

Award Accounts

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Multimetallic Bifunctional Asymmetric Catalysis Based on Proximity Effect Control

Shigeki Matsunaga* **and Masakatsu Shibasaki***

Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033

Received July 18, 2007; E-mail: smatsuna@mol.f.u-tokyo.ac.jp

Design and applications of multimetallic bifunctional asymmetric catalysts based on the proximity-effect-control concept are described. Suitable design of chiral ligands and selection of metals were important to realize cooperative bimetallic catalysis. Homo-multimetallic complexes, using linked-BINOLs (Zn, In, Y, and La), as well as hetero-multimetallic complexes, using a dinucleating Schiff base, BINOL, and pybox (Cu–Sm, La–Li, and Y–Li), were developed for asymmetric direct aldol reactions, Michael reactions, direct Mannich-type reactions, nitro-Mannich-type reaction, *aza*-Michael reactions, kinetic resolution of *tert*-nitroaldols, and cyanation reactions. Synergistic effects of two or more metals played a key role in promoting the reactions in high reactivity and enantioselectivity.

1. Introduction

Syntheses of optically active compounds through catalytic enantioselective reactions are important and rapidly growing areas in modern synthetic organic chemistry.[1] Catalytic asymmetric processes are potentially more economical and more environmentally friendly than processes using stoichiometric amount of chiral reagents. Current challenges in this field focus on the development of enantioselective catalysts with high activity and broad substrate generality. To address this issue, the basic concept of catalyst design is important. Our basic approach is to design an asymmetric multimetallic bifunctional catalysis to realize proximity effect control (Fig. 1a). In principle, chemical reactions involve the formations of bonds between two reacting units. If an asymmetric catalyst with two or more metal centers activates both a nucleophile and an electrophile at the positions defined by the two metal centers (dual activation), access to each substrate is controlled by the asymmetric catalyst and two substrates are fixed nearby in a transition state. Two substrates suitably arranged in an asymmetric environment should react smoothly under mild reaction conditions with high diastereo- and enantioselectivity (proximity effect control). This strategy occurs in nature as illustrated by the proposed transition state model of the class II metal-dependent aldolases (Fig. 1b).[2] The enzyme catalyzes an enantioselective direct aldol reaction between dihydroxyacetone phosphate (DHAP) and broad range of aldehydes under neutral conditions. In the transition state, the glutamate-73 residue functions as a Brønsted base to deprotonate α-proton of DHAP with the aid of Lewis acidic Zn^{2+}. At the same time, the tyrosine-113′ residue functions as a Brønsted acid to activate the aldehydes. Two substrates are thereby activated (dual activation) and fixed in close proximity (proximity effect control). Such dual activation and proximity effect control are essential to promote the reaction under mild conditions with perfect stereoselectivity. Inspired by the reaction mode of the class II aldolases, our group has been investigating bifunctional asymmetric metal catalysis. In this account, selected recent results on the research project in our group will be discussed. Other examples by us and other groups not covered in this account are nicely described in other review articles.[3,4]

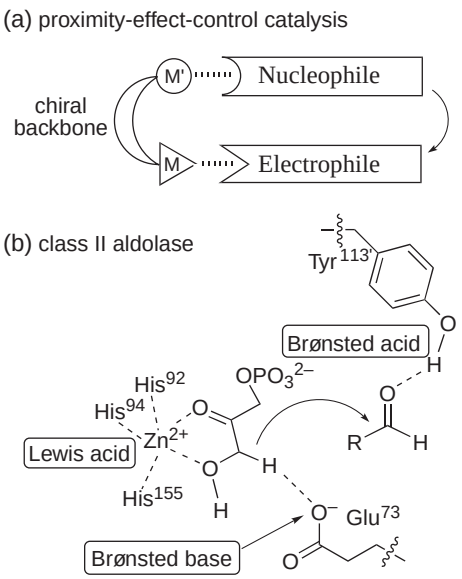

Fig. 1. (a) Multimetallic bifunctional asymmetric catalysis based on proximity-effect-control concept and (b) proposed transition state model of class II aldolase.

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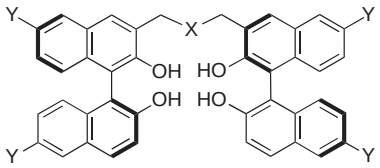


X = O, Y = H: (*S*,*S*)-linked-BINOL **1a**

X = O, Y = -Si(CH_3)$_3$: (*S*,*S*)-TMS-linked-BINOL **1b**

X = S, Y = H: (*S*,*S*)-*Sulfur*-linked-BINOL **1c**

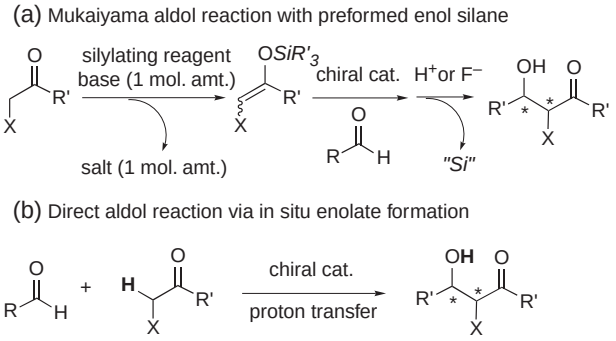
X = NMe, Y = H: (*S*,*S*)-*NMe*-linked-BINOL **1d**

Fig. 2. Structures of (*S*,*S*)-linked-BINOLs (**1a**, **1b**, **1c**, and **1d**).

2. Design and Applications of Linked-BINOL in Homo-Multimetallic Complexes

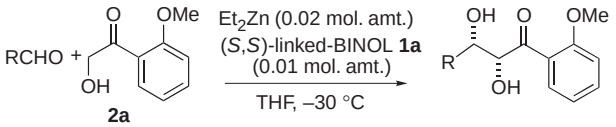
In asymmetric metal catalysis, the design of chiral ligands for metals is important when designing a new reaction and a new catalyst. The activity and selectivity of metals are tuned with the chiral ligands. A delicate balance between the steric and electronic properties of the catalyst determines the reaction efficiency.[5] To establish the concept of multimetallic bifunctional catalysis, we assumed that a multidentate and conformationally flexible chiral ligand would play a key role. We selected axially chiral 1,1′-bi-2-naphthol (BINOL) as a chiral framework, and decided to connect two BINOL units with a flexible linker (linked-BINOL **1**, Fig. 2).[6,7] One of the key issues in designing the linked-BINOL is the length and flexibility of the linker. The linker should be relatively short in order to somewhat limit the flexibility of the BINOL units, because the geometry is crucial for enantioselectivity. On the other hand, the asymmetric environment is adversely affected when the linker is too rigid. After investigating various types of linkers, we found that coordinating heteroatoms in the linker part of linked-BINOLs **1a** and **1b** (O), **1c** (S), and **1d** (N) were important for forming the desired multimetallic complexes. Among linked-BINOLs investigated, linked-BINOL **1a** with an ether linker showed the best performance. In contrast, linkers without coordinating heteroatoms showed poor reactivity and selectivity.

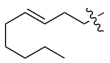
2.1 Et_2Zn/Linked-BINOL Complex for Direct Aldol Reactions. Inspired by the highly atom-efficient reaction mode of the Zn-dependent class II aldolases (Fig. 1), we investigated direct catalytic asymmetric aldol reactions of hydroxyketones using a Et_2Zn/linked-BINOL complex. The basic concept of the direct catalytic asymmetric carbon–carbon bond-forming reactions is summarized in Scheme 1.[8] Diastereo- and enantioselective aldol reactions have been intensively studied by many groups. In Mukaiyama-type aldol reactions, excellent yields and stereoselectivities have been achieved using chiral Lewis acid catalysts;[9] however, the processes require the preconversion of donor substrates into more reactive species, such as enol silyl ethers or ketene silyl acetals, using no less than stoichiometric amounts of silicon reagents and strong bases. From an atom-efficient point of view, the use of stoichiometric amounts of reagents, which afford waste salts, should be excluded from the process. In this regard, the direct catalytic asymmetric aldol reaction, utilizing an unmodified ketones, aldehydes, and carboxylic acid derivatives as nucleophiles, is desirable. Many researchers have directed considerable attention to this field, which is reflected in the rapidly increasing number of publications.[8]



Scheme 1. (a) Mukaiyama aldol reactions with preformed enol silane and (b) direct catalytic asymmetric aldol reaction.

Table 1. Direct Catalytic Asymmetric Aldol Reactions Promoted by Et_2Zn/Linked-BINOL **1a** Complex



Entry	Aldehyde: R	Time /h	Yield/%	dr (*syn*/*anti*)	ee/% (*syn*/*anti*)
1	$PhCH_2CH_2$–	20	94	89:11	92/89
2	*n*-pentyl	18	88	88:12	95/91
3		18	84	84:16	93/87
4		24	94	86:14	87/92
5	$BnOCH_2CH_2$–	18	81	86:14	95/90
6	$BnOCH_2$–	16	84	72:28	96/93
7	*i*Pr	24	83	97:3	98/—
8		16	92	96:4	99/—
9	Cyclohexyl	18	95	97:3	98/—

The aldol reaction of cyclohexanecarboxaldehyde with hydroxyacetophenone gave aldol adduct in 85% ee using 0.1 molar amout linked-BINOL **1a**.[10,11] After optimizations of the reaction conditions, the use of hydroxyketone **2a** improved both the reaction rate and enantioselectivity, giving products in 87–99% ee using various aliphatic aldehydes (Table 1).[12] The reaction proceeded smoothly in the presence of as little as 0.01 molar amount of linked-BINOL **1a** and 0.02 molar amount of Et_2Zn. Methoxyphenyl group was useful as a template for the conversion of aldol adducts into esters and amides via the Baeyer–Villiger oxidation and the Beckmann rearrangement.[12]

The structure of the Et_2Zn/linked-BINOL **1a** complex, which was prepared from 2 molar amount of Et_2Zn and 1 molar amount of linked-BINOL **1a**, was clarified to be a trinuclear Zn_3(linked-BINOL **1a**)$_2$ complex by using ^{1}H NMR, Cold-Spray-Ionization mass spectroscopy (CSI-MS),[13] and X-ray crystallographic analysis (Fig. 3).[14] The Zn_3(linked-BINOL **1a**)$_2$ complex formed even in the presence of a slightly

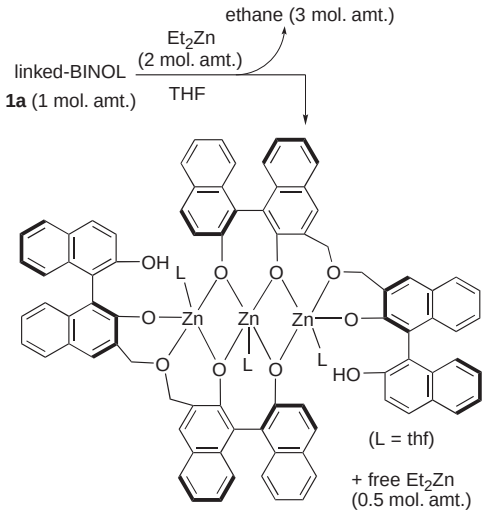


Fig. 3. Structure of trinuclear Zn_3(linked-BINOL **1a**)$_2$(thf)$_3$ determined by X-ray crystal analysis.

