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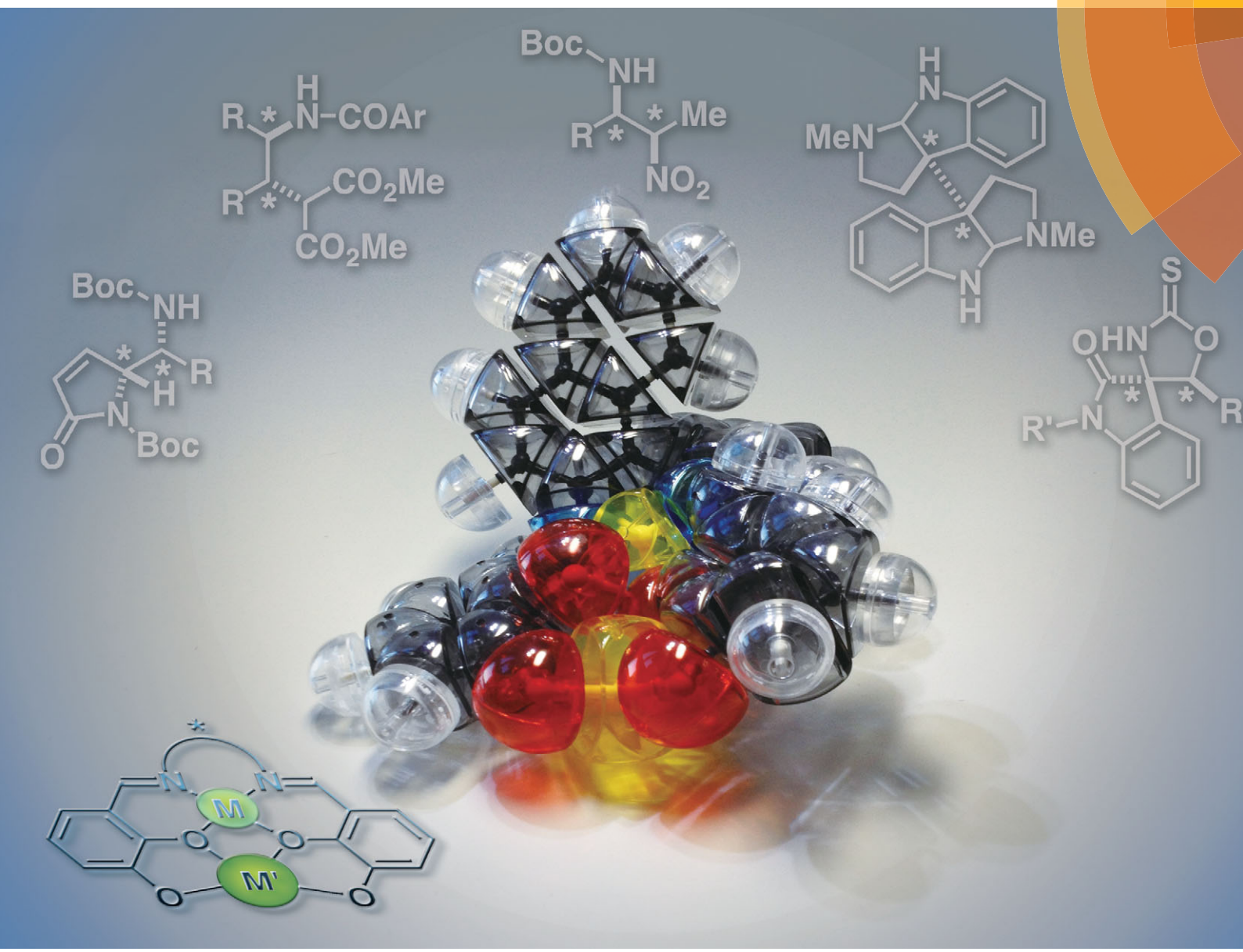

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FEATURE ARTICLE

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Recent advances in cooperative bimetallic asymmetric catalysis: dinuclear Schiff base complexes

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Cooperative catalysis has proven to be a powerful strategy for realizing high reactivity and selectivity in asymmetric transformations. A variety of cooperative asymmetric catalysts have been developed over the last two decades. In this feature article, recent advances from our research on cooperative asymmetric catalysis, focusing on dinuclear Schiff base catalysis, are described. Design of dinuclear Schiff base catalysts and their applications in several asymmetric C–C and C–N bond-forming reactions under simple proton transfer conditions with perfect atom-economy are discussed in detail.

Introduction

Asymmetric catalysis has established its firm position as an efficient method for constructing a wide range of enantiomerically enriched compounds. Intensive efforts have been devoted to this field over decades, leading to the development of numerous excellent asymmetric catalysts.[1] Many organic transformations can now be rendered into catalytic and enantioselective processes. The aim of synthetic methodology development has gradually shifted towards environmentally benign organic synthesis, and not only high yield and high stereoselectivity of organic transformations, but also atom-economy[2] and step-economy[3] of the processes are currently considered to be important factors. Conventional studies on asymmetric catalysis realized high yield as well as high regio- and stereoselectivity, but often with the help of stoichiometric activating reagents. It is highly desirable

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Shigeki Matsunaga

Shigeki Matsunaga is an associate professor at the University of Tokyo. He was born in 1975, and received his PhD from the University of Tokyo under the direction of professor M. Shibasaki. He started his academic career in 2001 as an assistant professor in professor Shibasaki's lab. He was promoted to a senior lecturer in 2008, and to his current position in 2011. He is the recipient of the Chemical Society of Japan Award for Young Chemists (2006), Mitsui Chemicals Catalysis Science Award of Encouragement (2009), Merck-Banyu Lectureship Award 2010, and others. His research interests are in cooperative asymmetric catalysis, C–H bond functionalization, and synthesis of biologically active compounds.

Masakatsu Shibasaki

Masakatsu Shibasaki received his PhD from the University of Tokyo in 1974 under the direction of the late professor Shun-ichi Yamada before conducting 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. Currently, he is a director of the Institute of Microbial Chemistry (Tokyo). His research interests include asymmetric catalysis and medicinal chemistry of biologically significant compounds.

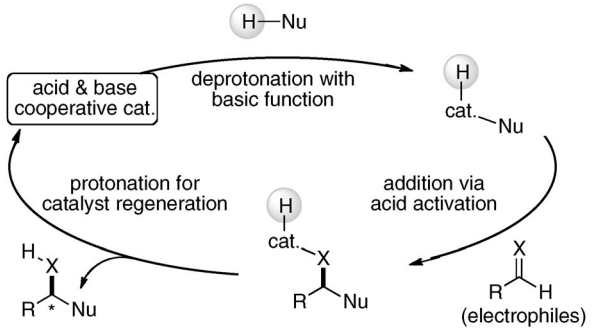


Fig. 1 Direct catalytic asymmetric reactions *via* a simple proton transfer process.

to minimize the waste and by-products to achieve high overall efficiency in organic synthesis and match the criteria of green chemistry.

