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Recent Progress in Asymmetric Bifunctional Catalysis Using Multimetallic Systems

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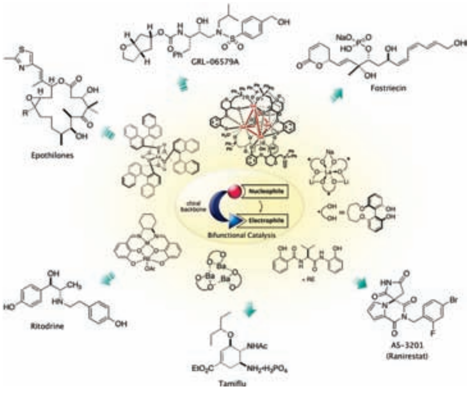

The concept of bifunctional catalysis, wherein both partners of a bimolecular reaction are simultaneously activated, is very powerful for designing efficient asymmetric catalysts. Catalytic asymmetric processes are indispensable for producing enantiomerically enriched compounds in modern organic synthesis, providing more economical and environmentally benign results than methods requiring stoichiometric amounts of chiral reagents. Extensive efforts in this field have produced many asymmetric catalysts, and now a number of reactions can be rendered asymmetric. We have focused on the development of asymmetric catalysts that exhibit high activity, selectivity, and broad substrate generality under mild reaction conditions. Asymmetric catalysts based on the concept of bifunctional catalysis have emerged as a particularly effective class, enabling simultaneous activation of multiple reaction components. Compared with conventional catalysts, bifunctional catalysts generally exhibit enhanced catalytic activity and higher levels of stereodifferentiation under milder reaction conditions, attracting much attention as next-generation catalysts for prospective practical applications.

In this Account, we describe recent advances in enantioselective catalysis with bifunctional catalysts. Since our identification of heterobimetallic rare earth—alkali metal—BINOL (REMB) complexes, we have developed various types of bifunctional multimetallic catalysts. The REMB catalytic system is effective for catalytic asymmetric Corey—Chaykovsky epoxidation and cyclopropanation. A dinucleating Schiff base has emerged as a suitable multidentate ligand for bimetallic catalysts, promoting catalytic *syn*-selective nitro-Mannich, *anti*-selective nitroaldol, and Mannich-type reactions. The sugar-based ligand GluCAPO provides a suitable platform for polymetallic catalysts; structural elucidation revealed that their higher order polymetallic structures are a determining factor for their function in the catalytic asymmetric Strecker reaction. Rational design identified a related ligand, FujiCAPO, which exhibits superior performance in catalytic asymmetric conjugate addition of cyanide to enones and a catalytic asymmetric Diels—Alder-type reaction. The combination of an amide-based ligand with a rare earth metal constitutes a unique catalytic system: the ligand—metal association is in equilibrium because of structural flexibility. These catalytic systems are effective for asymmetric amination of highly coordinative substrate as well as for Mannich-type reaction of α-cyanoketones, in which hydrogen bonding cooperatively contributes to substrate activation and stereodifferentiation. Most of the reactions described here generate stereogenic tetrasubstituted carbons or quaternary carbons, noteworthy accomplishments even with modern synthetic methods. Several reactions have been incorporated into the asymmetric synthesis of therapeutics (or their candidate molecules) such as Tamiflu, AS-3201 (ranirestat), GRL-06579A, and ritodrine, illustrating the usefulness of bifunctional asymmetric catalysis.

1. Introduction

The usefulness of asymmetric catalysis for producing enantiomerically enriched compounds with maximum efficiency is firmly established.[1] Catalytic asymmetric processes provide more economical and environmentally benign methodology over those using stoichiometric amounts of chiral

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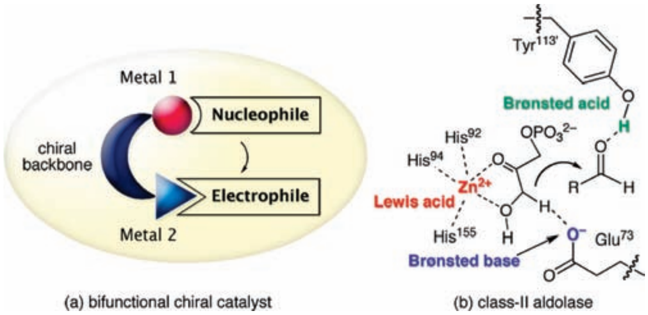
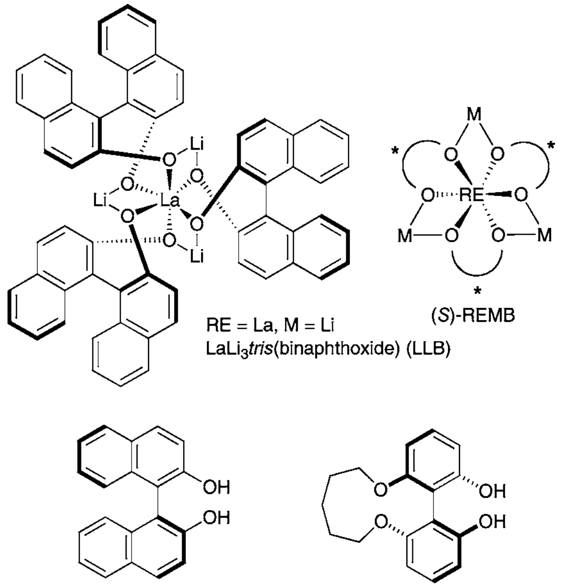


(a) bifunctional chiral catalyst (b) class-II aldolase

FIGURE 1

reagents. In most cases, the reaction of interest is a bimolecular reaction. The design of conventional asymmetric catalysts is largely focused on the principle of simple Lewis acid or Lewis base activation of one reaction partner. A number of asymmetric catalysts have been developed and now most of the reactions can be rendered asymmetric. In this context, the central interest in this field has shifted to the development of asymmetric catalysts that exhibit high activity, high selectivity, and broad substrate generality under mild reaction conditions. To address this issue, our particular focus has been directed toward the concept of bifunctional catalysis, where both reaction partners are simultaneously activated (dual activation) by fine-tuned asymmetric catalysts (Figure 1a). Compared with conventional catalysts, bifunctional catalysts generally exhibit enhanced catalytic activity and higher levels of stereodifferentiation under milder reaction conditions, attracting much attention as the next-generation catalysts for prospective practical applications. Nature harnesses the power of bifunctional catalysis in a number of vital enzymatic reactions. For example, the proposed transition state model of class II aldolase, a Zn-dependent aldolase, clearly illustrates the simultaneous activation of substrates.[2] The enzyme catalyzes an asymmetric aldol reaction of dihydroxyacetone phosphate (DHAP) and various aldehydes under neutral conditions. In the proposed transition state, the glutamate-73 residue in the proximity of Zn^{2+} functions as a Brønsted base to effect enolization of DHAP, whereas the phenol of the tyrosine-113′ residue activates an aldehyde as a Brønsted acid, achieving dual activation of the substrates (Figure 1b). Inspired by this intriguing mechanism, our group has engaged in the development of asymmetric bifunctional catalysts that enable otherwise difficult transformations. Herein, selected recent accomplishments in our group are discussed. Additional examples of bifunctional asymmetric catalysis that we and other groups have reported are summarized in other review articles.[3−5]



(*S*)-BINOL (*S*)-biphenyldiol **1**-H_2

FIGURE 2. Structures of heterobimetallic RE-M_3-tris(binaphthoxide) (REMB) catalyst (*S*)-LLB (RE = La, M = Li, LLB), BINOL, and biphenyldiol **1**-H_2.