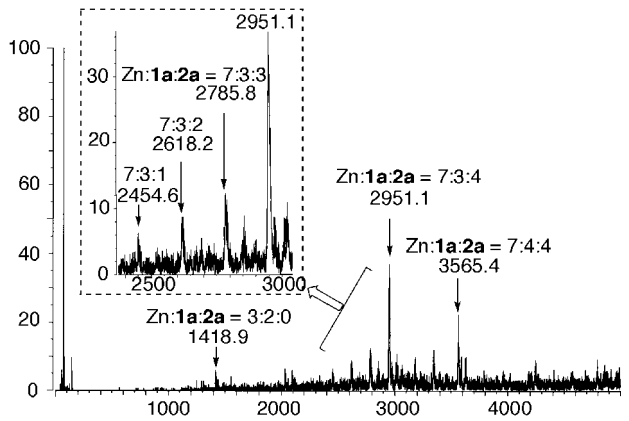
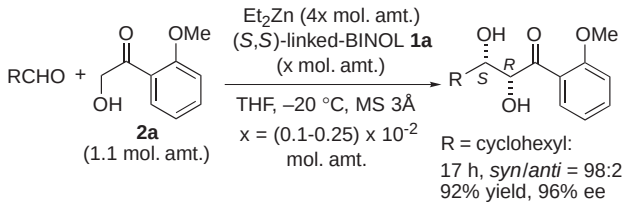


Fig. 4. CSI-MS analysis of Et_2Zn/linked-BINOL **1a** complex in the presence of excess hydroxyketone **2a**.

excess of Et_2Zn. Ethane gas emission measurement also supported that 0.5 molar amount of Et_2Zn remained in the Et_2Zn/linked-BINOL **1a** = 2:1 solution. In the crystal structure, the ether oxygen of the linker in the linked-BINOL coordinates to zinc and has crucial role in the construction of the Zn_3(linked-BINOL **1a**)$_2$ complex. Investigations on the reaction profiles of the aldol reaction using in situ generated catalyst and the isolated Zn_3(linked-BINOL **1a**)$_2$ crystal revealed that remaining 0.5 molar amount of Et_2Zn had beneficial effects on the reaction rate. Kinetic studies suggested that the addition of an excess amount of Et_2Zn accelerates the rate-determining product dissociation step. CSI-MS analysis in the presence of hydroxyketone **2a** suggested that the active species would be an oligomeric heptanuclear Zn/linked-BINOL **1a**/hydroxyketone **2a** complex (Fig. 4). On the basis of mechanistic studies, the reaction conditions were further optimized, and Et_2Zn/linked-BINOL **1a** in a 4:1 ratio in the presence of MS 3 Å gave the best results. Addition of 4 molar amount of Et_2Zn to linked-BINOL **1a** improved the reactivity without loss of enantioselectivity. The aldol reaction proceeded with $(0.1–0.25) \times 10^{-2}$ molar amount of linked-BINOL **1a** using 1.1 molar amount of hydroxyketone **3a** under the optimized



Scheme 2. Direct aldol reactions under modified conditions: Et_2Zn/linked-BINOL **1a** = 4/1 with MS 3 Å.

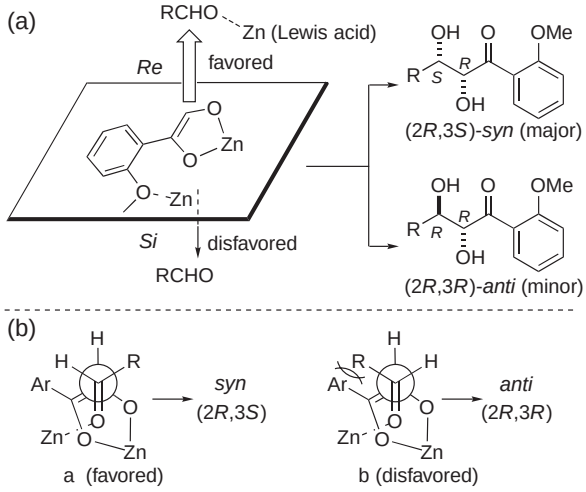


Fig. 5. (a) Relative and absolute configurations of aldol adducts and (b) postulated transition state model.

conditions (Scheme 2).[14]

Absolute and relative configuration of aldol adducts provided useful information on the mechanism of the present aldol reaction. Absolute configurations of products at the α-position of the carbonyl group were identical (2*R*) in both *syn*- and *anti*-aldol adducts. Both *syn*- and *anti*-isomers were obtained in similarly high ee (>87% ee), suggesting that the present catalyst nicely differentiates the enantioface of the zinc–enolate and that aldehydes, activated by Lewis acidic other Zn center, come from the *Re*-face of the zinc–enolate (Fig. 5). In the reaction, we assume that multi-Zn centers function cooperatively to promote the aldol reaction with high selectivity and reactivity (proximity effect control). Negative control experiments using BINOL as a ligand gave poor reactivity and enantioselectivity, possibly because the structure of the zinc complex was different due to the lack of the ether linker. The results implied that properly aligned multi-Zn centers in linked-BINOL **1a** complex are important. The postulated catalytic cycle for the direct aldol reaction is shown in Fig. 6. In the aldol reaction, the zinc complex functions as a bifunctional catalyst. In the presence of hydroxyketone **2a**, the putative oligomeric active complex (I) would be generated, as observed by CSI-MS analysis. Zn–OAr* (Ar*OH = linked-BINOL **1a**) moiety functions as a Brønsted base to deprotonate the α-proton in hydroxyketone **2a** to form zinc-enolate (II). Aldehyde comes from the *Re*-face of the enolate selectively to be activated by the Lewis acidic zinc center, and 1,2-addition occurs (IV). Protonation with the phenolic proton of linked-BINOL **1a** (Ar*OH), followed by ligand exchange with hydroxyketone **2a**, regenerate the catalyst (I).

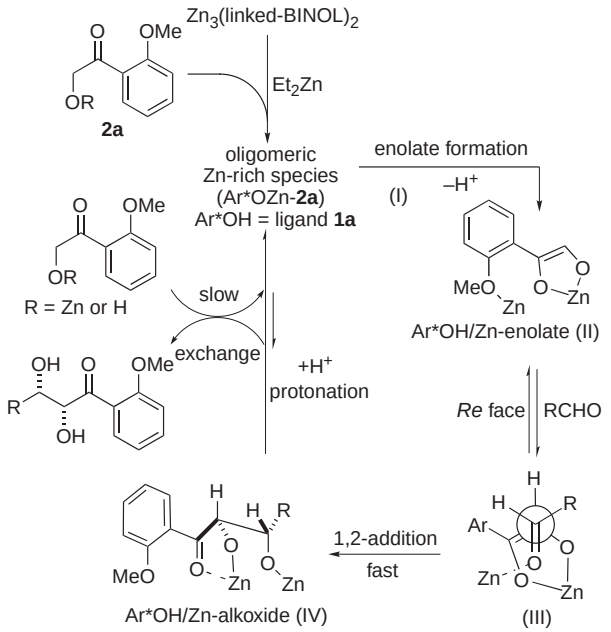
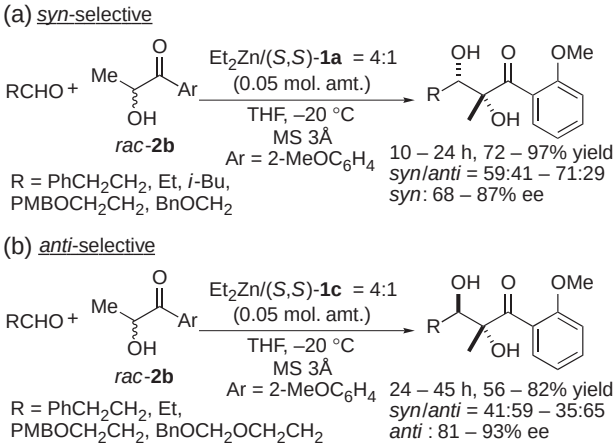


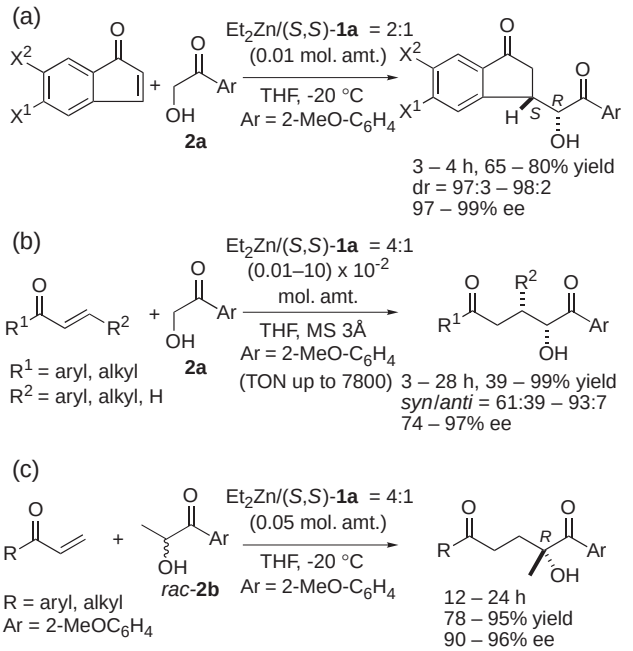
Fig. 6. Proposed catalytic cycle of the Zn-catalyzed direct aldol reaction.