Intermolecular direct catalytic asymmetric C–C bond-forming reactions are highly attractive because of their atom-economical processes.[4] In the direct C–C bond-forming reaction, an active carbon nucleophile, such as an enolate, is catalytically generated *in situ via* deprotonation of the pronucleophile (Nu–H in Fig. 1) with a Brønsted basic catalyst. Addition of the carbon nucleophile to an electrophile followed by protonation provides the product. In principle, the direct catalytic reaction proceeds with 100% atom economy under simple proton transfer conditions, thus providing useful building blocks without any waste derived from stoichiometric reagents. To induce high reactivity and stereoselectivity in the direct catalytic asymmetric C–C bond-forming reactions, the concurrent activation of pronucleophiles and electrophiles is highly desirable to control the stereochemical outcome of reactions, possibly through both Brønsted basic as well as Lewis acidic and/or Brønsted acidic sites of catalysts. Acid and base cooperative functions are often utilized in enzymes to promote enantioselective reactions under remarkably mild conditions *via* a simple proton transfer process. For example, the postulated transition state model of class II aldolase, a Zn-dependent metalloenzyme, clearly indicates the power of acid and base cooperative functions to activate both nucleophiles and electrophiles.[5] As shown in Fig. 2, the glutamate-73 residue functions as a Brønsted base to deprotonate a pronucleophile,

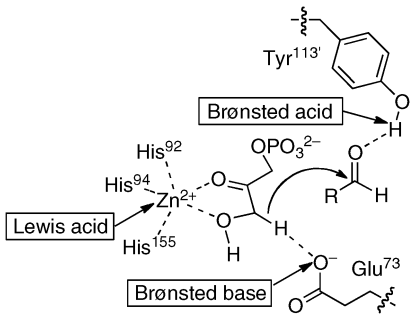


Fig. 2 Postulated acid and base cooperative mechanism of class II aldolase.

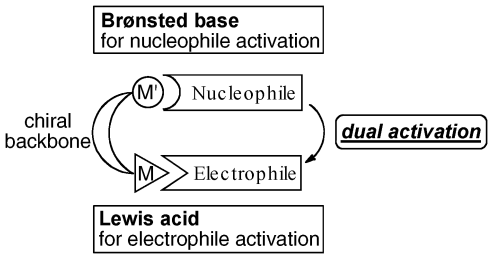


Fig. 3 Dual activation with bimetallic cooperative asymmetric catalysts.

dihydroxyacetone phosphate, which is activated by the coordination to Lewis acidic Zn^{2+}. On the other hand, the position of the aldehyde is controlled by the Brønsted acidic tyrosine-113′ residue. With the appropriate control of two reactants in close proximity, high reactivity, stereoselectivity as well as high atom-economy were achieved in enzymatic aldol reactions under mild reaction conditions.

Inspired by the intriguing cooperative mechanism of enzymes, a variety of artificial cooperative asymmetric metal- and organocatalysts have been developed over the last two decades.[6] Our group has intensively worked in this field and developed various bimetallic Lewis acid and Brønsted base cooperative asymmetric catalysts. The concept of bimetallic cooperative asymmetric catalysis is shown in Fig. 3. One metal center together with its counter ion acts as a Brønsted base to activate pronucleophiles, while the other Lewis acidic metal center activates electrophiles. Both reaction partners are simultaneously activated by fine-tuned bimetallic catalysts with an appropriate chiral environment. In this account, we highlight our own research on the development of a new family of bimetallic cooperative asymmetric catalysts, dinuclear Schiff base catalysts, and their applications in asymmetric C–C and C–N bond-forming reactions since 2007.

Heterodinuclear Schiff base catalysis

Design of dinucleating Schiff bases

When designing cooperative asymmetric catalysts, the construction of a suitable chiral environment for each targeted reaction is important for achieving efficient dual activation of nucleophiles and electrophiles through the cooperation of two metal centers. Optimization of enantioselectivity and reactivity requires a strategy for constructing a readily tunable chiral environment. Various chiral scaffolds have been utilized by our group to construct multimetallic self-assembled complexes for realizing efficient cooperative dual activation. At the early stage of our work, we mainly utilized BINOL-based ligands, and various multimetallic Lewis acid and Brønsted base cooperative asymmetric catalysts, such as heterobimetallic rare earth metal/alkali metal/binaphtholate = 1 : 3 : 3 complexes,[7] heterobimetallic group 13 metal/alkali metal/binaphtholate = 1 : 1 : 2 complexes,[8] a trinuclear Zn/linked-BINOL = 3 : 2 complex,[9] and others, have been developed (Fig. 4). Those BINOL-based multimetallic catalysts were powerful and promoted a variety of asymmetric reactions. The use of BINOL-based ligands, however, restricted the applicable metal sources to relatively oxophilic ones, such as

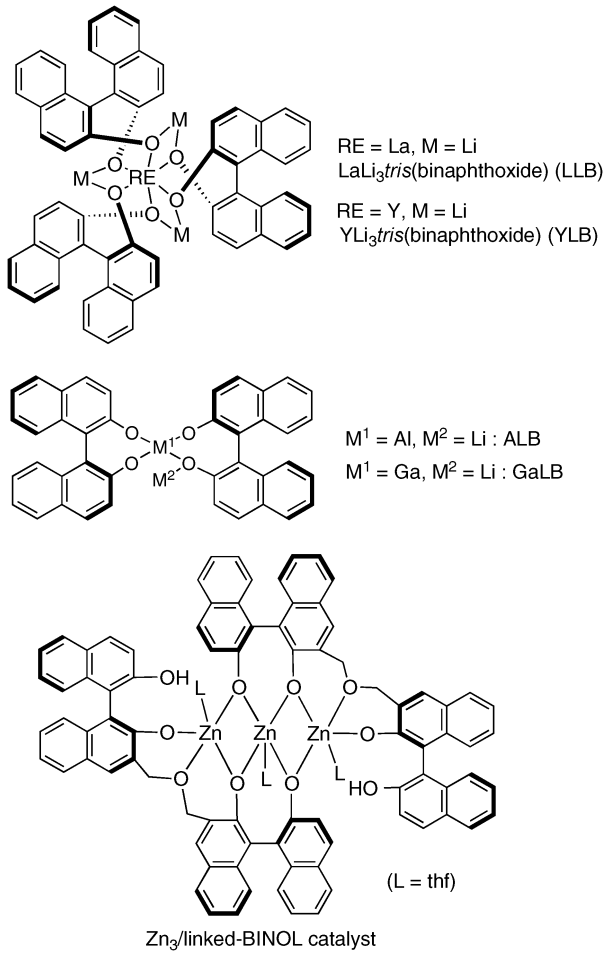


Fig. 4 Early examples of BINOL-based Lewis acid and Brønsted base multimetallic cooperative asymmetric catalysts.

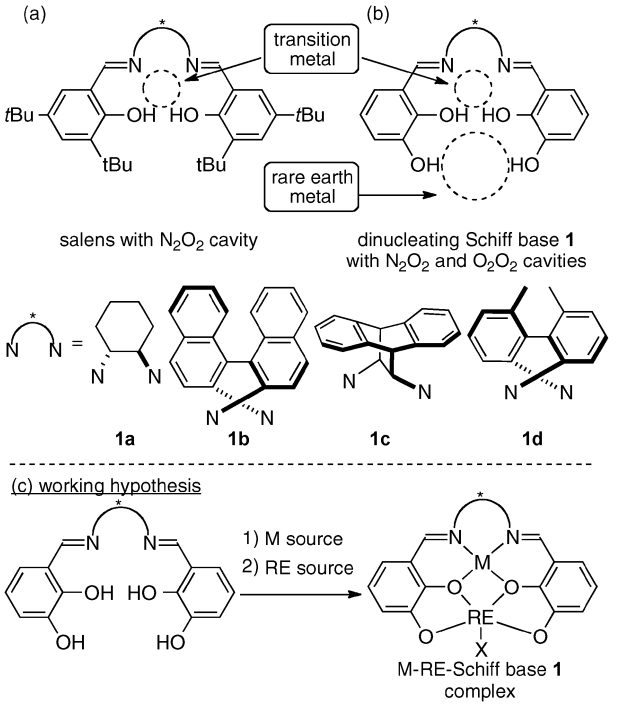


Fig. 5 (a) Salens for mononuclear complexes; (b) our design of dinucleating Schiff base **1** with two distinct cavities; (c) working hypothesis to form heterodinuclear cooperative Schiff base complexes with transition metal/rare earth metal combination.

alkali metals, rare earth metals, group 13 metals, zinc, and others. Transition metals, like Mn, Co, Ni, and Cu, are often not suitable for BINOL-based chiral ligands. In order to broaden the scope of bimetallic cooperative asymmetric catalysis, the development of new multidentate chiral ligands is highly desirable. We believe that new metal combinations will lead to novel catalytic activity and selectivity in cooperative catalysis.