2. Heterobimetallic Rare Earth−Alkali Metal−BINOL (REMB) Complexes

2.1. Introduction to REMB Catalysts. Since the first report of a catalytic asymmetric nitroaldol reaction using rare earth metal complexes,[6] we have continued to focus on the concept of multifunctional catalysis wherein the catalysts exhibit both Lewis acidity and Brønsted basicity. In particular, the development of heterobimetallic complexes that contain a rare earth metal, three alkali metals, and three 1,1′-bi-2-naphthols (BINOLs) offers a versatile framework for asymmetric catalysts. The structure of the rare earth−alkali metal−BINOL (abbreviated as REMB; RE = rare earth metal, M = alkali metal, B = BINOL) complex is shown in Figure 2. The synergistic effects of the two functions in REMB complexes enabled various transformations[7] (Figure 3) that were difficult to achieve using conventional monometallic catalysts with only Lewis acidity. A variety of enantioselective transformations have been realized by selecting combinations of metals based on the type of the reaction. REMB complexes have also been applied to the synthesis of many biologically active compounds, such as epothilone,[8a] fostriecin,[8b] and a human immunodeficiency virus (HIV) protease inhibitor GRL-06579A[8c,9] (Figure 4).

2.2. New Development in REMB Catalysts. Recently, we succeeded in expanding the utility of REMB complexes beyond the Lewis acid/Brønsted base catalysis. LLB (RE = La, M = Li) with an achiral phosphine oxide system was effective for the catalytic asymmetric Corey−Chaykovsky epoxida-

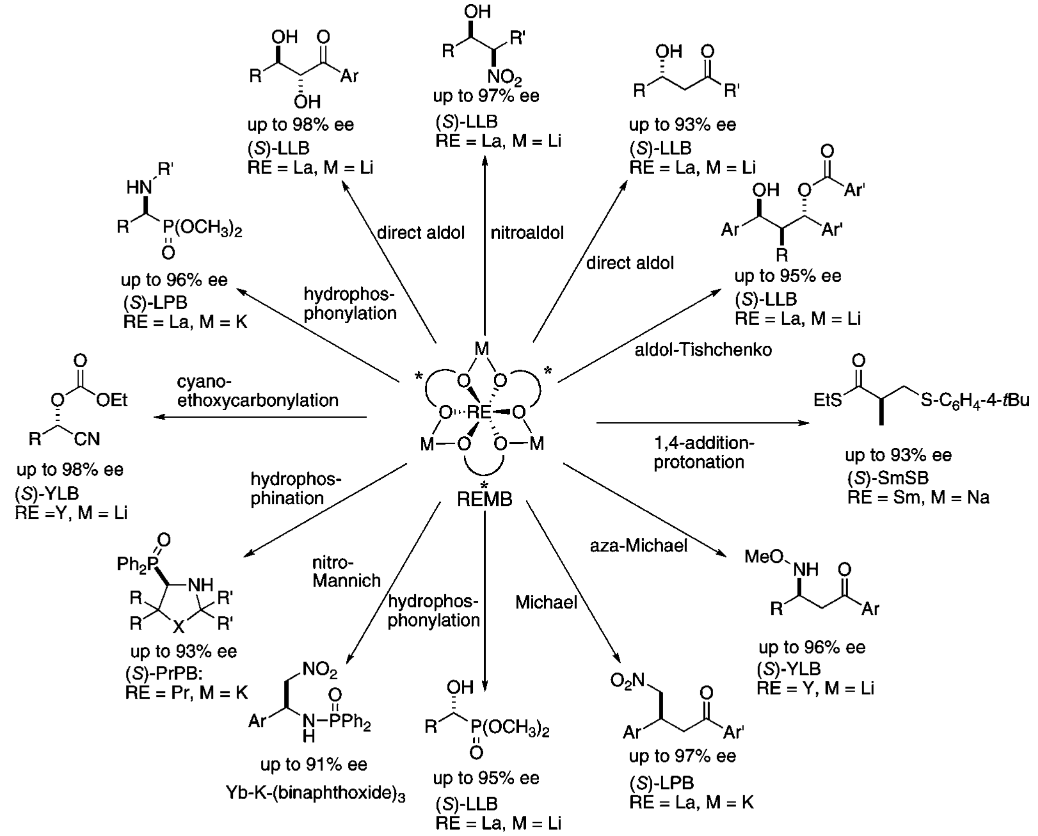


FIGURE 3. Representative catalytic asymmetric reactions promoted by REMB complexes.

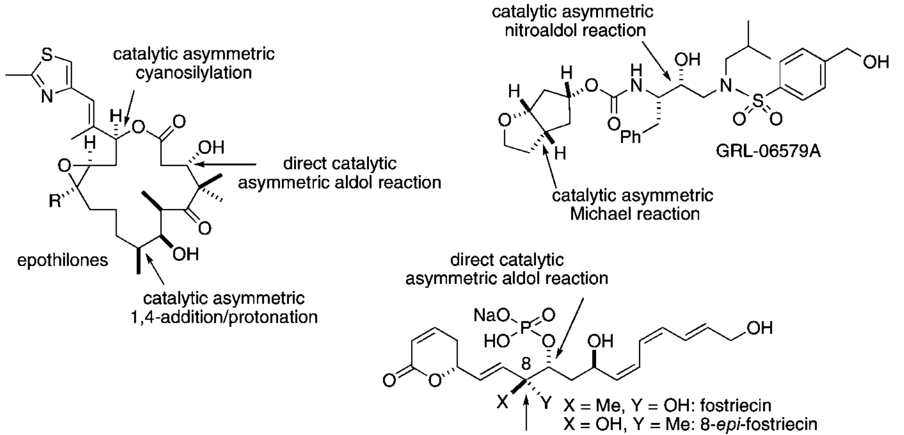
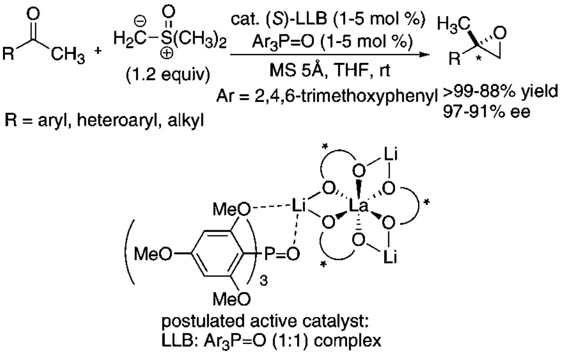