Scheme 3. Construction of tetrasubstituted carbon stereocenter by direct catalytic asymmetric aldol reactions with hydroxyketone **2b**.

Catalytic asymmetric construction of a chiral tetrasubstituted carbon stereocenter is one of the most important topics in recent synthetic organic chemistry.[15] We envisioned that the present asymmetric zinc catalysis would also differentiate the enantioface of tetrasubstituted enolate derived from 2-hydroxy-2′-methoxypropiophenone (**2b**, Scheme 3). The aldol reaction of **2b** would then afford products with a chiral tetrasubstituted carbon stereocenter. With 0.05 molar amount of linked-BINOL **1a**, the reaction proceeded *syn*-selectively in modest to good ee, although the *syn*/*anti* ratio was moderate (Scheme 3a). By changing the linker heteroatom of linked-BINOL from oxygen to sulfur (Sulfur-linked-BINOL **1c**, Fig. 2), the reaction proceeded *anti*-selectively in 81–93% ee (Scheme 3b).[14]

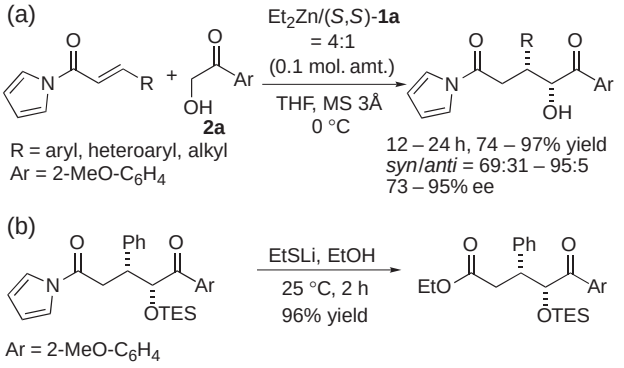
2.2 Et_2Zn/Linked-BINOL Complex for Direct Michael Reactions. We thought that an efficient enantioface selection



Scheme 4. Zn-catalyzed direct catalytic asymmetric Michael reactions of hydroxyketones **2a** and **2b**.

of the zinc–enolate would be applicable to other electrophiles, such as enones and imines. Michael adducts are chiral 2-hydroxy-1,5-dicarbonyl compounds. As shown in Scheme 4, Michael reaction[16] of hydroxyketone **2a** to indenones proceeded smoothly to afford Michael adducts in 97–99% ee (Scheme 4a).[17] The reaction proceeded with only a little, if any, polymerization of vinyl ketones (Scheme 4b, $R^2 = H$), suggesting a high chemoselectivity of the zinc catalyst to activate hydroxyketone **2a**. Under the optimized reaction conditions, using the Et_2Zn/linked-BINOL **1a** = 4:1 with MS 3 Å system, the catalyst loading was reduced to 0.01×10^{-2} molar amount. The Et_2Zn/linked-BINOL **1a** = 4:1 with MS 3 Å system was also effective for β-substituted enones, and the Michael adducts were obtained *syn*-selectively in good yield and ee (Scheme 4b, 74–97% ee). Cyclic enones were less reactive and 0.1 molar amount of linked-BINOL **1a** was required. Hydroxyketone **2b** was also effective for the reaction of vinyl ketones, affording Michael adducts with tetrasubstituted carbon stereocenter in 90–96% ee (Scheme 4c).[18]

To broaden the substrate scope to carboxylic acid derivatives, we used *N*-(α,β-unsaturated acyl)pyrrole (Scheme 5) as a monodentate and activated ester surrogate.[19,20] Because the lone pair on the nitrogen in the pyrrole ring is delocalized in an aromatic system, the reactivity of *N*-(α,β-unsaturated acyl)pyrrole is expected to be similar to those of the enones. Because the coordination mode of the *N*-acylpyrrole is similar to that of an aromatic ketone, the chiral environment optimized for enones should be applicable for *N*-acylpyrrole. The reactivity of *N*-(α,β-unsaturated acyl)pyrroles was slightly lower than enones, and the reaction was performed at 0 °C, affording products in good *syn*-selectivity and enantioselectivity (Scheme 5a). The *N*-acylpyrrole moiety of product was readily converted into ester by treatment with EtSLi in EtOH at 25 °C for 2 h (Scheme 5b).



Scheme 5. Utility of *N*-(α,β-unsaturated acyl)pyrrole as an ester surrogate in Michael reaction.

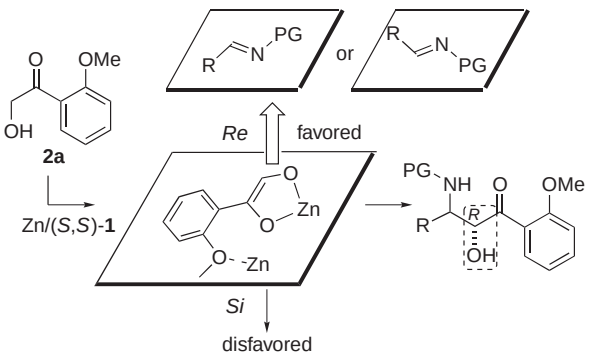
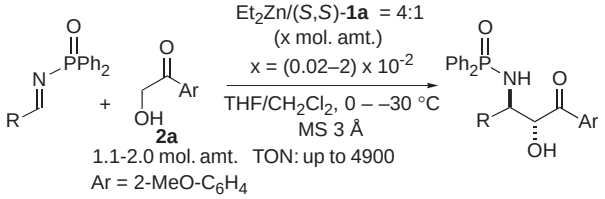


Fig. 7. Strategy to synthesize either *syn*- or *anti*-β-amino alcohols via Zn-catalyzed direct catalytic asymmetric Mannich-type reactions.

2.3 Et_2Zn/Linked-BINOL Complex for Direct Mannich-Type Reactions. Chiral β-amino alcohols are useful chiral building blocks found in various natural products, compounds with pharmacologically important activity, chiral auxiliaries, and chiral ligands.[21] Face selection of imines is important for achieving high diastereoselectivity. We hypothesized that either *anti*- or *syn*-β-amino-α-hydroxy ketones (Mannich adducts)[22,23] would be selectively obtained by choosing the proper protective group of imines that favor the *Si*-face or *Re*-face approach toward the zinc-enolate, respectively (Fig. 7).

N-Diphenylphosphinoyl-imines (Dpp-imine)[24] afforded *anti*-β-amino alcohols in high selectivity (Table 2).[25,26] When using various aryl and heteroaryl imines (Entries 1–12), the reaction completed within 24 h using 0.01 molar amount of linked-BINOL **1a**, giving products with high *anti*-selectivity (dr: 94:6– >98:2) and enantioselectivity (97– >99% ee). Catalyst loading was successfully reduced to 0.02×10^{-2} molar amount (TON = up to 4900, Entry 4). Imines from α,β-unsaturated aldehyde and enolizable aliphatic aldehyde showed less satisfactory diastereoselectivity (Entries 13–15).[27] On the other hand, the reaction proceeded *syn*-selectively with Boc-imines (Table 3).[28] *syn*-Adducts were obtained in good yield (67– >99%), diastereomeric ratio (*syn*/*anti* = 72:28–95:5), and enantioselectivity (89– >99% ee) using aryl and heteroaryl imines (Entries 1–14). Diastereoselectivity of alkenyl imine was, however, poor (Entry 15). With Boc-imines, reaction generally proceeded smoothly with 0.01–0.05 molar amount of linked-BINOL **1a**. Under optimized conditions, catalyst loading was successfully reduced to 0.05×10^{-2} molar amount (TON = up to 1760, Entry 3).

Table 2. *anti*-Selective Direct Catalytic Asymmetric Mannich-Type Reaction of Hydroxyketone **2a** and Dpp-Imines



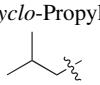
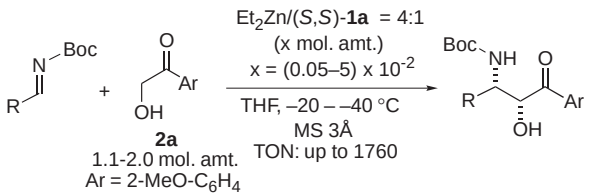
Entry	R	Cat loading (x mol amt.)	Time /h	Yield /%	dr (*anti*/*syn*)	ee/% (*anti*)
1	4-MeC_6H_4	1×10^{-2}	9	98	96:4	98
2	2-MeC_6H_4	1×10^{-2}	6	99	>98:2	99
3	2-MeC_6H_4	0.1×10^{-2}	6	95	96:4	99
4	2-MeC_6H_4	0.02×10^{-2}	24	98	98:2	97
5	Ph	1×10^{-2}	6	98	96:4	99
6	4-$MeOC_6H_4$	1×10^{-2}	6	97	95:5	99
7	4-$NO_2C_6H_4$	1×10^{-2}	9	96	97:3	98
8	4-ClC_6H_4	1×10^{-2}	4	97	97:3	98
9	4-BrC_6H_4	1×10^{-2}	4	97	95:5	98
10	1-Naphthyl	1×10^{-2}	6	97	98:2	>99
11	2-Naphthyl	1×10^{-2}	7	95	94:6	99
12	2-Furyl	1×10^{-2}	7	98	96:4	>99
13	(*E*)-Cinnamyl	1×10^{-2}	7	97	81:19	>99
14	*cyclo*-Propyl	1×10^{-2}	5	98	80:20	99
15		2×10^{-2}	24	92	82:18	96