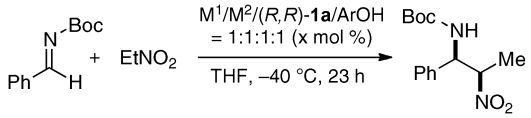
Chiral Schiff base ligands, such as salens, are one of the privileged ligand classes in asymmetric catalysis.[1c,10,11] Over the last two decades, various chiral transition metal–salen complexes have been widely utilized for a broad range of catalytic asymmetric reactions (Fig. 5a). As to the cooperative catalysis field, Jacobsen and coworkers have developed an elegant intermolecular bimolecular cooperative system using two metal–salen complexes.[12] Attempts to strengthen the catalytic cooperativity of two metal–salen complexes by linking two metal–salen units have also been reported.[13] Furthermore, several groups have expanded the potential of Schiff base ligands for heterobimetallic transition metal/alkali metal catalysts and transition metal/group 13 metal combined catalysts.[14] The advantages of heterobimetallic Schiff base complexes in comparison with mononuclear Schiff complexes for intermolecular bimolecular cooperative systems, however, had been rather limited at the time we started our project.

When developing bimetallic asymmetric catalysts for intramolecular cooperative catalysis, the design of a suitable multidentate ligand is important for appropriately controlling the positions of two metals in the complex. The positions of the two metals substantially affect the reactivity and stereoselectivity of the bimetallic complexes. At the initial stage of our study, we tried several dinucleating Schiff base ligands, and new dinucleating Schiff bases **1** with additional phenolic hydroxyl units, in comparison with standard salens, gave promising results (Fig. 5b). Based on precedents in the field of coordination chemistry,[15] we hypothesized that the Schiff bases **1** would selectively incorporate a transition metal into the N_2O_2 inner cavity and an oxophilic rare earth metal with a much larger ionic radius into the O_2O_2 outer cavity (Fig. 5c).

Heterobimetallic transition metal/Brønsted basic rare earth metal/Schiff base catalysts

As a model reaction to evaluate bimetallic Schiff base complexes, we selected aza-Henry reaction, which is a powerful C–C bond-forming reaction to provide chiral 1,2-diamines.[16] Effects of metal combination on the aza-Henry reaction are summarized in Table 1, runs 1–8. As expected, the selection of a suitable metal combination for the targeted reaction was critical for achieving good stereoselectivity. A heterobimetallic complex, prepared from $Cu(OAc)_2$, $Sm(O\text{-}iPr)_3$, and dinucleating Schiff base **1a** was the best, giving product in >20 : 1 *syn*-selectivity

Table 1 Effects of metal combination and achiral phenol in catalytic asymmetric aza-Henry reaction



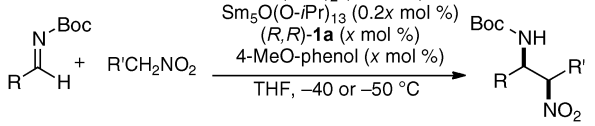
Run	M^1 source	M^2 source	x	ArOH	Yield (%)	*syn* : *anti*	ee (%)
1	$Cu(OAc)_2$	$La(O\text{-}iPr)_3$	10	None	73	3 : 1	5
2	$Cu(OAc)_2$	$Pr(O\text{-}iPr)_3$	10	None	82	1 : 1	9
3	$Cu(OAc)_2$	$Sm(O\text{-}iPr)_3$	10	None	96	>20 : 1	80
4	$Cu(OAc)_2$	$Eu(O\text{-}iPr)_3$	10	None	93	>20 : 1	64
5	$Cu(OAc)_2$	$Dy(O\text{-}iPr)_3$	10	None	89	7 : 1	48
6	$Zn(OAc)_2$	$Sm(O\text{-}iPr)_3$	10	None	0	—	—
7	$Mg(OAc)_2$	$Sm(O\text{-}iPr)_3$	10	None	0	—	—
8	$Ni(OAc)_2$	$Sm(O\text{-}iPr)_3$	10	None	0	—	—
9	$Cu(OAc)_2$	None	10	None	0	—	—
10	None	$Sm(O\text{-}iPr)_3$	10	None	14	2 : 1	29
11	$Cu(OAc)_2$	$Sm(O\text{-}iPr)_3$	10	4-*t*Bu-phenol	96	>20 : 1	94
12	$Cu(OAc)_2$	$Sm(O\text{-}iPr)_3$	5	4-*t*Bu-phenol	94	>20 : 1	87
13[a]	$Cu(OAc)_2$	$Sm_5(O)(O\text{-}iPr)_{13}$	5	4-*t*Bu-phenol	97	>20 : 1	94
14[a]	$Cu(OAc)_2$	$Sm_5(O)(O\text{-}iPr)_{13}$	5	4-MeO-phenol	93	>20 : 1	95

[a] 1 mol% of $Sm_5O(O\text{-}iPr)_{13}$ was used.

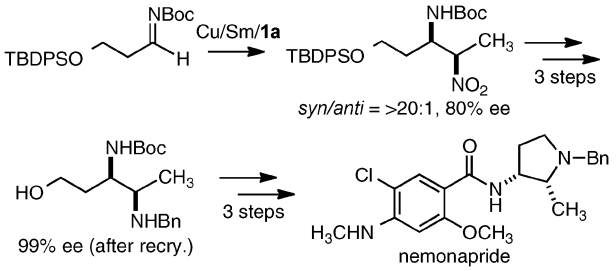
and 80% ee. Other metal combinations resulted in much lower selectivity and/or stereoselectivity. Either Cu or Sm alone resulted in poor reactivity and selectivity (runs 9–10), suggesting that both Cu and Sm are essential for good performance.[17] Further optimization studies revealed that an achiral phenol source improved the enantioselectivity. The use of oxo-samarium alkoxide, $Sm_5O(O\text{-}iPr)_{13}$, which has a well-ordered structure, gave better enantioselectivity when reducing the catalyst loading to 5 mol%.

Selected examples of the substrate scope of the Cu/Sm/**1a**-catalyzed aza-Henry reaction are shown in Table 2. Not only aryl and heteroaryl *N*-Boc-imines (runs 1–9 and 13–15), but also readily isomerizable aliphatic *N*-Boc-imines were applicable

Table 2 Cu/Sm/**1a**-catalyzed asymmetric aza-Henry reaction



Run	Imine (R)	Nitro-alkane (R′)	x	Time (h)	Yield (%)	*syn* : *anti*	ee (%)
1	C_6H_5	Me	5	27	93	>20 : 1	95
2	4-Me–C_6H_4	Me	5	40	99	>20 : 1	98
3	3-Me–C_6H_4	Me	5	24	81	>20 : 1	97
4	2-Me–C_6H_4	Me	5	48	87	>20 : 1	92
5	4-MeO–C_6H_4	Me	5	39	87	>20 : 1	96
6	4-Cl–C_6H_4	Me	10	23	81	>20 : 1	92
7	2-Naphthyl	Me	5	24	98	>20 : 1	96
8	2-Furyl	Me	5	27	86	>20 : 1	90
9	2-Thienyl	Me	5	48	87	>20 : 1	88
10	$C_6H_5CH_2CH_2$–	Me	8	39	74	>20 : 1	80
11	Isobutyl	Me	10	46	72	>20 : 1	81
12	*n*-Pentyl	Me	8	39	77	13 : 1	66
13	C_6H_5	Et	5	48	85	>20 : 1	96
14	4-Me–C_6H_4	Et	5	40	88	>20 : 1	97
15	2-Naphthyl	–CH_2OBn	10	21	86	>20 : 1	81



Scheme 1 Catalytic asymmetric synthesis of nemonapride.