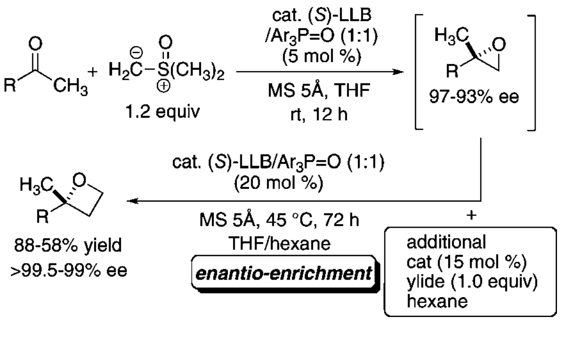
FIGURE 4. Structures of epothilones, fostriecin, 8-*epi*-fostriecin, and GRL-06579A synthesized through REMB-catalyzed reactions.

tion[10] of aryl, heteroaryl, and alkyl methyl ketones with a sulfur ylide, giving 2,2-disubstituted terminal epoxides in high yield and enantioselectivity (Scheme 1).[11] Because the enantioselective epoxidation of *gem*-disubstituted alkenes is rather difficult, the present method is synthetically useful. The achiral phosphine oxide is speculated to coordinate with LLB, thereby constructing a suitable chiral environment for the Corey–Chaykovsky epoxidation. In the reaction, we assume that the La metal center acts as a Lewis acid to activate a ketone, and the orientation of the sulfur ylide would be controlled through coordination with the Li metal center. The La/Li Lewis acid–Lewis acid cooperation is likely important for achieving high enantioselectivity in the reaction. The reaction was further extended to a one-pot synthesis of 2,2-disubstituted oxetanes through sequential additions of the sulfur ylide to ketones and intermediate epoxides (Scheme 2).[12] It is noteworthy that the oxetanes were produced with >99.5–99% ee, an enantioselectivity higher than that achieved with the intermediate epoxides. Mechanistic studies suggest that LLB is also effective for kinetic resolution of

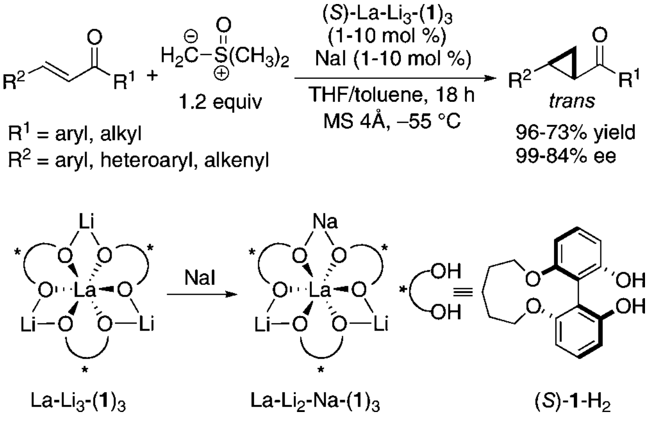
SCHEME 1. Catalytic Asymmetric Synthesis of 2,2-Disubstituted Epoxides by Corey–Chaykovsky Epoxidation of Various Methyl Ketones with the LLB/Ar_3P=O (1:1) System



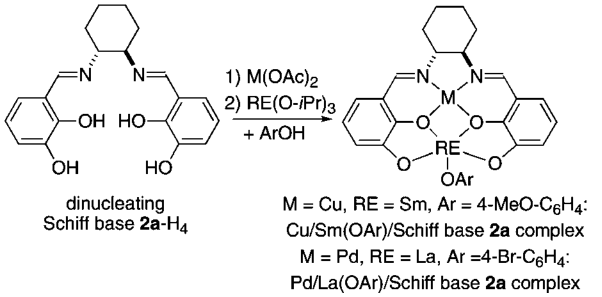
SCHEME 2. Catalytic Asymmetric Synthesis of 2,2-Disubstituted Oxetanes via One-Pot Sequential Addition of Sulfur Ylide to Ketones with Enantio-enrichment



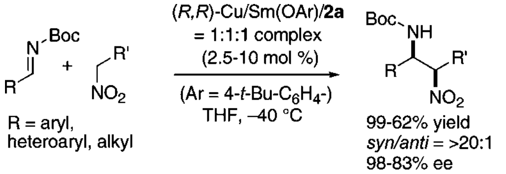
SCHEME 3. Catalytic Asymmetric Corey–Chaykovsky Cyclopropanation of Enones with LLB + NaI Mixed Alkali Metal System



SCHEME 4. Preparation of Transition Metal–Rare Earth Metal Heterobimetallic Schiff Base Complex from (*R,R*)-Dinucleating Schiff Base **2a**-H_4



SCHEME 5. *syn*-Selective Catalytic Asymmetric Nitro-Mannich Reactions with Cu/Sm(OAr)/Schiff Base **2a** Complex



2,2-disubstituted terminal epoxides, leading to the enantio-enrichment in the epoxide ring-expansion step. For the Corey–Chaykovsky cyclopropanation of enones and an α,β-unsaturated *N*-acylpyrrole[13] as an ester surrogate, biphenyldiol **1**-H_2 gave better enantioselectivity than BINOL (Scheme 3).[14,15] In cyclopropanation, a NaI additive also played a key role to improve enantioselectivity. Electrospray ionization mass spectrometry (ESI-MS) analysis, as well as control experiments, indicated that a partial alkali metal exchange occurred *in situ* to afford a La–Li_2–Na–tris(biphenoxide **1**) complex as the most reactive and enantioselective active species (Scheme 3).

3. Bimetallic Schiff Base Catalysts

The previous section describes successful heterobimetallic combinations of rare earth metals and alkali metals. To develop heterobimetallic complexes, the design of a suitable multidentate ligand is important to control the position of the two different metals in the complex. The position of the two metals has crucial effects on the reactivity as well as the stereoselectivity of the heterobimetallic complex. In addition, different combinations of metals often result in different functionality. To realize bimetallic asymmetric catalysis using transition metal and rare earth metal combinations, we utilized a new dinucleating Schiff base **2a** (Scheme 4). We hypothesized that the Schiff base **2a** would incorporate a transition metal into the N_2O_2 inner cavity and an oxophilic rare earth metal with a large ionic radius into the O_2O_2 outer cavity.