Table 3. *syn*-Selective Direct Catalytic Asymmetric Mannich-Type Reaction of Hydroxyketone **2a** and Boc-Imines



Entry	R	Cat loading (x mol amt.)	Time /h	Yield /%	dr (*syn*/*anti*)	ee/% (*syn*)
1	Ph	5×10^{-2}	19	94	88:12	99
2	Ph	0.1×10^{-2}	15	90	83:17	99
3	Ph	0.05×10^{-2}	48	88	84:15	98
4	4-$MeOC_6H_4$	5×10^{-2}	25	>99	85:15	99
5	4-$MeOC_6H_4$	1×10^{-2}	51	91	85:15	99
6	4-MeC_6H_4	5×10^{-2}	20	>99	87:13	>99
7	3-MeC_6H_4	5×10^{-2}	20	80	83:17	99
8	2-MeC_6H_4	5×10^{-2}	21	87	93:7	>99
9	4-ClC_6H_4	5×10^{-2}	27	82	83:17	98
10	1-Naphthyl	5×10^{-2}	27	85	95:5	99
11	2-Naphthyl	5×10^{-2}	26	80	85:15	99
12	2-Furyl	5×10^{-2}	26	>99	82:18	>99
13	2-Thiophenyl	5×10^{-2}	21	>99	86:14	99
14	3-Pyridyl	5×10^{-2}	21	67	72:28	89
15	(*E*)-Cinnamyl	5×10^{-2}	30	81	63:37	99

2.4 Design of Non-C_2-Symmetric Linked-BINOL. As

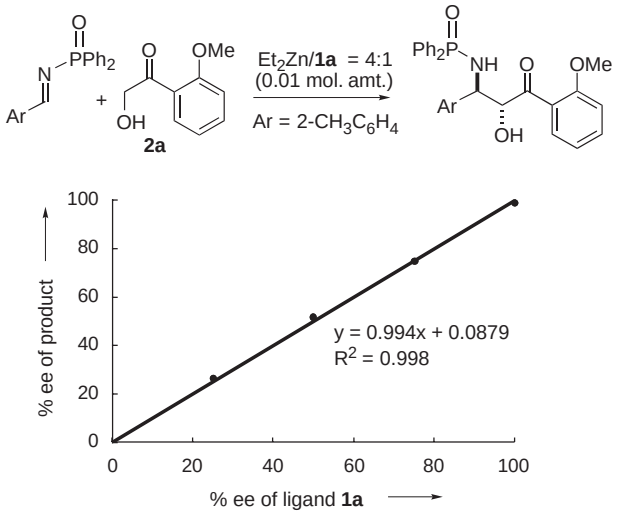


Fig. 8. Linear relationship between Mannich-adduct and linked-BINOL **1a** observed in direct Mannich-type reaction.

mentioned in the introduction, a delicate balance between the steric and electronic properties of the catalyst determines the reaction efficiency. Thus, a chiral ligand with a readily tunable framework is desirable for applications in a variety of reactions. The structure of Zn_3(linked-BINOL)$_2$ complex in Fig. 3 suggested that 1) C_2-symmetry of linked-BINOL **1a** is not important, and 2) one of the phenolic OH groups would not be required for zinc complex. Mechanistic studies suggested that the active species of the Zn catalysis is not a monomeric species; however, there was a linear relationship between the enantiomeric excess of Mannich adduct and linked-BINOL **1a** used in the Mannich-type reaction of Dpp-imine and hydroxyketone **2a** (Fig. 8), suggesting that 3) a homo-chiral complex is more favorable than a hetero-chiral complex. We hypothesized that one of the chiral binaphthol units in linked-BINOL **1a** can be replaced with an achiral unit such as *atropisomeric*-biphenol or achiral phenol derivatives. Chirality would be transferred to the flexible achiral unit upon complexation with zinc metals and a similar chiral environment would be obtained with a chirally economical ligand.[29]

The structures of the evaluated ligands (**3a–3f**) are summarized in Fig. 9. The potentials of the ligands were evaluated in a direct catalytic asymmetric Mannich-type reaction of Dpp-imine and hydroxyketone **2a** using 0.05 molar amount of ligand **1a** or **3** and 0.20 molar amount of Et_2Zn at $-20\,^{\circ}C$. With the original linked-BINOL **1a**, the reaction completed within 1 h, and Mannich-adduct was obtained in 99% yield, *anti*/*syn* = 98:2, and >99% ee. A control experiment with 0.10 molar amount of simple BINOL had a much lower reaction rate and enantiomeric excess (68 h, 24% ee). Ligand **3a**, which lacks one phenolic OH group, gave results similar to those obtained with **1a**. Ligand **3b** with an *atropisomeric*-biphenol unit was also efficient, suggesting that the chirality of the biphenol unit was controlled by complexation with zinc metals. Even an achiral unit like **3c** gave excellent results (1 h, 99% yield, 99% ee), whereas ligand **3d**, which has a phenolic-OH group in the 2′-position, exhibited a poor reaction rate and poor enantioselectivity (23 h, 74% yield, 9% ee). Ligand **3e**

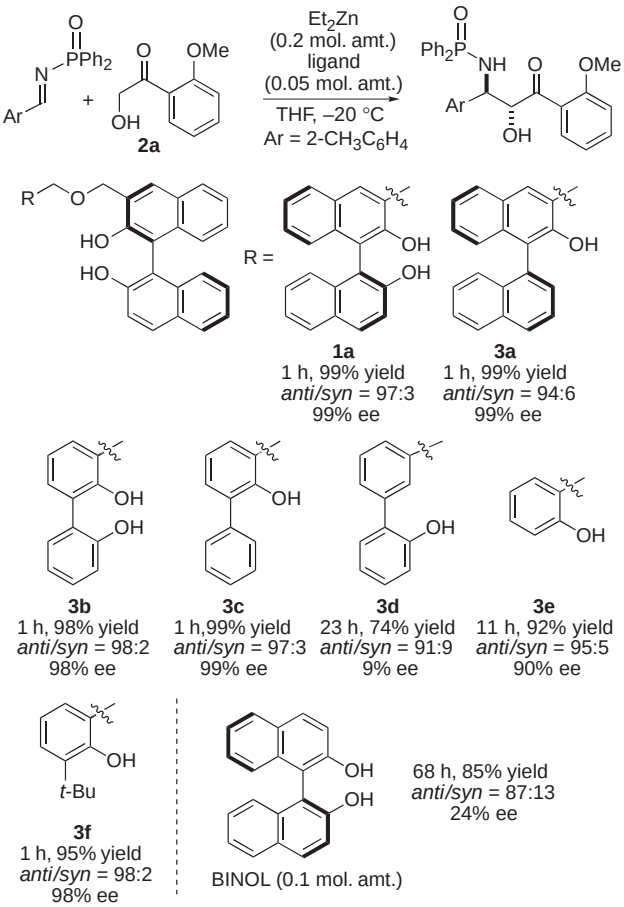
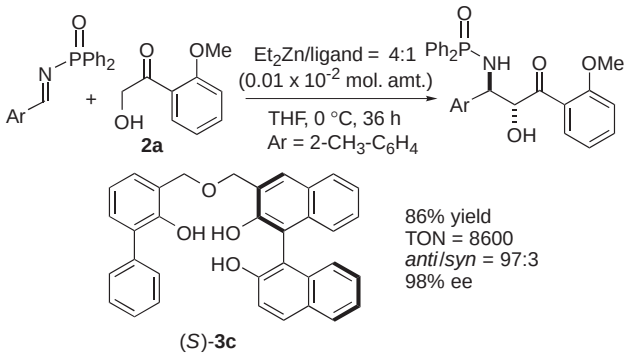


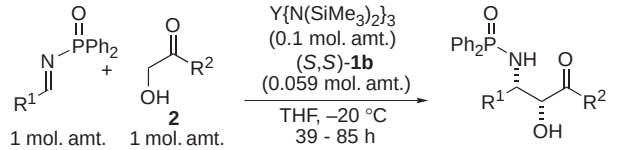
Fig. 9. Structures of non-C_2-symmetric linked-BINOL derivatives **3a–3f** and their applications in Mannich-type reaction.



Scheme 6. Trials to reduce catalyst loading using linked-BINOL derivative **3c**.

also produced an unsatisfactory reaction rate and only modest enantioselectivity, whereas ligand **3f** gave satisfactory results. The results implied that both the phenolic-OH group at the proper position and a substituent on the aromatic ring are required. Reaction profiles with each ligand were monitored carefully, and ligands with achiral units had a better reaction rate than the original linked-BINOL **1a** with two chiral units. Furthermore, with ligand **3c**, catalyst loading was successfully reduced to as little as 0.01×10^{-2} molar amount (TON = 8600, Scheme 6).[30]

Table 4. Y-Catalyzed Direct Asymmetric Mannich-Type Reactions of Various Hydroxyketones **2**

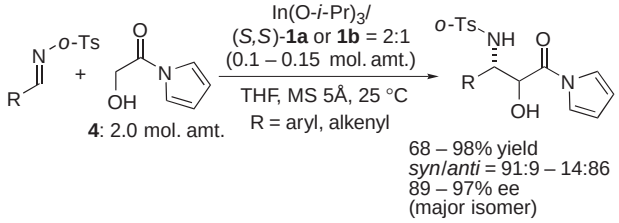


Entry	Imine: R^1	Ketone **2**: R^2	Yield /%	*syn*/*anti*	ee /%
1	Ph	4-MeO–C_6H_4–	89	91:9	98
2	Ph	4-Me–C_6H_4–	91	91:9	96
3	Ph	4-Cl–C_6H_4–	94	81:19	86
4	Ph	2-Furyl	94	94:6	93
5	Ph	2-Thienyl	95	95:5	92
6	4-Cl–C_6H_4–	Ph	78	94:6	95
7	4-MeO–C_6H_4–	Ph	90	95:5	94
8	2-Furyl	Ph	93	95:5	96
9	2-Thienyl	Ph	95	96:4	97
10	PhCH=CH–	Ph	87	96:4	95
11	4-Cl–C_6H_4–CH=CH–	Ph	94	95:5	93
12	4-Me–C_6H_4CH=CH–	Ph	92	93:7	91
13	2-FurylCH=CH–	Ph	89	96:4	94