(runs 10–12). The Cu/Sm/**1a**-catalyst was also applicable to β-silyloxy-substituted aliphatic imine, and the utility of the present reaction was demonstrated in a concise catalytic asymmetric synthesis of nemonapride, which is used clinically as an antipsychotic agent (Scheme 1).[18]

To obtain insight into the structure of the active species and the role of the achiral phenol source, a mixture of the Cu : Sm : ligand **1a** = 1 : 1 : 1 system was analyzed by ESI-MS with and without added achiral phenol. In the absence of any achiral phenol, no peak corresponding to the monomeric Cu : Sm : ligand **1a** = 1 : 1 : 1 complex was detected. Instead, several peaks corresponding to oligomeric species, such as the μ-oxo-trimer $[Cu_3Sm_3O(\text{ligand } \mathbf{1a})_3]^+$, a hexamer, a heptamer, an octamer, and a decamer, were observed. In the presence of an achiral phenol, the peak due to the μ-oxo-trimer $[Cu_3Sm_3O(\text{ligand } \mathbf{1a})_3]^+$ (m/z = 1710) was similarly observed. Peaks for higher m/z for higher order oligomers, however, became much weaker, suggesting that such higher order oligomers partially dissociate into the μ-oxo-μ-aryloxy trimer in the presence of an achiral phenol (Fig. 6). On the basis of these ESI-MS observations as well as the positive non-linear-effects observed in this system, we speculated that the μ-oxo-μ-aryloxy trimer complex is the most enantioselective active species. Based on the initial kinetic studies and kinetic isotope effect studies, the catalytic cycle shown in Fig. 7 was postulated for this reaction. For this catalyst system, the results shown in Table 1 demonstrate that both Cu and Sm are essential. We assume that the cooperative dual activation of nitroalkanes and imines with Cu and Sm-aryloxide is important to achieve this *syn*-selective catalytic asymmetric aza-Henry reaction. The Sm-aryloxide moiety in the catalyst would act as a Brønsted base to generate Sm-nitronate, while Cu(II) would act as a Lewis acid to control the position of the *N*-Boc-imine. Among the possible transition states, the sterically less hindered TS-1 is more favorable than TS-2. Thus, the stereoselective C–C bond-formation *via* TS-1 followed by protonation by the phenolic proton affords the *syn*-product and regenerates the catalyst.

In the bimetallic system, the choice of transition metal and rare earth metal combination drastically affected the enantioselectivity of aza-Henry reaction, as observed in Table 1. We assumed that a variety of chiral environments could be readily constructed using the same ligand **1a** just by changing each component of the heterobimetallic complex, transition metal, rare earth metal, and an achiral phenol additive. As a proof of concept, we applied the dinucleating Schiff base **1a** to the

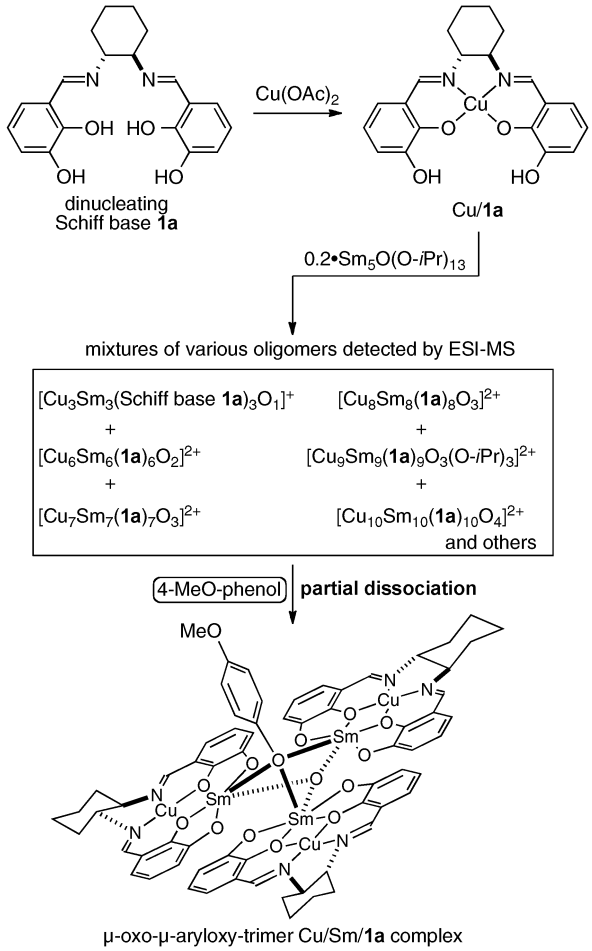


Fig. 6 Postulated role of achiral phenol additive and the postulated structure of the μ-oxo-μ-aryloxy-trimer Cu/Sm/**1a** active species.

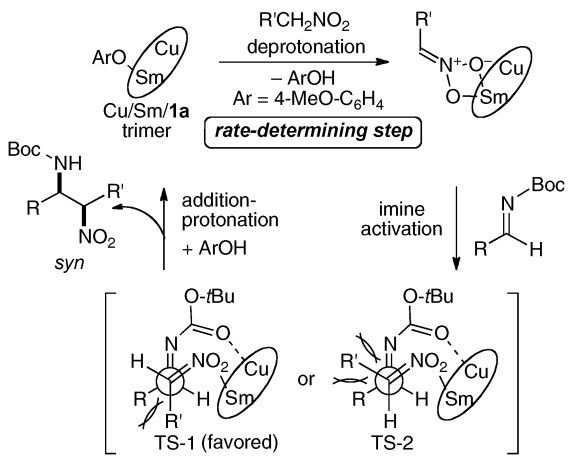
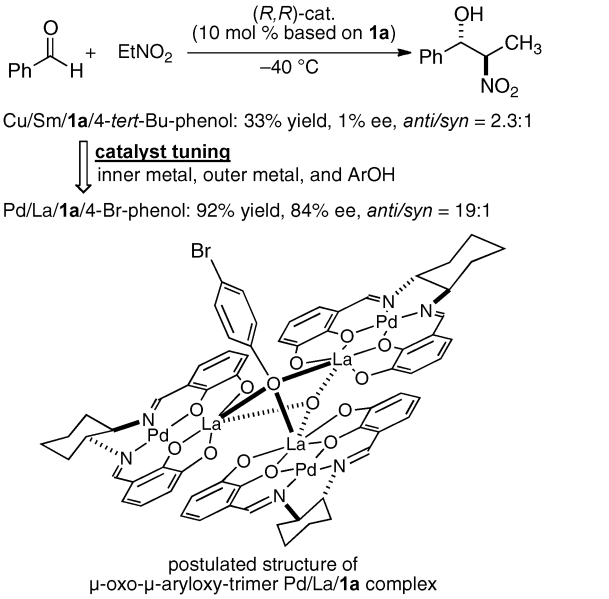
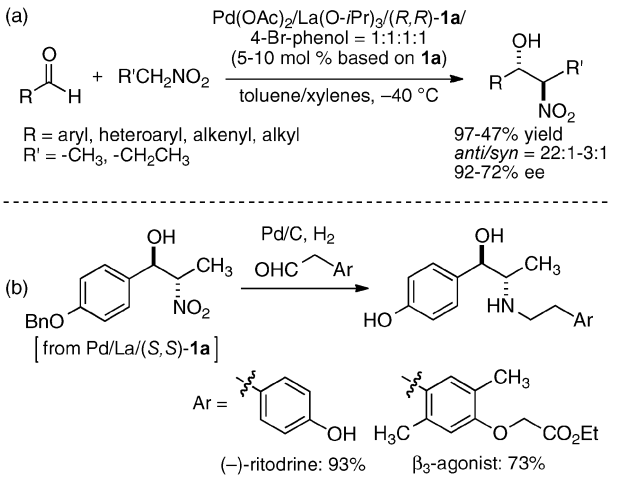