As predicted, selecting a metal combination based on the targeted reaction was important to achieve high stereoselectivity. For a *syn*-selective nitro-Mannich-type reaction,[16] a heterobimetallic complex prepared from $Cu(OAc)_2$, Sm(O-*i*Pr)$_3$, and dinucleating Schiff base **2a** with 4-*t*-Bu-phenol was the best, giving products with good yield, high *syn*-selectivity, and enantioselectivity (Scheme 5).[17] The proposed catalytic cycle is shown in Figure 5; the Sm-OAr moiety would function as a Brønsted base to generate Sm-nitronate, and Cu would act as a Lewis acid to activate the imine. Suitably aligned Cu and Sm

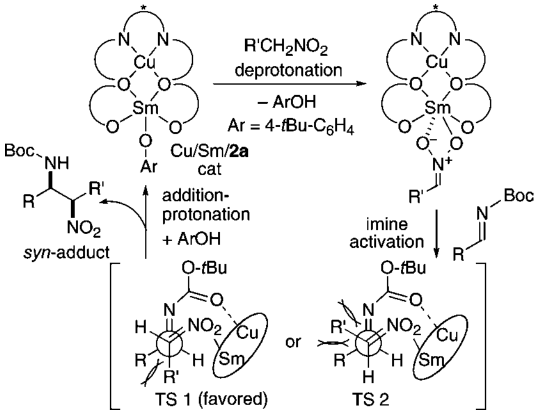
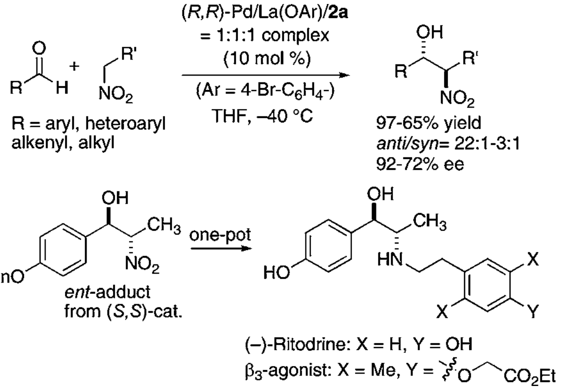
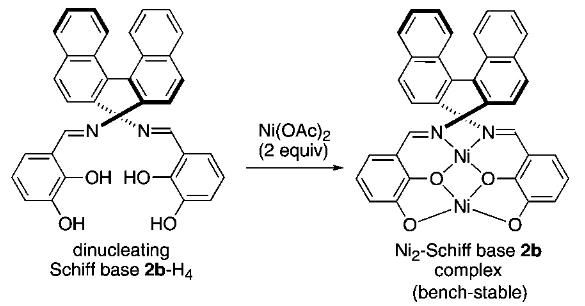


FIGURE 5. Postulated catalytic cycle and transition state models.

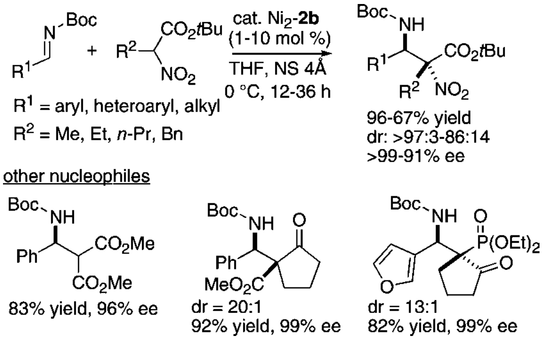
SCHEME 6. *anti*-Selective Catalytic Asymmetric Nitroaldol Reaction with Pd/La(OAr)/Schiff Base **2a** Complex



SCHEME 7. Preparation of a Bench-Stable Ni_2–Schiff Base **2b** Catalyst from (*R*)-Binaphthyldiamine-Based Dinucleating Schiff Base **2b**-H_4



SCHEME 8. Direct Catalytic Asymmetric Mannich-Type Reaction of Nitroacetates, Malonate, *β*-Keto Ester, and *β*-Keto Phosphonate Using the Bench-Stable Ni_2–Schiff Base **2b** Catalyst



metal centers in the dinucleating Schiff base **2a** function cooperatively to fix imine and nitronate in close proximity, resulting in high *syn*-selectivity from TS-1 (Figure 5). By changing the metal combination to Pd/La with Schiff base **2a**, an *anti*-selective catalytic asymmetric nitroaldol reaction was accomplished (Scheme 6).[18,19] The utility of the *anti*-selective nitroaldol reaction was demonstrated through one-pot syntheses of ritodrine and a β_3-adrenoceptor agonist (Scheme 6).

Schiff base **2a** derived from *trans*-1,2-diaminocyclohexane selectively incorporated a transition metal into the N_2O_2 inner cavity and an oxophilic rare earth metal with a large ionic radius into the O_2O_2 outer cavity. To further expand the utility and diversity of the dinuclear Schiff base complexes, we developed a new dinucleating Schiff base that incorporates metals with a smaller ionic radius than that of rare earth metals into the O_2O_2 outer cavity. Screening of diamine units indicated that a Schiff base **2b** (Scheme 7) derived from 1,1′-binaphthyl-2,2′-diamine was suitable because of the conformational difference between *trans*-1,2-diaminocyclohexane and 1,1′-binaphthyl-2,2′-diamine. The Ni_2–Schiff base **2b** complex was applicable to Mannich-type reactions of *N*-Boc imines and α-substituted nitroacetates to afford *anti*-α,β-diamino acid surrogates with an α-tetrasubstituted carbon stereocenter (Scheme 8).[20] The homodinuclear Ni_2–Schiff base **2b** complex is bench-stable and can be stored for prolonged periods without loss of activity. The results shown in Scheme 8 were obtained using the Ni_2/Schiff base **2b** complex stored for more than 3 months under air at ambient temperature. Control experiments using mononuclear Ni–**2b** and Ni–salen complexes, however, resulted in poor reactivity and stereoselectivity, indicating the importance of the two Ni centers for high reactivity and selectivity. We speculate that the Ni–aryloxide moiety functions as a Brønsted base to generate the Ni–enolate, and another Ni-center controls the orientation of the *N*-Boc imine. The homobimetallic Ni_2/**2b** complex was also applicable to other donors, such as malonates, a *β*-keto ester,[20a] and *β*-keto phosphonates,[20b] giving products in high enantioselectivity and diastereoselectivity (Scheme 8).