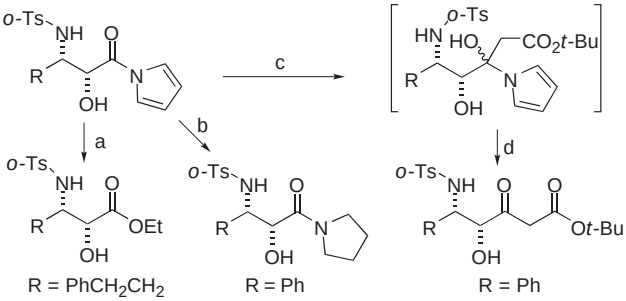
2.5 Y{N(SiMe$_3$)$_2$}$_3$/Linked-BINOL Complex for Direct Mannich-Type Reactions. Although high catalyst turnover number and high ee were achieved in Mannich-type reaction using the Et_2Zn/linked-BINOL **1a** complex, a few problems remained: 1) Modest *syn*-selectivity with Boc-imine; diastereoselectivity strongly depended on the imines used. Especially, α,β-unsaturated imines gave poor *syn*-selectivity (Table 3, Entry 15). 2) Use of the nucleophile hydroxyketone **2a** was essential to achieve good selectivity, i.e., there was no nucleophile generality. To overcome the drawbacks, we investigated other metal sources in combination with the linked-BINOLs for the Mannich-type reaction.

In contrast to our initial assumption, the reaction of Dpp-imine proceeded *syn*-selectively with rare earth metal/linked-BINOL complexes. After screening and optimizations, the best diastereo- and enantioselectivity were obtained with a Y{N(SiMe$_3$)$_2$}$_3$/linked-BINOL **1a** = 1.7:1 complex. Rare earth metal alkoxides were not suitable for the present Mannich-type reaction. Modification at the 6,6′,6″,6‴-positions of the linked-BINOL further improved stereoselectivity, and TMS-linked-BINOL **1b** (Fig. 2) gave the best results. Reaction proceeded smoothly with an equimolar amount of the nucleophile. The Y{N(SiMe$_3$)$_2$}$_3$/TMS-linked-BINOL **1b** = 1.7:1 complex was applicable to various aryl and heteroaryl hydroxyketones **2** as well as various aryl, heteroaryl, and alkenyl imines. High ee and high *syn*-selectivity were achieved (Table 4).[31]

2.6 In(O-*i*Pr)$_3$/Linked-BINOL Complex for Direct Mannich-Type Reactions. The Et_2Zn and Y{N(SiMe$_3$)$_2$}$_3$/linked-BINOL complexes afforded various β-amino-α-hydroxyketones in high enantio- and diastereoselectivity using hydroxyketones as donors. On the other hand, the use of donor substrates with the oxidation state of carboxylic acid is still a formidable task due to the much higher pK_a value of the α-proton in carboxylic acid derivatives than that in ketones. Catalytic in situ generation of enolate from carboxylic acid derivatives is much more difficult than that from ketones. The development of a suitably activated ester equivalent donor and/or a new asymmetric catalyst are required to realize direct carbon–carbon bond-forming reactions using ester equivalent donors.[32] As a donor substrate for investigation, we selected *N*-acylpyrrole as an achiral template.[20,33] We supposed that *N*-acylpyrrole would be useful as an ester equivalent donor, because the aromaticity should assist enolate formation.



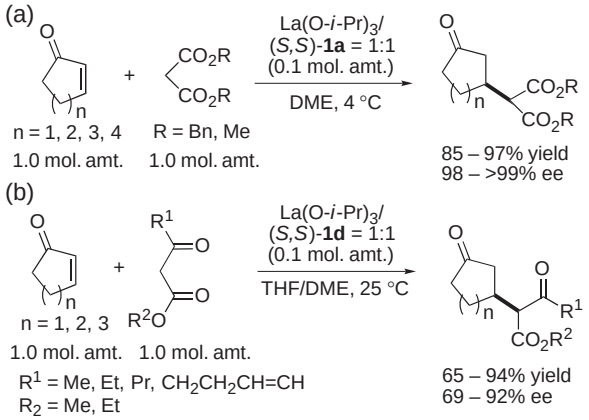
Scheme 7. In-catalyzed direct Mannich-type reactions using *N*-acylpyrrole as an ester equivalent donor.



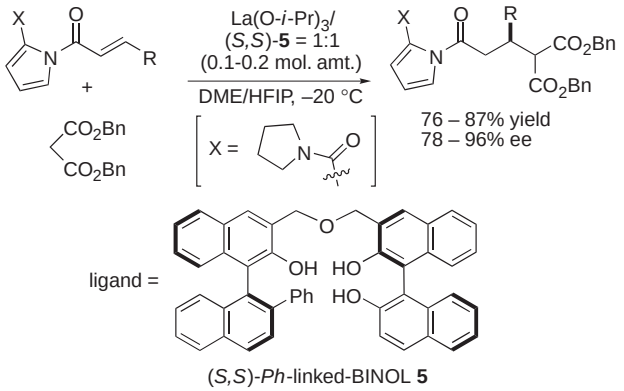
Scheme 8. Transformations of *N*-acylpyrrole moiety: Reagents and Conditions: a) NaOEt, EtOH, 0 °C to room temperature, 5 min, y. quant.; b) pyrrolidine, DBU, THF, 40 °C, 1 h, y. quant.; c) LDA, *t*-Bu-acetate, THF, −78 °C, 10 min; d) DBU, CH_2Cl_2, room temperature, 5 min, y. 62% (2 steps).

The Et_2Zn/linked-BINOL complex promoted the reaction of *N*-acylpyrrole **4** with Ts-imine only in poor yield. Neither Zn nor rare earth metals were suitable for efficiently generating a metal enolate from *N*-acylpyrrole **4**. After optimization, we found that the reaction proceeded in a catalytic manner by using an In(O-*i*Pr)$_3$/linked-BINOL **1a** or **1b** complex. The Mannich-type reaction of α,β-unsaturated imines proceeded *syn*-selectively in good yield and ee (Scheme 7).[33] With aromatic imines, diastereoselectivity was modest. *N*-Acylpyrrole unit in Mannich adduct was readily transformed into various functional groups, such as ester (quant. yield), amide (quant. yield), and β-keto ester (Scheme 8).

2.7 La(O-*i*Pr)$_3$/Linked-BINOL Complex for Michael Reaction of Malonates. We have previously reported that a La(O-*i*Pr)$_3$/BINOL = 1:1 complex promoted the Michael reaction of malonates with cyclic enones in up to 95% ee.[34] With the linked-BINOL **1a** as a ligand, Michael adducts were obtained in much higher ee (>99% ee) using 5–8 membered ring cyclic enones (Scheme 9a).[35] In the Michael reaction, the La–OAr moiety functions as a Brønsted base to generate a lanthanum–enolate. La also acts as a Lewis acid to activate enones. The La(O-*i*Pr)$_3$/linked-BINOL **1a** = 1:1 complex was stable under air at room temperature, and was storable as a powder for at least four weeks without loss of reactivity



Scheme 9. Catalytic asymmetric Michael reactions of malonates and β-keto esters using La(O-*i*Pr)$_3$/linked-BINOL complexes.



Scheme 10. Catalytic asymmetric Michael reactions of a malonate and *N*-(α,β-unsaturated acyl)pyrrole using La(O-*i*Pr)$_3$/Ph-linked-BINOL **5** complex.

and enantioselectivity. In the Michael reaction, a heterobimetallic La(O-*i*Pr)$_3$/Et$_2$Zn/linked-BINOL was also effective, affording Michael adducts in up to 96% ee.[35c] For the Michael reaction of β-keto esters, NMe-linked-BINOL **1d** (Fig. 2) was more effective than linked-BINOL **1a** (Scheme 9b).[36] For acyclic carboxylic acid derivatives, C_2-symmetric linked-BINOLs **1** were not effective. Non-C_2-symmetric Ph-linked-BINOL **5** with additional steric bulkiness around La metal center was effective.[37] The Michael reaction of dibenzyl malonate to 2′-amide-substituted α,β-unsaturated *N*-acylpyrroles proceeded in up to 96% ee (Scheme 10).[38]

3. Design and Application of Heterobimetallic Complexes

In the previous section, homo-multimetallic Zn, Y, In, and La catalysts prepared from multidentate linked-BINOLs were introduced. For constructing diverse chiral environments and achieving diverse reactivity, the combination of two or more different metals is more attractive than the use of a homo-multimetallic system. On the other hand, catalyst design is crucial to utilize two or more distinct metals with different properties in a cooperative manner. In this section, our recent efforts to design and apply heterobimetallic catalysis will be introduced.

3.1 La(OAr)$_3$/Pybox + LiOAr Mixed Catalyst for Direct Mannich-Type Reactions.

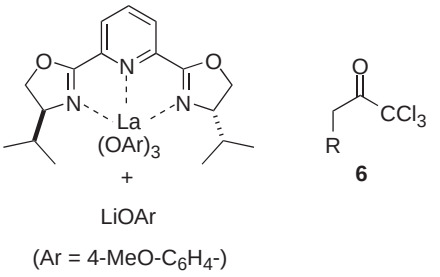
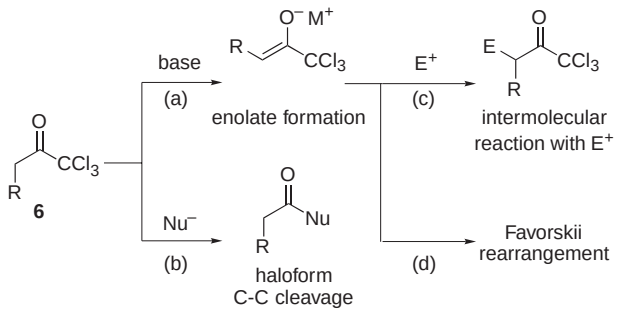


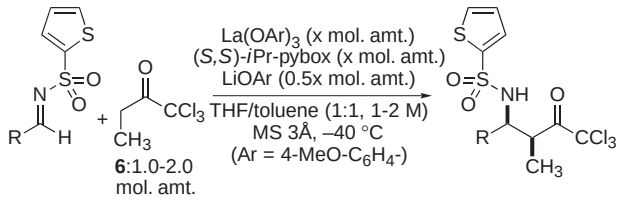
Fig. 10. Structures of La(OAr)$_3$/*i*Pr-pybox + LiOAr (Ar = 4-MeO–C_6H_4–) complex and trichloromethyl ketones **6**.