Fig. 7 Postulated catalytic cycle of aza-Henry reaction under hetero-bimetallic cooperative catalysis.

anti-selective asymmetric Henry reaction.[19,20] As shown in Scheme 2, the Cu–Sm–Schiff base complex gave poor results in the reaction with aldehyde, giving the product in only 33% yield, *anti/syn* ratio = 2.3 : 1, and 1% ee. Screening of the transition metal, rare earth metal, phenol additive, and other reaction



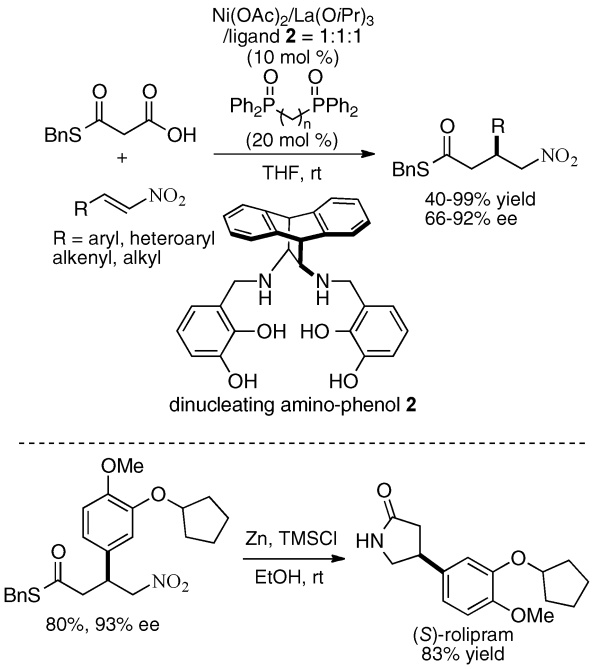
Scheme 2 Catalyst tuning for *anti*-selective Henry reaction and a postulated structure of the Pd–La–**1a** complex.



Scheme 3 (a) Pd/La/**1a**-catalyzed *anti*-selective catalytic asymmetric Henry reaction; (b) catalytic asymmetric synthesis of β-adrenoceptor agonists.

conditions finally revealed that Pd/La/Schiff base **1a** with the 4-bromophenol additive was optimum, giving the product in 92% yield, *anti/syn* ratio = 19 : 1, and 84% ee. The results support our initial assumption that the dinucleating Schiff base is suitable for constructing diverse chiral environments which enable optimization of targeted asymmetric reactions by appropriate selection of each catalyst component. With the optimized Pd–La–**1a** system, the *anti*-selective catalytic asymmetric Henry reaction of various aldehydes proceeded with up to 92% ee and 22 : 1 *anti*-selectivity (Scheme 3a).[21] The reaction was also applied to the short syntheses of some β-adrenoceptor agonists (Scheme 3b).

The heterobimetallic system with transition metal and Brønsted basic rare earth metal alkoxide was further expanded to include the use of a reduced-type dinucleating amino-phenol



Scheme 4 Heterobimetallic Ni–La system for decarboxylative 1,4-addition of malonic acid half-thioester.

ligand **2**.[22] A catalyst prepared from $Ni(OAc)_2$, $La(O\text{-}iPr)_3$, and ligand **2** in a ratio of 1 : 1 : 1 was the best for catalytic asymmetric decarboxylative 1,4-addition of a malonic acid half-thioester. The addition of achiral phosphine oxide was effective in improving the reactivity of the catalyst, possibly by enhancing the Brønsted basicity of the lanthanum aryloxide moiety. Decarboxylated 1,4-adducts were obtained in 40–99% yield and 66–92% ee (Scheme 4).[23] The products of this reaction are useful synthetic intermediates for γ-amino acids,[24] and the Ni/La/ligand **2** catalyst was applied to the catalytic asymmetric synthesis of (*S*)-rolipram, an anti-deppresant agent.

Heterobimetallic catalysts containing cationic rare earth metal as a Lewis acid unit

In the previous section, heterobimetallic systems including Brønsted basic rare earth metal aryloxide moieties were described. As to rare earth metal sources, cationic rare earth metal sources have also been widely utilized as Lewis acids.[25] If a cationic rare earth metal can be incorporated into the outer cavity of dinucleating Schiff bases, the resulting heterobimetallic system should be also useful as different types of cooperative asymmetric catalysts.

To incorporate a cationic rare earth metal into the outer O_2O_2 cavity of a dinucleating Schiff base, we utilized Schiff base **3** derived from *o*-vanillin (Fig. 8). We selected α-additions of α-isocyanoacetamides to aldehydes as a model reaction because a salen–Al catalyst gave only modest enantioselectivity and reactivity for the transformation.[26,27] Our working hypothesis for bimetallic Schiff base catalysis is shown in Fig. 9. We assumed that the bimetallic Schiff base complex would not only activate the aldehyde with one metal, but might also interact with the α-isocyanoacetamide through the other metal

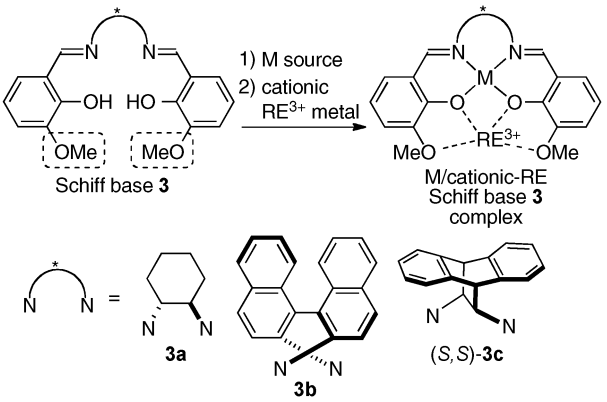


Fig. 8 Design of Schiff bases **3** for the preparation of heterobimetallic complexes incorporating cationic rare earth metals (RE^{3+}).

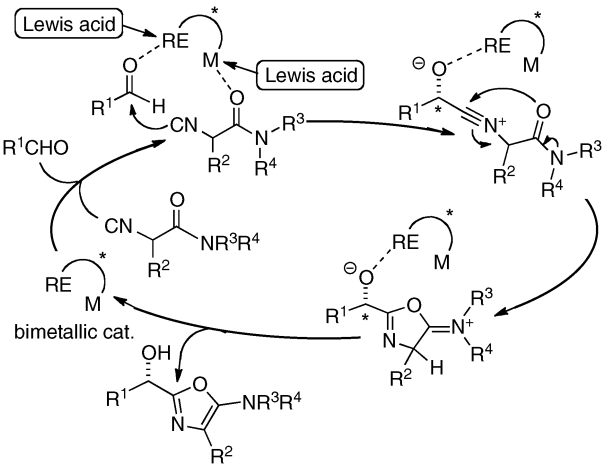
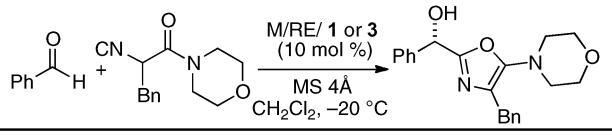


Fig. 9 Working hypothesis for Lewis acid/Lewis acid cooperative catalysis with a heterobimetallic complex including a cationic rare earth metal.