4. Homopolymetallic Asymmetric Catalysis

4.1. Design of a FujiCAPO Ligand. In 2000, we developed GluCAPO ligands **3**–**5** derived from D-glucose (Figure 6).[3a,d] Rare earth metal complexes of GluCAPO are useful enantioselective catalysts for various reactions, including cyanosilylation of ketones, Strecker reaction of ketimines, conjugate

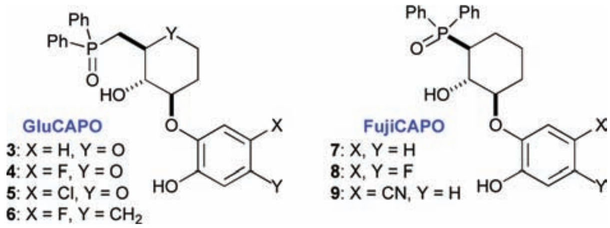
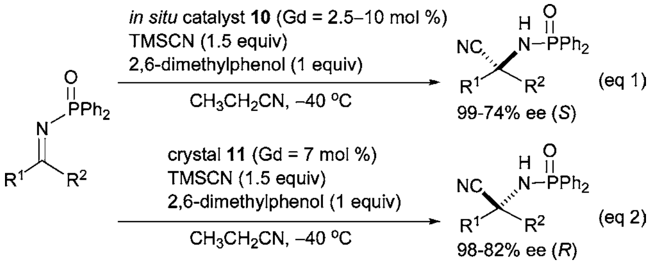
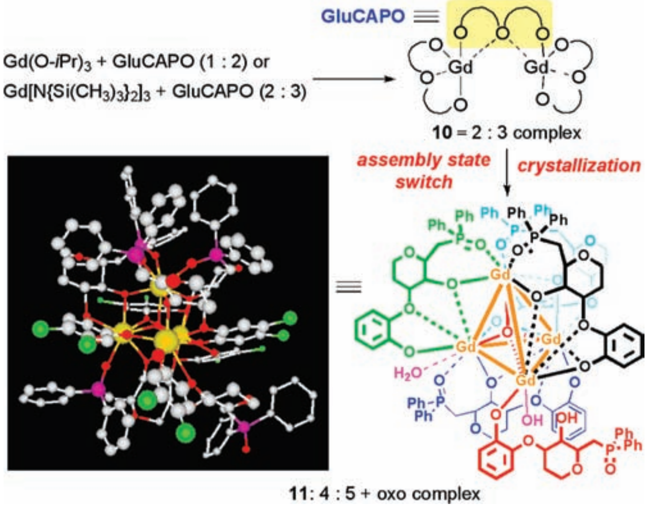


FIGURE 6

SCHEME 9



SCHEME 10



addition of TMSCN to α,β-unsaturated *N*-acyl pyrroles, and ring-opening reactions of *meso*-aziridines with TMSCN and $TMSN_3$.[3a,d]

Structural studies of the asymmetric catalyst indicated that the active catalysts are self-assembled poly rare earth metal complexes with defined higher-order structures. In the Strecker reaction of ketimines, a catalyst generated from Gd(O-*i*Pr)$_3$ and GluCAPO in a 1:2 ratio or from $Gd[N\{Si(CH_3)_3\}_2]_3$ and GluCAPO in a 2:3 ratio produced (*S*)-products with up to 99% ee (Scheme 9, eq 1). Based on ESI-MS studies, the active catalyst was a Gd/GluCAPO = 2:3 complex **10** (Scheme 10).

To elucidate the three-dimensional structure of the asymmetric catalyst, crystallization of the catalytic species was attempted. Unexpectedly, the Gd/GluCAPO (**5**) = 4:5 + oxo complex **11** was obtained as colorless prisms in 80% yield from a propionitrile–hexane solution of the catalyst generated from Gd(O-*i*Pr)$_3$ and **5** in a 2:3 ratio (Scheme 9). Obviously, the assembly state of the complex changed through the crystallization process (from 2:3 complex **10** to 4:5 + oxo complex **11**). Based on MS studies, complex **11** was stable under air, and the higher-order structure was maintained in solution.

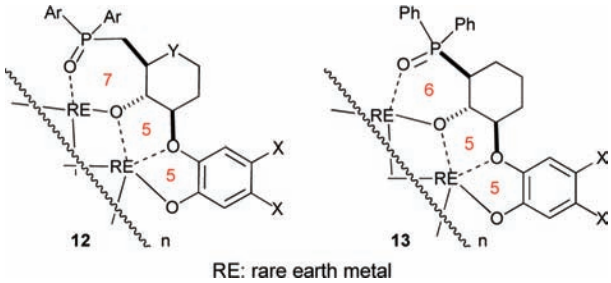


FIGURE 7

Intriguing relationships between higher-order structures and asymmetric catalytic function were identified in the catalytic enantioselective Strecker reaction of ketimines.[21] The function of crystal **11** as an enantioselective catalyst was evaluated by Strecker reaction of ketimines. To our surprise, the enantioselectivity was completely reversed when crystal **11** was used as a catalyst (Scheme 9, eq 2), compared with catalyst **10** prepared *in situ*. The reaction rate using catalyst **11** was approximately 5–50 times slower than that using catalyst **10**. Because the absolute configuration of the chiral ligand, rare earth metal, and other reaction conditions were identical, the dramatic difference in asymmetric catalytic function (enantioselectivity and catalyst activity) was attributed to the change in the higher-order structure of the chiral polymetallic catalyst. This discovery changed the paradigm of our chiral ligand design: *higher-order structure, not the structure of each module, is the determining factor for the function of asymmetric polymetallic catalysts.* New chiral ligand design for asymmetric polymetallic catalysts should take the assembled structure into consideration.

Because *de novo* design of higher-order structures of chiral polymetallic complexes is nearly impossible, we directed our ligand design toward unifying the higher-order structure by designing a more stable module. Module **12**, containing a 7,5,5-membered fused chelation ring system, was identified in the crystal structure of **11** (Figure 7). If the 7-membered chelation in **12** is substituted by a presumably more stable 6-membered chelation, the resulting module **13** should be more stable than **12**. Based on this consideration, we designed a new ligand, FujiCAPO (**7** and **8**).[22,23]

The Gd complex of FujiCAPO **8** induced higher performance (especially in catalyst activity) than that of GluCAPO **4** in catalytic desymmetrization of *meso* aziridines with

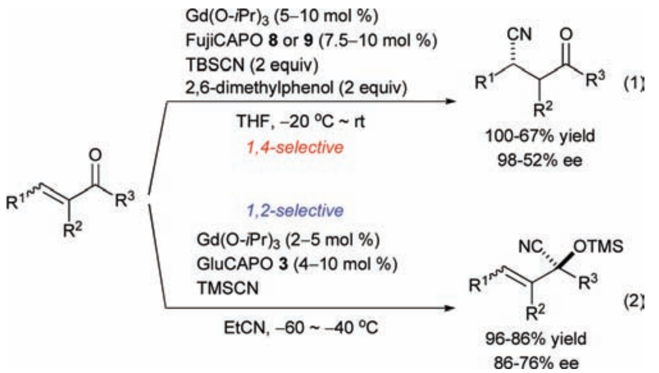
TMSCN[22a] and catalytic enantioselective conjugate addition of TMSCN to α,β-unsaturated *N*-acyl pyrroles.[22b] The absolute configuration of the products was the opposite, despite the fact that **8** and **4** had the same chirality. The sharp contrast in asymmetric catalytic functions is not due to the absence of an oxygen atom in the core 6-membered ring, because a Gd catalyst derived from **6** demonstrated the same tendency as **4**. MS studies indicated that the Gd−FujiCAPO complex is a 5:6 + oxo + OH complex. Therefore, a small difference in the chiral ligand structure was amplified in the higher-order structure, resulting in a great difference in the asymmetric catalytic function.