Scheme 11. Possible reaction pathways of trichloromethyl ketones under basic conditions.

Initially, we investigated various metal/linked-BINOL complexes[44] for trichloromethyl ketones; however, all of them resulted in poor enantioselectivity (<10% ee). Therefore, we screened various Lewis acid–chiral ligand–Brønsted base combinations to activate both **6** and the imine. High diastereoselectivity and enantioselectivy were realized by using La(OAr)$_3$/*i*Pr-pybox + LiOAr (Ar = 4-MeO–C_6H_4–) system and *N*-thienylsulfonyl imine[45] (Table 5).[46] Various non-enolizable aryl, heteroaryl, and alkenyl imines afforded products in good yield and selectivity (Entries 1–9). The product was obtained in good yield even with reduced amounts of **6** (Entries 2 and 3). It is noteworthy that isomerizable aliphatic imines were

Table 5. Direct Catalytic Asymmetric Mannich-Type Reaction of Aryl, Heteroaryl, Alkenyl, and Alkyl Imines with Trichloromethyl Ketones[a)]



Entry	Imine: R	La/pybox (x mol amt.)	Time /h	Yield /%	dr (*syn*/*anti*)	ee/% (*syn*)
1	Ph	0.10	9	96	21:1	96
2[b)]	Ph	0.10	24	96	18:1	95
3[c)]	Ph	0.10	36	90	17:1	94
4	*p*-Cl–C_6H_4–	0.10	20	97	20:1	96
5	*p*-Me–C_6H_4–	0.10	20	>99	25:1	96
6	*p*-MeO–C_6H_4–	0.10	21	96	22:1	95
7	2-Furyl	0.10	4	98	8:1	96
8	2-Thienyl	0.10	19	98	20:1	95
9	(*E*)-PhCH=CH–	0.10	19	75	21:1	96
10	Cyclohexyl	0.10	22	85	>30:1	96
11[d)]	*i*Bu	0.10	25	72	30:1	98
12	Ph	0.050	14	96	30:1	95
13	2-Thienyl	0.050	29	93	17:1	92
14	Ph	0.025	16	98	18:1	96

a) Reaction was run using 2.0 mol. amt. of **6**, La(OAr)$_3$/*i*Pr-pybox/LiOAr in a 1:1:0.5 ratio, unless otherwise noted. b) 1.2 mol. amt. of **6** was used. c) 1.0 mol. amt. of **6** was used. d) Reaction was run in the absence of LiOAr.

also usable (Entries 10 and 11). Catalyst loading was successfully reduced to 0.050 and 0.025 molar amounts (Entries 12–14). La(OAr)$_3$/*i*Pr-pybox alone also promoted the reaction in high stereoselectivity, albeit at a lower reaction rate. In contrast, La(OTf)$_3$/*i*Pr-pybox[47,48] alone resulted in no reaction, suggesting the importance of La–OAr moiety as a Brønsted base[49] in the reaction to generate La–enolate in situ. We assumed that the La(OAr)$_3$/*i*Pr-pybox + LiOAr system works as a Lewis acid–Brønsted base catalyst. Kinetic studies suggested that LiOAr accelerates the rate-determining enolate formation step. Hypothetical role of LiOAr is shown in Fig. 11. We assumed that LiOAr would interact with the La(OAr)$_3$/*i*Pr-pybox complex to generate a more Brønsted-basic heterobimetallic complex, accelerating the deprotonation of trichloromethyl ketone **6**. Further mechanistic studies to clarify the precise role of LiOAr are ongoing. The utility of the trichloromethyl ketone template was demonstrated by transformations in Scheme 12, in which the Mannich adduct was converted into ester and dithiane in good yield. Either *syn*- or *anti*-trichloromethyl carbinol, a unique building block, was also selectively obtained.[50]

3.2 Cu–Sm-Dinuclear Schiff Base Complex for Nitro-Mannich-Type Reactions. For the design of heterobimetallic complexes, the design of a suitable multidentate ligand is important to control the position of two different metals in the complex. Position of two metals should have strong effects on the reactivity as well as stereoselectivity of the heterobimetallic complex. We have recently found the utility of dinucleating Schiff base **7** (Scheme 13)[51–53] to achieve cooperative

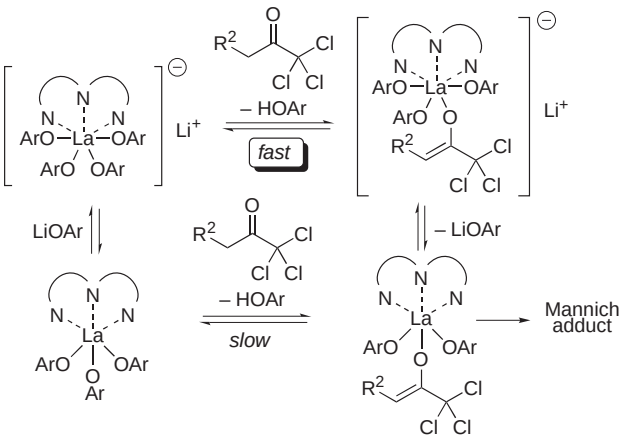
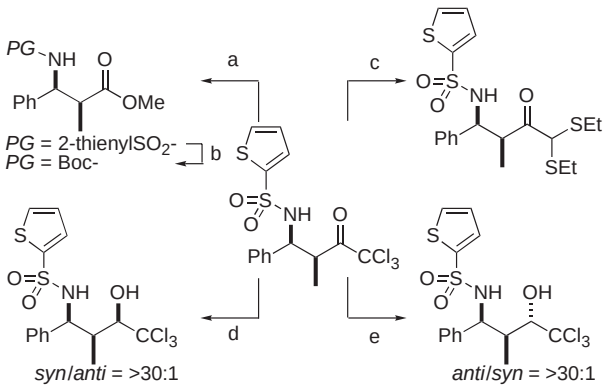


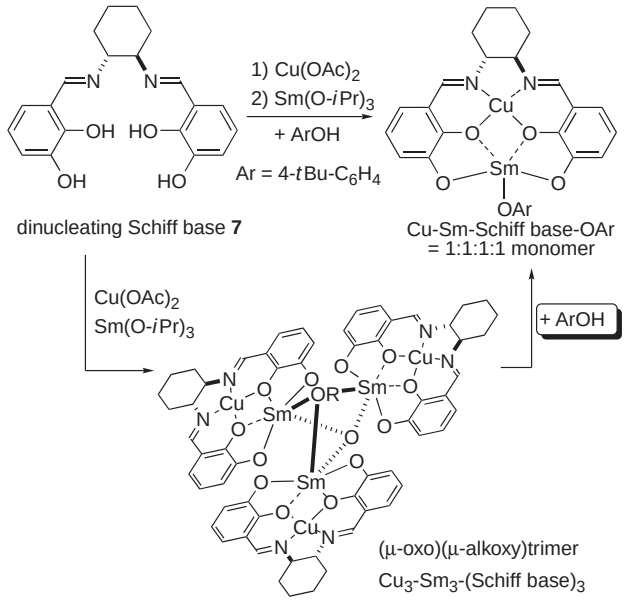
Fig. 11. Hypothetical role of LiOAr to accelerate the La-enolate-forming step.



Scheme 12. Transformation of the Mannich adduct. Reagents and conditions: a) NaOMe, MeOH, 0 °C, 20 min, quant; b) i) Boc_2O, DMAP, CH_3CN, rt, 98%; ii) Mg, MeOH, rt, 95%; c) EtSH, BuLi, THF, 0 °C, 30 min, 79%; d) DIBAL, CH_2Cl_2, −78 to −40 °C, 7.5 h, quant, *syn*/*anti* = >30:1; e) DIBAL/$Ph_3P(O)$ (1:2), THF, −78 to −40 °C, 2 h, 99%, *anti*/*syn* = >30:1.

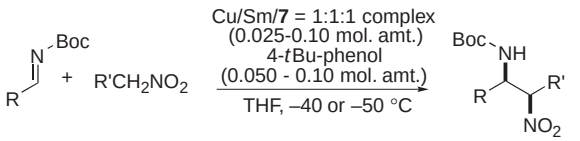
catalysis of transition metal/rare earth metal combination. Schiff base **7** is speculated to incorporate transition metals in the N_2O_2 inner cavity and rare earth metals with large ionic radius in the O_2O_2 outer cavity.

The suitable selection of the two metals utilized was crucial to achieve good reactivity and selectivity. The Cu–Sm–Schiff base complex prepared from Cu(OAc)$_2$, Sm(O-*i*Pr)$_3$, dinucleating Schiff base **7**, and achiral additive 4-*t*-butylphenol was suitable for unprecedented *syn*-selective asymmetric nitro-Mannich-type reaction.[51,54,55] Mechanistic studies suggested that both Cu and Sm are essential. ESI-MS analysis with and without 4-*t*-butylphenol additive revealed that 4-*t*-butylphenol caused a drastic structural change (Scheme 13). In the absence of 4-*t*-butylphenol, a (μ-oxo)(μ-alkoxy)(Cu–Sm–Schiff base)$_3$ trimer complex was observed,[56] whereas a monomeric Cu–Sm–Schiff base–OAr complex was detected in the presence of 4-*t*-butylphenol. At the moment, we believe the monomer complex is the more enantioselective species in the nitro-Mannich-type reaction. Various non-enolizable aryl, heteroaryl, and enolizable aliphatic imines afforded products in good yield, high *syn*-selectivity and enantioselectivity



Scheme 13. Dinucleating Schiff base ligand **7** and postulated structures of heterobimetallic Cu–Sm–**7**–OAr complex and (μ-oxo)(μ-alkoxy)trimer complex.