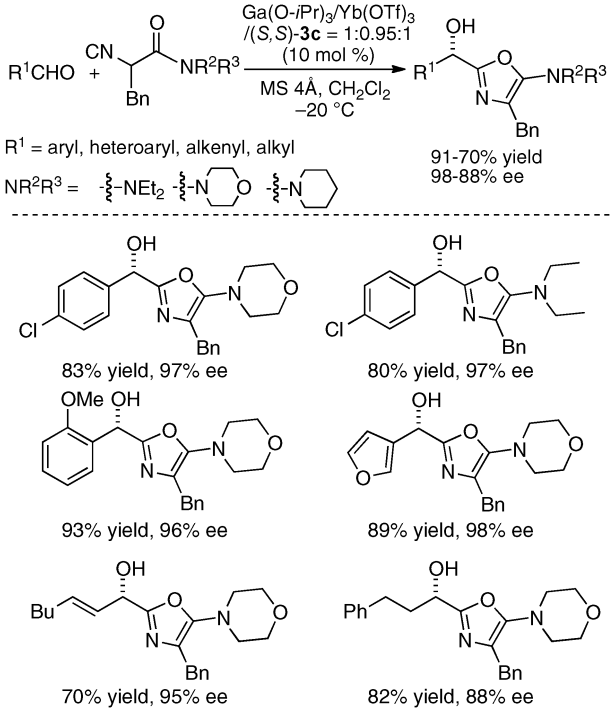
to effectively control the orientation of the two substrates in the enantio-discriminating step (Fig. 9, Lewis acid/Lewis acid cooperative catalysis). After screening suitable metal combinations for Schiff base **3**, $Ga(O\text{-}iPr)_3/Yb(OTf)_3$ was found to afford promising results. The chiral diamine backbone affected both the reactivity and enantioselectivity (Table 3, runs 1–3). Schiff base **3a** gave unsatisfactory results, but **3b** containing a binaphthyl diamine unit gave 78% ee (run 2). The best reactivity and selectivity were achieved using Schiff base **3c** with an anthracene-derived diamine unit (run 3, 67% yield, 94% ee). After optimization of the Ga/Yb ratio (1 : 0.95), the product was obtained in >95% yield and 96% ee after 24 h (run 4). To confirm the utility of the $Ga(O\text{-}iPr)_3/Yb(OTf)_3$ combination, several control experiments were performed with the best ligand **3c** (runs 5–12). Neither Ga–**3c** alone nor Yb–**3c** alone efficiently promoted the reaction (runs 5–6). For $Ga(O\text{-}iPr)_3$ and other rare earth metal triflates, the reactivity decreased in correlation with the Lewis acidity of the rare earth metal (Yb > Gd > Nd > La),[28] while good to excellent enantioselectivity was maintained in runs 7–9 (89–96% ee). We investigated Et_2AlCl, $Al(O\text{-}iPr)_3$, and $In(O\text{-}iPr)_3$ as other sources of group 13

Table 3 Effects of metal combination and Schiff bases for α-addition of isocyanoacetamide to benzaldehyde

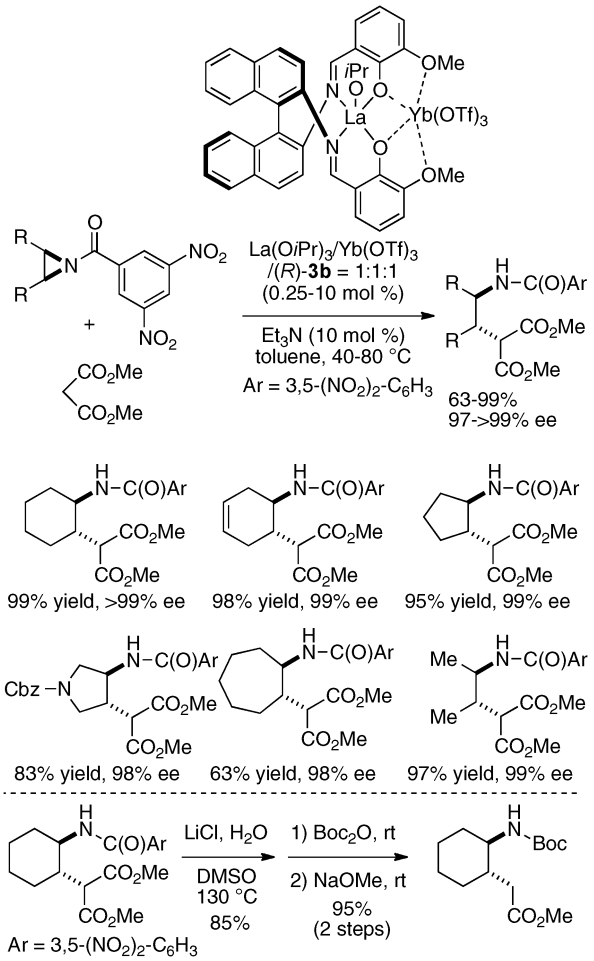


Run	M source	RE source (x mol%)	Ligand	Time (h)	Yield (%)	ee (%)
1	$Ga(O\text{-}iPr)_3$	$Yb(OTf)_3$ (10)	**3a**	74	55	29
2	$Ga(O\text{-}iPr)_3$	$Yb(OTf)_3$ (10)	**3b**	71	27	78
3	$Ga(O\text{-}iPr)_3$	$Yb(OTf)_3$ (10)	**3c**	74	67	94
4	$Ga(O\text{-}iPr)_3$	$Yb(OTf)_3$ (9.5)	**3c**	24	>95	96
5	$Ga(O\text{-}iPr)_3$	None	**3c**	24	Trace	—
6	None	$Yb(OTf)_3$ (10)	**3c**	24	Trace	—
7	$Ga(O\text{-}iPr)_3$	$Gd(OTf)_3$ (9.5)	**3c**	24	62	96
8	$Ga(O\text{-}iPr)_3$	$Nd(OTf)_3$ (9.5)	**3c**	24	33	95
9	$Ga(O\text{-}iPr)_3$	$La(OTf)_3$ (9.5)	**3c**	24	11	89
10	Et_2AlCl	$Yb(OTf)_3$ (9.5)	**3c**	48	68	37
11	$Al(O\text{-}iPr)_3$	$Yb(OTf)_3$ (9.5)	**3c**	24	>95	79
12	$In(O\text{-}iPr)_3$	$Yb(OTf)_3$ (9.5)	**3c**	24	55	80
13	$Ga(O\text{-}iPr)_3$	$Yb(OTf)_3$ (9.5)	**1c**	24	Trace	—

metals for the inner cavity (runs 10–12), but the results were less satisfactory than that of entry 4. In entry 13, Schiff base **1c** (Fig. 5) was utilized instead of Schiff base **3c**, but no reaction occurred. The results described in runs 5–13 indicated that the $Ga(O\text{-}iPr)_3/Yb(OTf)_3$ combination as well as Schiff base **3c** derived from *o*-vanillin were essential for obtaining high reactivity and enantioselectivity in the present reaction. The optimized Lewis acid–Lewis acid cooperative system was applicable to a broad range of aryl, heteroaryl, alkenyl, and alkyl aldehydes, giving products in 88–98% ee (Scheme 5).[29]



Scheme 5 Catalytic asymmetric α-addition of isocyanides to aldehydes under heterobimetallic Lewis acid/Lewis acid cooperative catalysis.



