>[66–68]</sup> Supplementary use of AgOAc/PPh<sub>3</sub> for activation of the alkyne group in the (*S*)-**1a**/La catalytic system gave rise to an effective bimetallic

catalyst for the Conia-ene reaction of **22**, affording the desired enantioenriched product **23** (Scheme 12).<sup>[14]</sup> As described in Sections 2.1 and 2.2, an N-protected  $\alpha$ -alkoxycarbonyl amide can be used in this catalytic system. Reactions did not proceed in the absence of (*S*)-**1a**/La or AgOAc/PPh<sub>3</sub>, thus

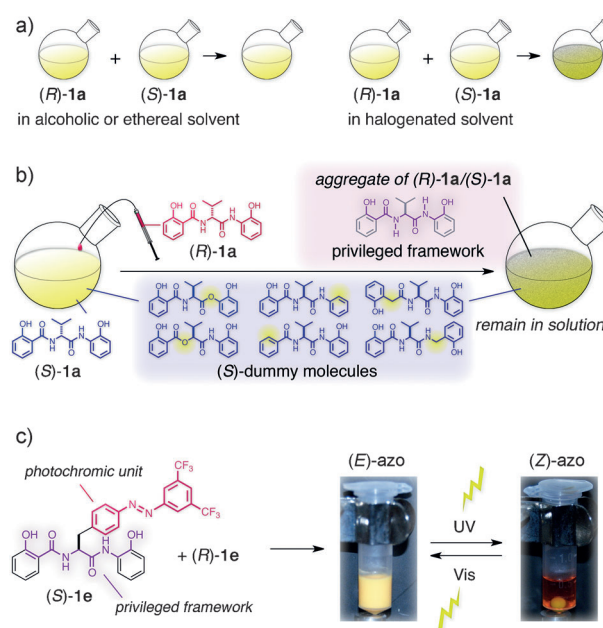


**Scheme 12.** Catalytic asymmetric Conia-ene reaction promoted by the (*S*)-**1**/La/Ag/PPh<sub>3</sub> heterobimetallic catalyst.

suggesting that the cooperative action of (*S*)-**1a**/La and AgOAc/PPh<sub>3</sub> is essential to promote the reaction. In some cases, the amide-based ligand (*S*)-**1d**, derived from *L*-*tert*-butyl glycine, outperformed (*S*)-**1a** in terms of enantioselectivity.

## 5. Heterochiral Aggregation

The strong and unique hydrogen-bond interaction of amide-based ligand **1** is evidenced by an intriguing solvent-dependent heterochiral aggregation.<sup>[15,16,69]</sup> The primary focus of this review is asymmetric catalysis, and the aggregation is beyond the scope of the review, but it is worthwhile to briefly note the aggregation property of amide-based ligand **1**. Whereas mixing of (*R*)-**1a** and (*S*)-**1a** in alcoholic or ethereal solvents affords a homogeneous racemic solution, a precipitate of the heterochiral aggregate is immediately formed upon mixing (*R*)-**1a** and (*S*)-**1a** in halogenated solvents (Figure 4a). X-ray crystallographic analysis of the aggregate in CHCl<sub>3</sub> showed that (*R*)-**1a** and (*S*)-**1a** alternatively align to form a tight hydrogen-bond interaction. The heterochiral aggregation is highly specific to the hydrogen-bond array of **1a**; (*R*)-**1a** and (*S*)-**1a** formed the insoluble heterochiral aggregate with high fidelity in an ensemble of eight structurally related molecules, thus implying that the diamide moiety and the two phenol groups constitute a privileged framework for the heterochiral aggregation (Figure 4b).<sup>[14]</sup> For the photochromic amide-based ligand **1e**, which features an azobenzene unit and the privileged framework, the heterochiral aggregation could be reversibly manipulated by UV-Vis irradiation (Figure 4c).<sup>[15,70]</sup> When the azobenzene is in *E* configuration, **1e** forms a heterochiral aggregate because of the privileged hydrogen-bond framework. Upon irradiation with UV light at 365 nm, the *E* form of azobenzene is isomerized to the *Z* form and the hydrogen-bond interaction is weakened, thus dissociating the insoluble aggregate and



**Figure 4.** Heterochiral aggregation of amide-based ligand **1**. a) Solvent-dependent heterochiral aggregation. b) Specific aggregation of (*R*)-**1a** and (*S*)-**1a** in the presence of structurally related molecules. c) Reversible heterochiral aggregation of photochromic diamide **1e**.

affording a homogeneous solution. Reversion to the *E* form by irradiation with visible light (Vis) at a wavelength of more than 422 nm leads to the heterochiral aggregation, and this process can be repeated.

## 6. Conclusion

We have developed a catalytic system based on an amide-based ligand **1** and a rare-earth metal (RE), in which metal-ligand complexation is in dynamic equilibrium and the dissociated state is dominant. **1**/RE is not a “preformed” metal complex but rather assembles with substrates to form an organized transition state with the aid of metal coordination and hydrogen bonding, thus eliciting its catalytic function. The characteristic properties of the catalytic system were used in the asymmetric catalysis of reactions with highly coordinative substrates, and in functional switching of catalysts. The **1**/RE catalytic system can accommodate additional metals to produce a heterobimetallic catalyst, thus further expanding the utility. Significant hydrogen-bond interaction is evidenced by the heterochiral aggregation of the ligand itself, and recent efforts have rendered the aggregation process reversible by photoirradiation. Further developments in asymmetric catalysis utilizing **1**/RE catalysts and of catalysts switching their function as a result of reversible aggregation are currently underway.

We express our deep gratitude to a group of highly talented co-workers whose names appear in the references. In particular, Dr. Tomoyuki Mashiko, Dr. Tatsuya Nitabaru, Ms. Noriko Takahashi are gratefully acknowledged for their efforts in the early stage of this project. Financial support was

provided by MEXT KAKENHI (grant number 15002003, 20200053) and JSPS KAKENHI (grant number 20229001, 19790008).

Received: August 15, 2012

Published online: November 23, 2012

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