4.2. Catalytic Enantioselective Conjugate Addition of Cyanide to Enones. FujiCAPO has critical advantages over GluCAPO based on the findings from a catalytic enantioselective conjugate addition of cyanide to enones.[24] Although there were previous examples of catalytic enantioselective conjugate addition of cyanide to α,β-unsaturated carboxylic acid derivatives,[3d,22b,25] there had been no reports of the corresponding reaction to enones, despite the high synthetic utility of the reaction. The main difficulty in developing a catalytic enantioselective conjugate addition of cyanide to enones compared with α,β-unsaturated carboxylic acid derivatives is due to the ambident characteristics of enones: both the carbonyl and β-carbon of enones can be the reaction site. An asymmetric catalyst should differentiate the two possible reaction pathways (1,2- and 1,4-addition), as well as the two enantiotopic faces.

Two Gd catalysts derived from GluCAPO **4** and FujiCAPO **8** were first compared in enantioselective conjugate addition of TMSCN to 3-hepten-2-one at room temperature in the absence of any additives. The 1,4-selectivity and enantioselectivity of the conjugate addition product were markedly higher when using **8** [1,4-product/1,2-product = 52 (40% ee)/48, 62% combined yield] than when using **4** [1,4-product/1,2-product = 19 (15% ee)/81, 63% combined yield]. After careful optimization using **8**, the 1,4-product was obtained exclusively in 77% yield with 92% ee by using TBSCN as a cyanide source and 2,6-dimethylphenol as an additive at −20 °C.

The general scheme of this first example of catalytic enantioselective conjugate addition of cyanide to enones is shown in Scheme 11, eq 1. The generality of carbonyl substituents of enones is very broad, and linear and branched aliphatic and aromatic substituents are tolerated. For the substituents at the β-position, linear aliphatic groups produced excellent results. As for cyclic enones, an electronically tuned ligand **9** afforded significant improvements over **8**.

SCHEME 11

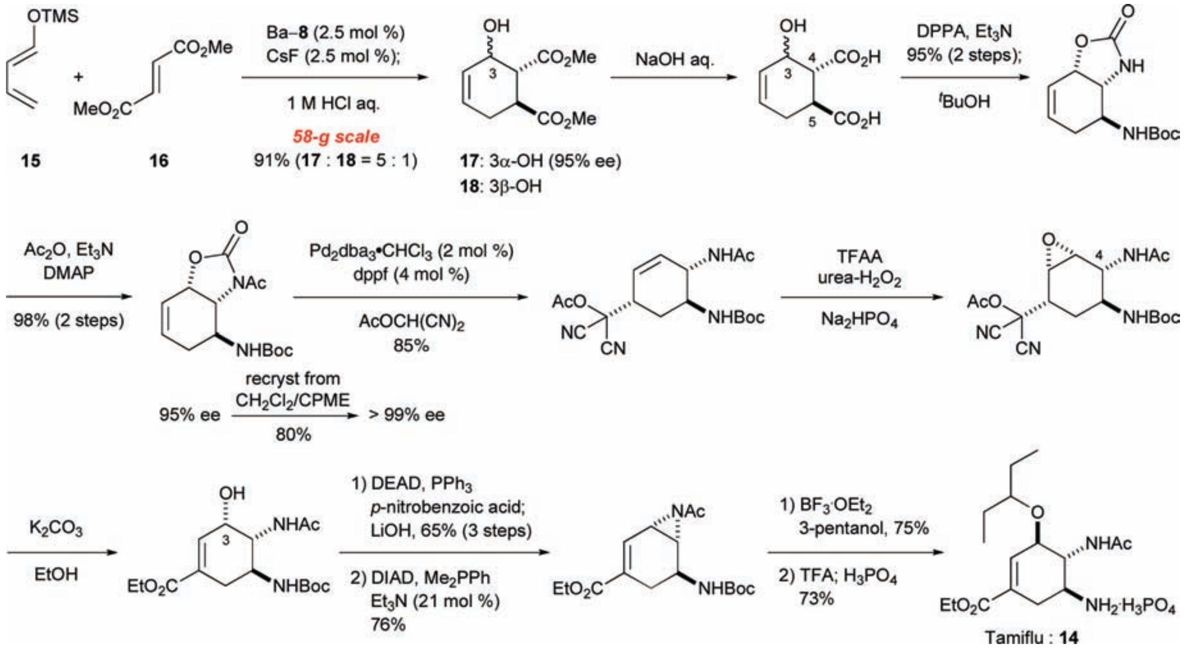


By combining the previously developed exclusively 1,2-selective cyanosilylation of enones using GluCAPO **3** in the absence of a protic additive (Scheme 11, eq 2),[3a] both 1,2- and 1,4-products can be selectively produced with high enantioselectivity from enones.

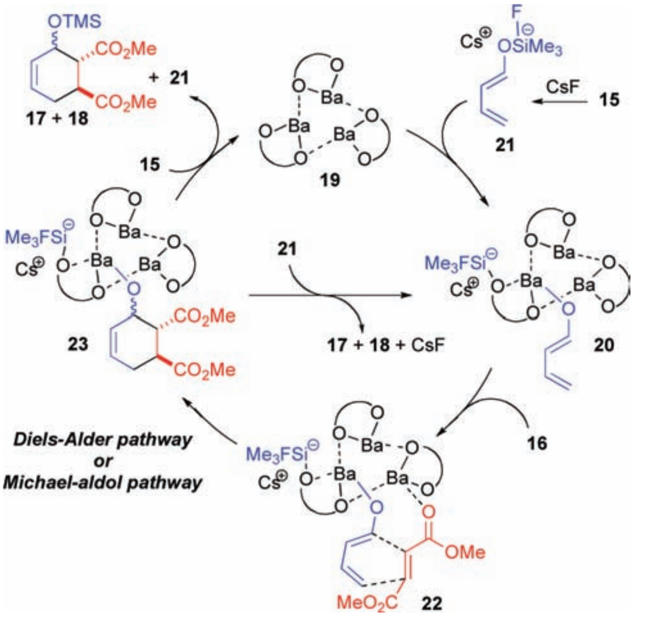
4.3. Catalytic Asymmetric Synthesis of Tamiflu. An influenza pandemic is currently one of the greatest fears worldwide. Tamiflu (**14**)[26] is thought to be effective for protecting human beings against a possible influenza pandemic. Developing a truly efficient synthetic route by which Tamiflu can be produced in sufficient amounts to satisfy a worldwide demand is an ongoing project in our group.[27,28] We recently reported a concise asymmetric synthesis of Tamiflu starting from the Diels−Alder-type reaction between siloxy diene **15** and dimethyl fumarate (**16**) catalyzed by a Ba−FujiCAPO complex (Scheme 12).[29]