Scheme 6 Catalytic asymmetric ring opening of *meso* aziridines promoted by a heterodinuclear rare earth metal Schiff base **3c** catalyst and its application to cyclic γ-amino acid synthesis.

The utility of the dinucleating Schiff bases **3** derived from *o*-vanillin[30] was further expanded to a heterobimetallic catalyst composed of two distinct rare earth metals, a cationic Lewis acidic rare earth metal and a Brønsted basic rare earth metal alkoxide. Lewis acidic $Yb(OTf)_3$ and Brønsted basic $La(O\text{-}iPr)_3$ were successfully placed onto the same dinucleating ligand **3b**, and the heterobimetallic La/Yb/**3b** = 1:1:1 catalyst promoted the asymmetric ring-opening reaction of *meso* aziridines[31] with malonates. The desymmetrized ring-opening adducts were obtained in 63–99% yield and 98–99% ee from cyclic and acyclic *meso* aziridines (Scheme 6).[32] The utility of the products was demonstrated through transformation of the ring-opened products into cyclic γ-amino acids, which are useful building blocks in foldamer research.[33]

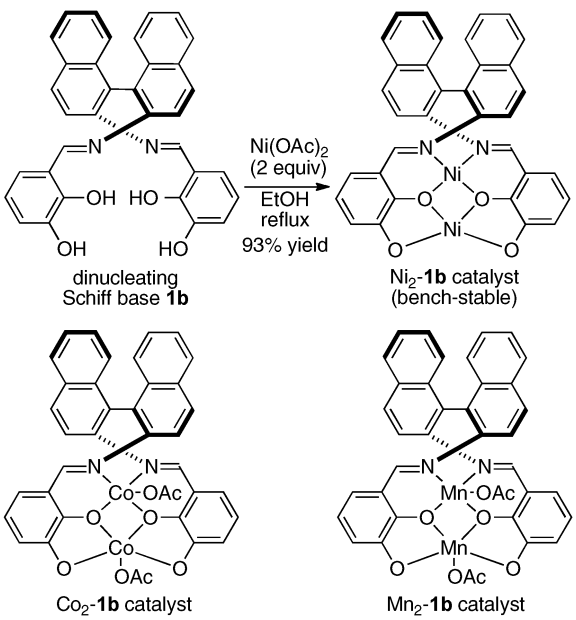
Homobimetallic first-row transition metal catalysts

In the heterodinuclear Schiff base catalysts described in previous sections, it is important to establish the method of obtaining uniform catalytically active species by selectively

placing two different metals into two distinct cavities. If different heterodinuclear complexes exist in equilibrium, that may lead to low enantioselectivity. To avoid difficulty in the preparation of dinuclear Schiff base complexes, the possible metal combination was limited to some extent, that is, large and oxophilic rare earth metals were used as the second metal to be selectively incorporated into the outer O_2O_2 cavity. In order to further expand the diversity of dinuclear Schiff base catalysis, we planned to develop dinuclear Schiff base cooperative catalysts without using rare earth metals.

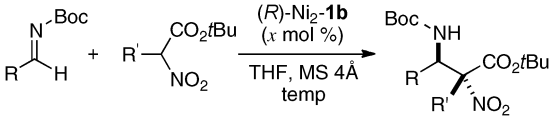
To avoid difficulty in the two metals-one-ligand complexation process, we decided to use the two same metals in the design of dinuclear cooperative catalysts. For creating unique catalytic intramolecular cooperative activity of homodinuclear catalysts different from mononuclear metal–salen intermolecular cooperative systems, it would be desirable to place the two metals into two distinct cavities because two metals in a coordinatively different environment should have different functions.[34] While addressing this issue, dinucleating Schiff base **1b** derived from 1,1′-binaphthyl-2,2′-diamine was found to be the best. Because the size of the O_2O_2 outer cavity in **1b** was smaller than that in related Schiff bases derived from other diamines, various first-row transition metals were successfully incorporated into the O_2O_2 outer cavity. As shown in Scheme 7, the reaction of the dinucleating Schiff base **1b** with two equivalents of $Ni(OAc)_2 \cdot 4H_2O$ gave a homodinuclear Ni_2–**1b** catalyst in 93% yield as a bench-stable solid.[35] Homodinuclear Co_2–**1b** catalyst[36] and Mn_2–**1b** catalyst[37] were also synthesized starting from corresponding metal acetates under dry air-atmosphere without difficulty.

Homodinuclear transition metal–**1b** complexes were utilized for the catalytic asymmetric carbon–carbon bond-forming reactions with pronucleophiles bearing a relatively acidic proton.



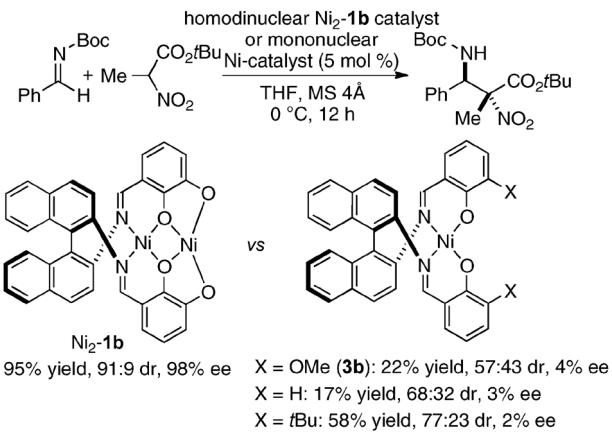
Scheme 7 Preparation of bench-stable homodinuclear transition metal catalysts from dinucleating Schiff base **1b** derived from 1,1′-binaphthyl-2,2′-diamine.

Table 4 Ni_2–**1b**-catalyzed asymmetric direct Mannich-type reaction



Run	Imine (R)	Nitro-acetate (R′)	x	Temp (°C)	Time (h)	Yield (%)	dr *anti*:*syn*	ee (%)
1	C_6H_5	Me	5	0	12	95	91:9	98
2	4-MeO–C_6H_4	Me	5	0	12	92	87:13	98
3	4-Me–C_6H_4	Me	5	0	12	90	89:11	97
4	4-Cl–C_6H_4	Me	5	0	12	87	86:14	97
5	4-F–C_6H_4	Me	5	0	12	91	90:10	91
6	3-Thienyl	Me	5	0	12	96	91:9	99
7	C_6H_5	Et	5	0	12	91	94:6	99
8	C_6H_5	*n*Pr	5	0	12	92	92:8	>99
9	C_6H_5	Bn	5	0	12	94	88:12	94
10	$C_6H_5CH_2CH_2$–	Me	10	−40	36	73	>97:3	95
11	*n*Bu	Me	10	−40	36	67	>97:3	93
12	iBu	Me	10	−20	24	85	>97:3	91
13	C_6H_5	Me	1	25	12	93	88:12	98

As summarized in Table 4, the homodinuclear Ni_2–**1b** catalyst promoted direct Mannich-type reaction[38] of *N*-Boc imines with α-substituted nitroacetates. Not only aryl and heteroaryl imines, but also isomerizable alkyl imines were applicable, and products were obtained in 91 → 99% ee and 86:14 → 97:3 diastereoselectivity.[35] Products were readily converted into α,β-diamino acids with an α-tetrasubstituted stereocenter. As shown in run 13, catalyst loading was successfully reduced to 1 mol%, while maintaining high enantioselectivity. The homodinuclear Ni_2–**1b** catalyst showed unique catalytic activity and stereoselectivity in comparison with related mononuclear Ni–Schiff base complexes as summarized in Scheme 8. Mononuclear Ni–Schiff base complexes gave only poor reactivity, diastereoselectivity, and enantioselectivity. Thus, we believe that the cooperative function of the two Ni centers would be important. The postulated cooperative mechanism of the dinuclear Ni-catalysis is shown in Fig. 10. One of the Ni–O bonds in the outer O_2O_2 cavity works as a Brønsted base to deprotonate the nitroacetate and generate a nickel-nitronate *in situ*. The other nickel in the inner N_2O_2 cavity functions as a



Scheme 8 Catalytic activity difference between homodinuclear Ni_2–**1b** catalyst and mononuclear Ni–Schiff base catalysts.