Table 6. *syn*-Selective Catalytic Asymmetric Nitro-Mannich Reactions with Various *N*-Boc Imines



Entry	Imine (R)	Nitro-alkane: R′	Cat. (*x* mol amt.)	Time /h	Yield /%	*syn*/*anti*	ee/% (*syn*)
1	Ph	Me	0.10	23	96	>20:1	94
2	2-Naphthyl-	Me	0.10	48	87	>20:1	93
3	4-Me–C_6H_4–	Me	0.10	48	90	>20:1	98
4	3-Me–C_6H_4–	Me	0.10	48	77	>20:1	96
5	4-MeO–C_6H_4–	Me	0.10	48	87	>20:1	94
6	4-Cl–C_6H_4–	Me	0.10	48	81	>20:1	90
7	2-Furyl	Me	0.10	48	71	>20:1	91
8	$C_6H_5CH_2CH_2$–	Me	0.10	48	62	>20:1	83
9	Ph	Et	0.10	44	84	>20:1	88
10	4-Me–C_6H_4–	Et	0.10	48	68	>20:1	95
11	4-MeO–C_6H_4–	Et	0.10	48	64	>20:1	91
12	Ph	Me	0.050	44	92	>20:1	96
13	Ph	Me	0.025	72	99	>20:1	97

(Table 6, 62–99% yield, *syn*/*anti* = >20:1, 83–98% ee). Proposed catalytic cycle is shown in Fig. 12. Sm–OAr moiety would function as a Brønsted base to generate Sm–nitronate, and Cu would work as a Lewis acid to activate imine. The properly aligned Cu and Sm in the dinucleating Schiff base **7** function cooperatively to fix imine and nitronate in close proximity, resulting in high stereoselectivity from TS-1 in Fig. 12.

3.3 Mixed-Ligand La–Li Complex for Kinetic Resolution of *tert*-Nitroaldols. Since the early 1990s, we have reported a series of rare earth–alkali metal heterobimetallic complexes that enable various catalytic asymmetric reactions.[57,58] The structure of the rare earth–alkali metal heterobimetallic com-

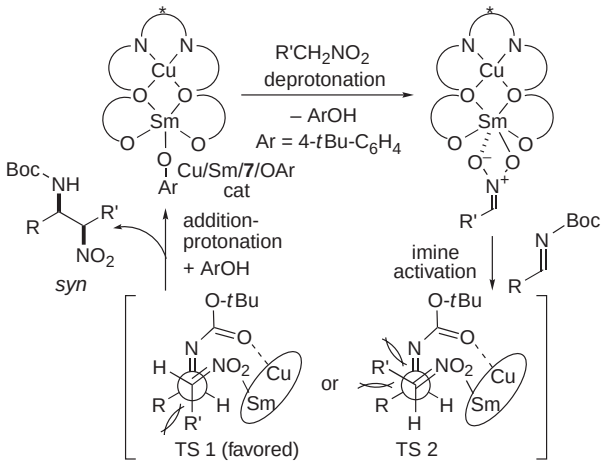


Fig. 12. Postulated catalytic cycle and transition state models.

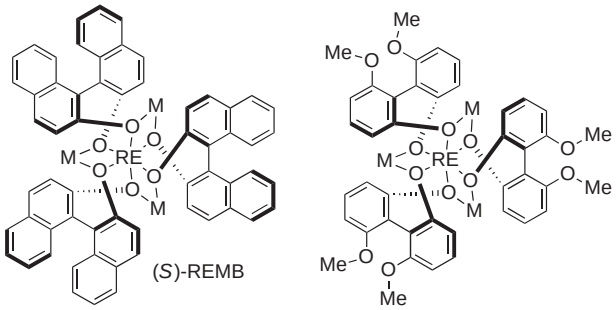
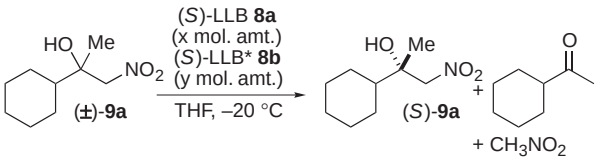


Fig. 13. Structures of heterobimetallic LLB **8a**, LLB* **8b**, and YLB **8c**.

plexes, determined by using X-ray, mass spectrometry, and NMR analysis, consisted of one rare earth metal (RE), three 1,1′-bi-2-naphthol (BINOL), and three alkali metals (M) (REMB **8**, Fig. 13).[58,59] The asymmetric environment of REMB is finely tunable by varying the combination of rare earth metals and alkali metals. In the REMB complexes, three same BINOL units and three same alkali metals have been utilized. To increase the diversity of chiral environment, we became interested in using mixed-ligand as well as mixed-alkali metal complexes.

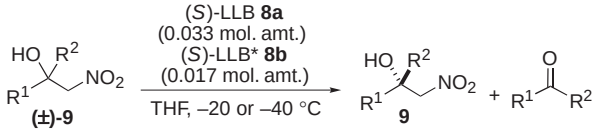
Inspired by recent reports of a mixed-ligand chiral catalyst screening strategy,[60] we examined the mixture of two chiral ligands using BINOL and biphenyldiols.[61] As shown in Table 7, LLB catalyst (Fig. 13) was effective for the kinetic resolution of *tert*-nitroaldols via retro-nitroaldol reactions (Entry 1).[62,63] The best selectivity was obtained when using (*S*)-LLB **8a** and (*S*)-LLB* **8b** (Fig. 13) in a ratio of 2:1 (Entry 2, 90% ee, 50% yield, $s = 58.4$). Neither a 2:1 ratio of **8a**/**8b** nor **8b** alone had satisfactory selectivity (Entries 3 and 4). The optimized conditions were applicable to the resolution of several *tert*-nitroaldols, giving chiral *tert*-nitroaldols in 85–97% ee and 30–47% recovered yield (s = up to 58, Table 8).[64] Mechanistic studies using ESI-MS suggested that ligand exchange between LLB **8a** and LLB* **8b** occurs to generate a mixed-

Table 7. Effects of LLB **8a**/LLB* **8b** Ratio on Kinetic Resolution of Tertiary Nitroaldol (±)-**9a**



Entry	LLB (x mol amt.)	LLB* (y mol amt.)	Time /h	Recov. of **9a**/%	ee/%	s
1	5	0	24	48	86	23.8
2	3.33	1.67	23	50	90	58.4
3	1.67	3.33	24	51	52	5.5
4	0	5	48	58	14	1.7

Table 8. Kinetic Resolution of Tertiary Nitroaldols (±)-**9** Catalyzed by Mixed Catalyst System



Entry	Substrate: **9** R^1	Substrate: **9** R^2	Time /h	Conv. /%	Yield of **9**/%	ee/%
1	Cyclohexyl	Me	23	50	47	90
2	*i*-Bu	Me	15	58	40	97
3		Me	24	58	41	85
4		Me	15	58	40	95
5	Ph	Me	26	69	30	88
6	*i*-Bu	Et	13	65	33	88

ligand La–Li_3–$(BINOL)_2$/(biphenyldiol) complex in equilibrium,[65] which would be the most enantioselective and reactive catalyst (Fig. 14).

3.4 Heterobimetallic Y–Li–BINOL Complex as Lewis Acid–Lewis Acid Catalysis. In previous reports of the REMB heterobimetallic catalysts, only nucleophiles with protons with a relatively low pK_a value (ca. 10–19 in H_2O), such as nitroalkane, malonate, ketone, and thiol, have been used due to the limitation of the Brønsted basicity of the catalysts.[58] Nucleophiles with a higher pK_a value were not applicable to REMB catalysts. To broaden the substrate scope of nucleophiles in REMB catalysis, we used the same REMB heterobimetallic catalysts in a different reaction mode: Lewis acid–Lewis acid cooperative catalysis[66] in asymmetric *aza*-Michael reaction of alkoxylamine.[67]

YLB complex **8c** (Fig. 13) was effective for the *aza*-Michael reaction of methoxyamine to enones, giving products in 84–97% ee and 57–97% yield (Scheme 14a).[68] Catalyst loading was successfully reduced to as little as 0.3×10^{-2} molar amount (TON = up to 320). *N*-(α,β-Unsaturated acyl)-pyrroles as ester surrogates were also applicable, albeit with a somewhat decreased reactivity (Scheme 14b).[69] Products were successfully converted into aziridines and β-amino acids (Scheme 14c). Proposed catalytic cycle of the reaction based on kinetics and NMR studies is shown in Fig. 15. Methoxyamine should coordinate to YLB in a rapid equilibrium, and