We identified a complex generated from Ba(O-*i*Pr)$_2$ and **8** in a 1:1 ratio as a superb asymmetric catalyst for the Diels−Alder-type reaction between **15** and **16**; the reaction proceeded in the presence of 2.5 mol % Ba-**8** and 2.5 mol % CsF (possibly acting as a transmetalation accelerator through hypervalent silicate formation), and the products (*endo* **17** + *exo* **18** isomers) were obtained in 91% yield (**17**/**18** = 5:1) with 95% ee of desired **17** (Scheme 12). The reaction is scalable, and to date a 58-g reaction has been successfully performed. Mechanistic studies of this Diels−Alder-type reaction indicated that the asymmetric catalyst is a Ba/**8** = 3:3 complex (**19**), and the barium complex activates diene **15** through transmetalation. The proposed catalytic cycle is shown in Scheme 13. First, the active barium dienolate **20** is generated through transmetalation between catalyst **19** and siloxy diene **15**. In this step, the chiral ligand is partially silylated. The cocatalyst, CsF, would facilitate the generation of **20** through the formation of pentavalent silicate **21**; **20** should be sufficiently reactive, and cyclization with **16** occurs in either a concerted manner (Diels−Alder pathway) or a stepwise man-

SCHEME 12



SCHEME 13



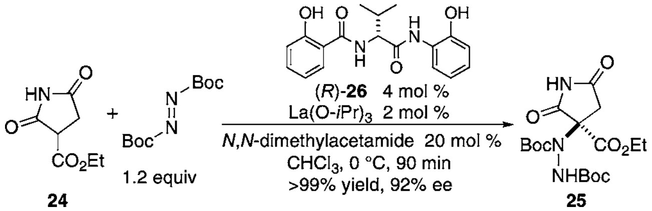
ner (Michael–aldol pathway), producing intermediate barium alkoxide **23**. Due to the existence of multiple barium metals of different electronic characteristics in a catalyst molecule, it is possible that the catalyst promotes the reaction through an intramolecular transfer of the barium dienolate to an activated dienophile by a Lewis acidic barium (**22**). Finally, product barium alkoxide in **23** attacks the trimethylsilyl group attached to the ligand, and catalyst **19** is regenerated while silylated products **17** and **18** are liberated from the catalytic cycle. Alternatively, **23** reacts with another molecule of siloxy diene **21**, liberating the products while regenerating active barium dieonolate **20**. The nucleophile activation (HOMO-raising) mechanism is the key to successful promotion of the catalytic asymmetric Diels–Alder-type reaction using acid-labile diene **15**.

Extension of the synthetic route shown in Scheme 12 to an industrial scale synthesis of Tamiflu is currently under investigation in collaboration with a pharmaceutical company.

5. Amide-Based Ligand/Rare Earth Metal Catalyst

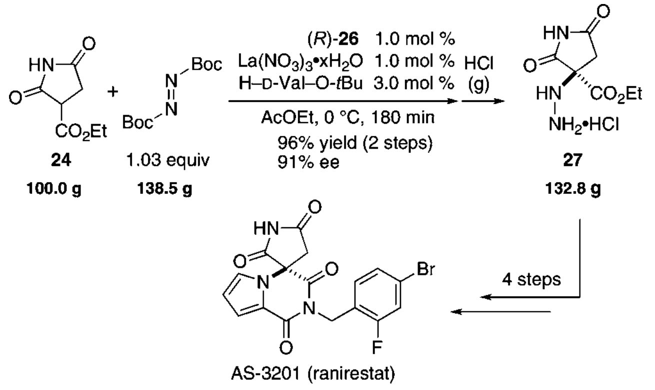
5.1. Catalyst Design. Nature has selected polypeptide chains of α-amino acids (generally 50–2000 amino acids long) as the backbone of functional and catalytic proteins. Peptides have attracted considerable attention in the development of catalytic processes. Indeed, enzymatic catalysts, catalytic antibodies, and oligopeptide-based asymmetric catalysts have been developed and applied with great success. We hypothesized that a catalyst comprising small amide-based ligands derived from α-amino acids and rare earth metals would constitute a catalytic system to miniaturize enzymes with flexible structural dynamics because (i) amide ligands possess reasonable rigidity (amide plane) and conformational flexibility (α-carbon) and (ii) rare earth metals exhibit multiple coordination modes and coordination numbers depending on the peripheral chemical environments.[30]

SCHEME 14. Catalytic Asymmetric Amination of **24** with **26**/La(O-*i*Pr)$_3$ Catalyst



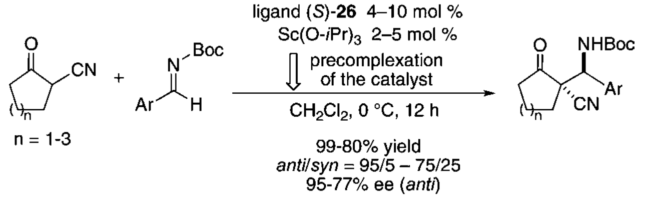
5.2. Catalytic Asymmetric Amination. Our specific focus was directed toward a catalytic asymmetric amination of protecting group-free succinimide **24**, which shows multiple coordination modes and hampers the efficient stereodifferentiation by various asymmetric catalysts reported in the literature. The development of a cost-effective protocol for a highly enantioselective amination of **24** is attractive from both the scientific and therapeutic points of view, because the amination product **25** is key in the asymmetric synthesis of AS-3201 (ranirestat), a highly potent aldose reductase inhibitor under clinical development for the treatment of diabetic complications.[31,32] We focused on a combination of rare earth metal and amide-based ligand bearing phenols, in which a rare earth metal would be surrounded by ligands to avoid unfavorable coordination of **24** due to the highly coordinative nature of amides. We anticipated that the high coordination number of the rare earth metal would allow for the additional coordination of **24** in a specific coordination mode, where hydrogen bonds would work cooperatively to control the coordination mode of **24**. Studies based on this assumption led to the identification of an amide ligand (*R*)-**26**, derived from D-valine in a chromatography-free four-step sequence, as a promising ligand for the asymmetric amination of **24**. Among rare earth metals examined, the catalyst prepared from (*R*)-**26**/La(O-*i*Pr)$_3$ in a 2:1 ratio promoted the amination of **24** to afford **25** in >99% yield and 92% ee (Scheme 14).[32,33] A catalytic amount of *N*,*N*-dimethylacetamide enhanced the reaction rate, likely due to partial fragmentation of catalyst oligomers. The use of La(O-*i*Pr)$_3$, however, is not suitable from a practical standpoint because of the occasional fluctuation of catalytic activity and stereoselectivity depending on the production lot of La(O-*i*Pr)$_3$ as well as its high-price, limited availability, and instability to moisture. In our search for cheap and stable lanthanum salts, we identified La(NO$_3$)$_3$·*x*H$_2$O as meeting our criteria. The second generation catalyst comprising (*R*)-**26**, La(NO$_3$)$_3$·*x*H$_2$O, and D-valine *tert*-butyl ester promoted the amination of **24** in a highly reproducible manner. The reaction was run on 100-g scale with 1 mol % catalyst loading, and the amination product was subjected to acidic removal of the Boc group to afford hydrazine HCl salt **27** in 96% yield (two steps) and 91% ee (Scheme 15).[34] The four-step transformation from **34** gave AS-3201 (ranirestat).[32]

SCHEME 15. Catalytic Asymmetric Amination of **24** with **26**/La(NO$_3$)$_3$/H-D-Val-O-*t*Bu Ternary Complex for Efficient Asymmetric Synthesis of AS-3201

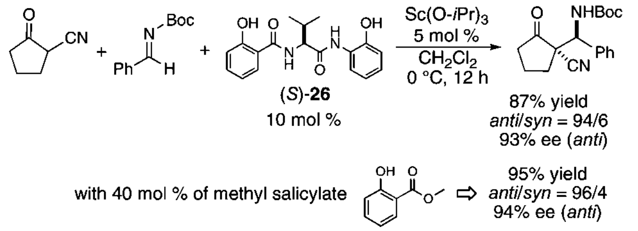


SCHEME 16. *anti*-Selective Mannich-Type Reaction with (*S*)-**26**/Sc Catalyst

(a) Precomplexation of the catalyst



(b) One-shot addition of substrates and catalyst components



5.3. Catalytic Asymmetric Mannich-Type Reaction of α-Cyanoketones. The combination of amide-based ligand (*S*)-**26** and rare earth metal was effective for direct catalytic asymmetric Mannich-type reaction of α-cyanoketones and *N*-Boc imines. The Mannich-type reaction of α-cyanoketones or *β*-ketoesters provides products furnished with a stereogenic quaternary carbon, whose construction via intermolecular asymmetric reaction is still a challenging task in asymmetric catalysis. The catalyst prepared by mixing (*S*)-**26** and Sc(O^{i}Pr)$_3$ in a 2:1 ratio promoted the Mannich-type reaction of α-cyanoketones and *N*-Boc imines in CH$_2$Cl$_2$ at −20 °C, affording *anti*-Mannich product in high yield and enantioselectivity (Scheme 16a).[35] The reported examples of catalytic asymmetric Mannich-type reactions of *β*-ketoesters provide *syn*-Mannich products; thus the reaction with the (*S*)-**33**/Sc catalyst is complementary. Both diastereo- and enantioselectivity were uniformly high at temperatures ranging from −20 to 40 °C, suggesting that the entropic contribution would be predominant in stereoselectivity. ^{1}H NMR of the catalyst mixture is complicated and a nonordered ensemble of the ligand, Sc^{3+}, and substrates is proposed to organize through coordination to Sc^{3+} and hydrogen bonding. The reaction can be conducted by one-shot addition of all the reaction components without any detrimental effects, even in the presence of 40 mol % of dummy phenolic ligand (Scheme 16b).

6. Summary and Outlook

In this Account, we describe recent advances in asymmetric bifunctional asymmetric catalysis using multimetallic systems. These developments illustrate the efficiency of the concept of bifunctional catalysis, rendering otherwise less accessible enantioselective transformations feasible. The use of novel ligands and the recognition of oligomeric complexes leads to new platforms for asymmetric catalysis. The reactions described here include those generating stereogenic tetrasubstituted carbons and quaternary carbons (cyclopropanation of ketones, Mannich-type reaction of nitroacetates, β-keto ester, β-keto phosphonates, and α-cyanoketones, Strecker reaction of ketimines, amination of **31**), which remain challenging tasks in modern organic synthesis. The usefulness of the asymmetric bifunctional catalysis is demonstrated by the efficient enantioselective synthesis of therapeutics (or their candidate molecules) such as Tamiflu, AS-3201 (ranirestat), GRL-06579A, epothilones, fostriecin, and ritodrine. We are currently working to dissect the origin of bifunctional catalysis more in detail through comprehensive mechanistic studies, which will provide more specific guidelines for the rational improvement of catalytic activity and the development of new bifunctional catalyzes.

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BIOGRAPHICAL INFORMATION

Masakatsu Shibasaki received his Ph.D. from the University of Tokyo in 1974 under the direction of the late Professor Shunichi Yamada before doing postdoctoral studies with Professor E. J. Corey at Harvard University. In 1977, he returned to Japan and 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. He has received Fluka Prize (Reagent of the Year, 1996), the Elsevier Award for Inventiveness in Organic Chemistry (1998), the Pharmaceutical Society of Japan Award (1999), ACS Award (Arthur C. Cope Senior Scholar Award) (2002), the National Prize of Purple Ribbon (2003), Japan Academy Prize (2005), the Rare Earth Society of Japan Award (2006), ACS Award for Creative Work in Synthetic Organic Chemistry (2008), Centenary Medal and Lectureship (2008), Prelog Award Medal (2008), and many others. His research interests include asymmetric catalysis and medicinal chemistry of biologically significant compounds.

Motomu Kanai was born in 1967 in Tokyo, Japan, and received his Ph.D. from Osaka University in 1995 under the direction of Professor Kiyoshi Tomioka before doing postdoctoral studies with Professor Laura L. Kiessling at the University of Wisconsin. In 1997, he returned to Japan and joined Professor Shibasaki's group in the University of Tokyo as an assistant professor. He is currently an associate professor in Shibasaki's group. He has received The Pharmaceutical Society of Japan Award for Young Scientists (2001) and Merck-Banyu Lectureship Award (2005). His research interests entail design and synthesis of functional molecules.

Shigeki Matsunaga received his Ph. D. from the University of Tokyo under the direction of Prof. M. Shibasaki. He started his academic career in 2001 as an assistant professor in Prof. Shibasaki's group at the University of Tokyo and was promoted to lecturing professor in 2008. He is the recipient of the Chemical Society of Japan Award for Young Chemists (2006), Thieme Journals Award (2008), Mitsui Chemicals Catalysis Science Award of Encouragement (2009), and others. His current research interests are in the development of new catalytic reactions, including asymmetric catalysis, based on the cooperative functions of multinuclear metal complexes.

Naoya Kumagai was born in 1978 and raised in Ibaraki, Japan. He received his Ph.D. in 2005 from the University of Tokyo under the supervision of Prof. Masakatsu Shibasaki. After pursuing postdoctoral research at Harvard University with Professor Stuart L. Schreiber in 2005−2006, he joined Prof. Shibasaki's group as an assistant professor. His research interests are in the development of new methodology in asymmetric catalysis and its application to bioinspired dynamic processes.

FOOTNOTES

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