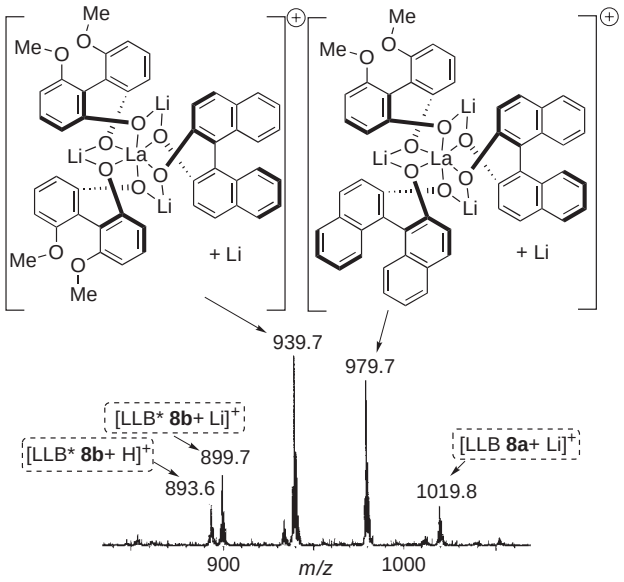
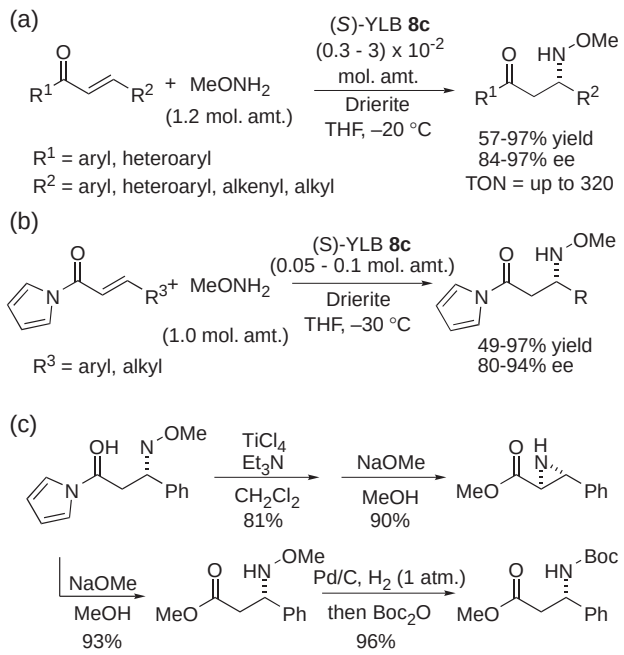


Fig. 14. ESI-MS chart of a 2:1 mixture of LLB **8a**/LLB* **8b**.



Scheme 14. Catalytic asymmetric *aza*-Michael reactions of methoxyamine and transformations of *aza*-Michael adduct.

the C–N bond-forming step is the rate-determining step. Mechanistic studies suggested that the heterobimetallic cooperative function of the Y and Li metal centers play a key role in achieving high reactivity and selectivity. Neither Li–BINOL nor Y–BINOL, nor Y–K–BINOL complex was effective for the reaction at all. We believe that YLB **8c** complex would function as a Lewis acid–Lewis acid catalyst: Y activates enones, and Li would interact with the oxygen atom of methoxyamine. Methoxyamine would then be positioned close to the enone, and the addition reaction should be accelerated due to proximity effect control (Fig. 16).

3.5 Asymmetric Cyanation with Y–Li–BINOL Complex.

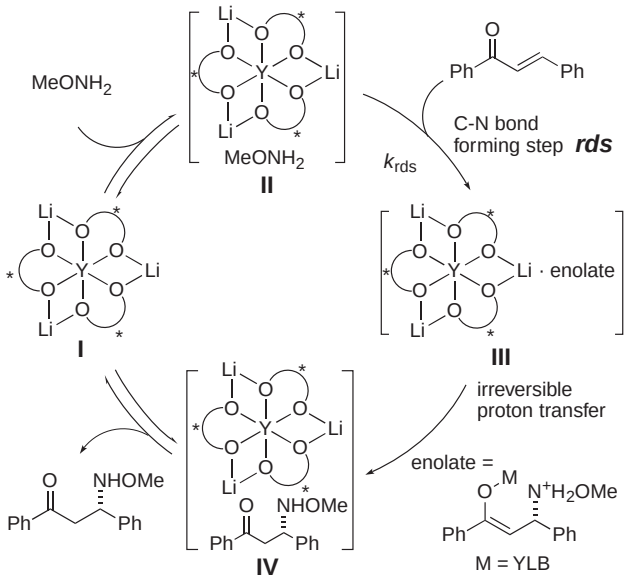


Fig. 15. Proposed catalytic cycle of *aza*-Michael reaction.

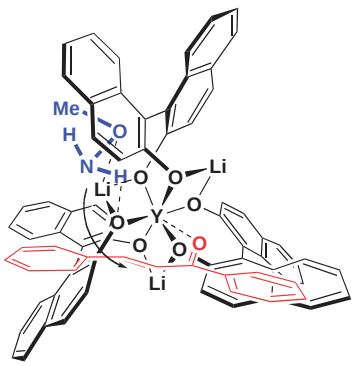
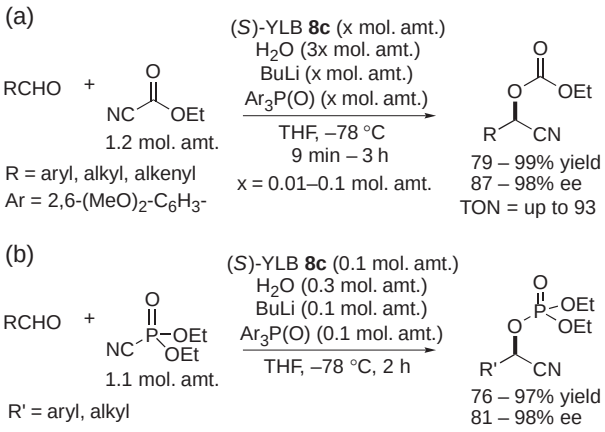


Fig. 16. Postulated transition state model of Lewis acid–Lewis acid cooperative catalysis.

Addition of an achiral additive is an effective way to modify the chiral environment of the catalyst. In the catalytic asymmetric cyano-ethoxycarbonylation reaction[70,71] using the YLB **8c** complex, H_2O, BuLi, and $Ar_3P(O)$ (Ar = 2,6-$(MeO)_2$-C_6H_3) additives[72] were important to achieve high reactivity and enantioselectivity. The optimized conditions were applicable not only in a cyanoethoxycarbonylation reaction (Scheme 15a, 87–98% ee),[73] but also in cyano-phosphorylation reaction (Scheme 15b, 81–98% ee).[74] Under the optimized reaction conditions, the reaction completed within 9 min. The catalyst loading was successfully reduced to 0.01 molar amount (TON = up to 93). To demonstrate the utility of cyanation products, we applied the present reaction to total synthesis of (+)-patulolide C.[75] Mechanistic studies, including React-IR analysis, kinetic studies, and NMR analysis, suggested that the self-assembled YLB + H_2O + LiCN + $Ar_3P(O)$ = 1:1:1:1 complex would be the active species (Fig. 17a).[76] NMR analysis suggested that H_2O reversibly coordinated to the YLB complex, thereby modifying the chiral environment. Kinetic studies also implied that $Ar_3P(O)$ would increase the nucleophilicity of LiCN through coordination to Li. A proposed catalytic cycle is shown in Fig. 17b. React-IR studies suggested that the addition of cyanide was irreversible at



Scheme 15. Catalytic asymmetric one-pot cyanation–protection sequences using YLB **8c**/H_2O/BuLi/$Ar_3P(O)$ system.

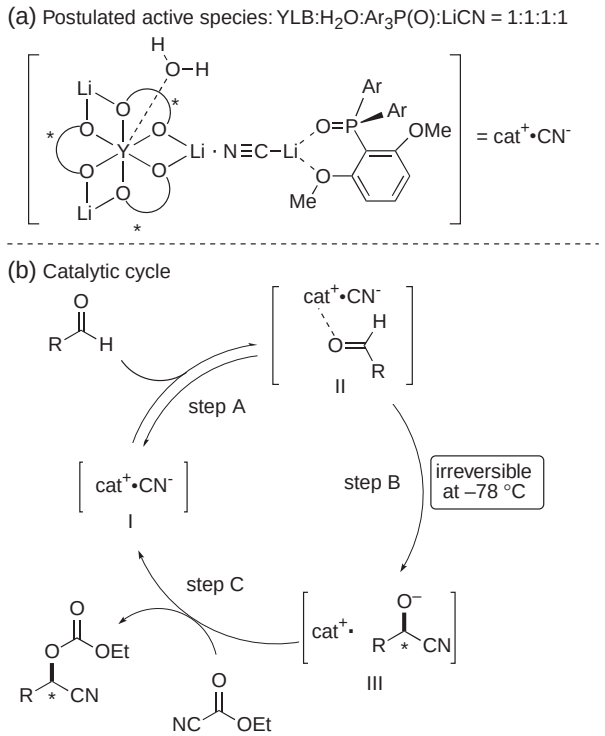


Fig. 17. (a) Postulated self-assembled active species, and (b) catalytic cycle of asymmetric cyano-ethoxycarbonylation.

−78 °C and the enantioselectivity was determined at the cyanide addition stage before trapping with ethyl cyanoformate.

4. Summary

In summary, our recent efforts to develop multimetallic asymmetric catalysis based on the proximity-effect-control concept were described.[77] In many cases, the reaction afforded enantiomerically enriched products without the generation of waste salts. Synergistic functions of two or more metal centers play a key role in achieving high reactivity and stereoselectivity in these reactions. In the homo-multimetallic catalysts, multidentate linked-BINOLs with a linker containing a coordi-

nating heteroatom were effective to form multimetallic complexes. To expand further the possibility of present multimetallic asymmetric catalysis, we believe the combined use of two or more different metals, such as transition metals and rare earth metals, is important for the future studies. We are now intensively studying the use of dinucleating Schiff base ligands in various metal combinations, which will be reported in the near future. Further studies towards establishing other reliable strategies to align two or more different metals as designed in heterobimetallic catalysts are also ongoing.

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Shigeki Matsunaga was born in 1975 in Kyoto and received his Ph.D., with a thesis on the development of a novel chiral ligand linked-BINOL, 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. He is the recipient of the Yamanouchi Award of Synthetic Organic Chemistry, Japan (2001), and The Chemical Society of Japan Award for Young Chemists (2006). His current research interests are in the development of new catalytic reactions, including asymmetric catalysis, based on the cooperative functions of multinuclear metal complexes, mechanistic studies of catalytic reactions, and the synthesis of biologically active compounds.

Masakatsu Shibasaki received his Ph.D. from the University of Tokyo in 1974 under the direction of the late Professor Shun-ichi 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 the 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) and many others.