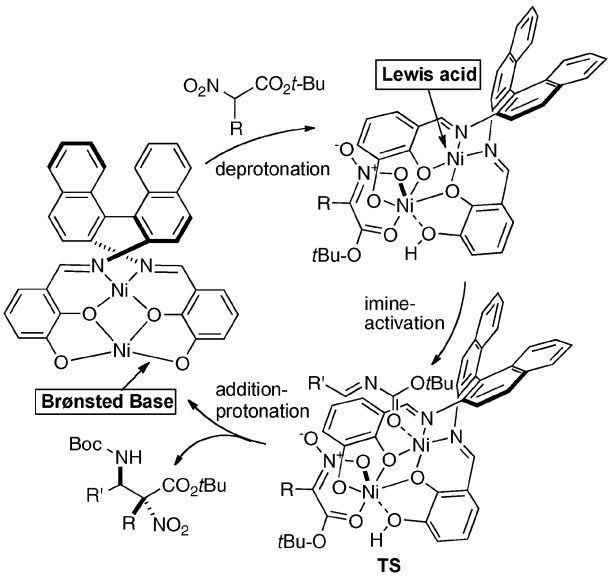
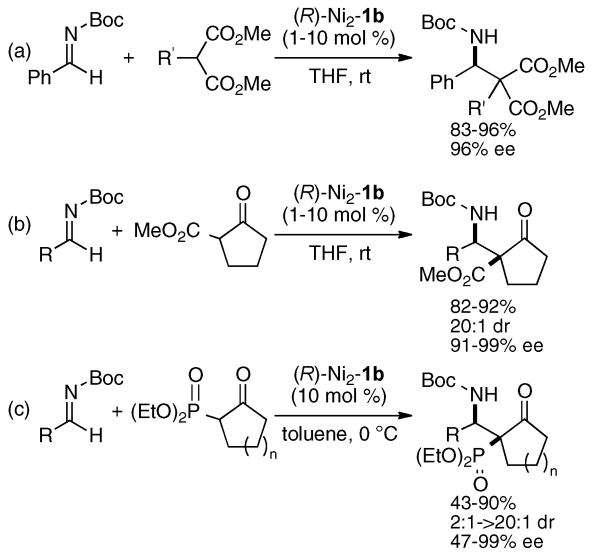


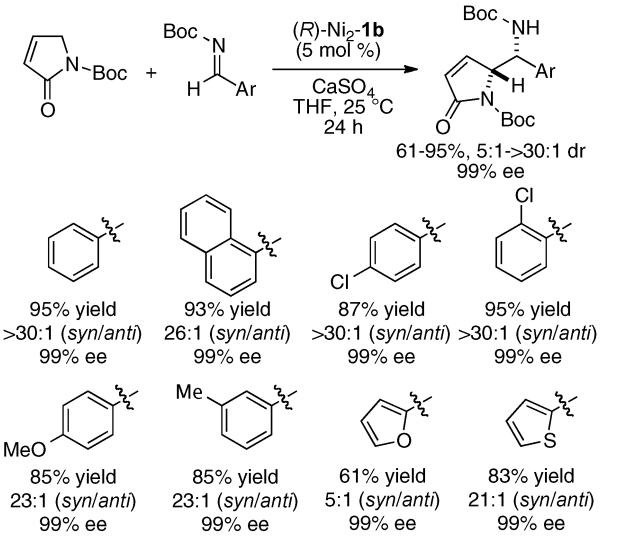
Fig. 10 Postulated Lewis acid–Brønsted base cooperative mechanism of homodinuclear Ni_2–**1b** catalyst.

Lewis acid to control the position of the imines. The carbon–carbon bond-formation, followed by protonation, affords the Mannich product and regenerates the Ni_2–**1b** catalyst.

The same Ni_2–**1b** catalyst was also suitable for the direct catalytic asymmetric Mannich-type reaction of malonates,[35] β-keto esters,[35] and β-keto phosphonates,[39] as summarized in Scheme 9. The scope of the Ni_2–**1b** catalysis was further expanded to direct catalytic asymmetric vinylogous Mannich-type reaction.[40] The reaction of *N*-Boc imines with an α,β-unsaturated γ-butyrolactam proceeded with good to high *syn*-selectivity and enantioselectivity at 25 °C (99% ee, Scheme 10).[41] In the vinylogous Mannich-type reaction, the scope of imines was,



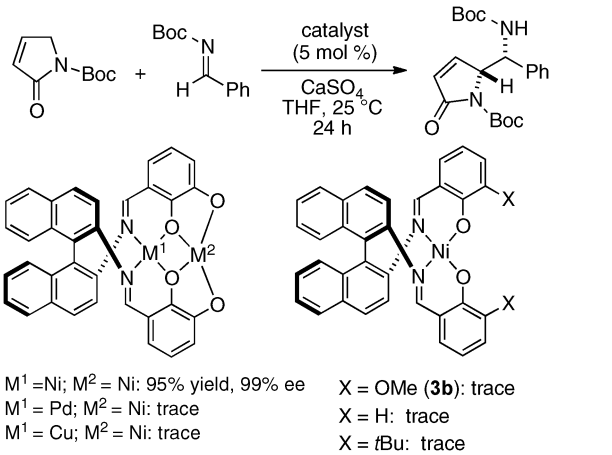
Scheme 9 Direct catalytic asymmetric Mannich-type reactions of (a) malonates, (b) β-keto esters, and (c) β-keto phosphonates under dinuclear Ni-catalysis.



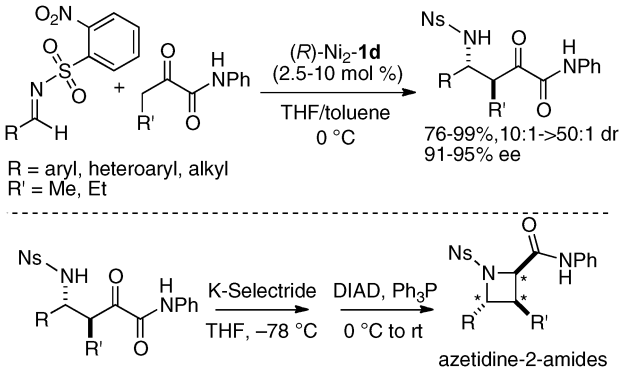
Scheme 10 Direct catalytic asymmetric vinylogous Mannich-type reaction of α,β-unsaturated γ-butyrolactam.

however, limited to non-isomerizable aryl and heteroaryl *N*-Boc imines. When using isomerizable alkyl *N*-Boc imines, undesirable isomerization of imines to enamides *via* α-deprotonation of alkyl *N*-Boc imines competed with desired vinylogous Ni-enolate formation from the α,β-unsaturated γ-butyrolactam, thereby resulting in poor yield of Mannich products. The negative control experiments of the vinylogous Mannich-type reaction using heterodinuclear Pd or Cu–Ni–**1b** complexes and mononuclear Ni–Schiff base complexes resulted in trace, if any, products (Scheme 11). Thus, the importance of the cooperative functions of two Ni-centers in distinct cavities was confirmed again. We believe that the vinylogous Mannich-type reaction of α,β-unsaturated γ-butyrolactam was promoted in a similar manner as discussed in Fig. 10 for the Mannich-type reaction of nitroacetates.

When using 1,2-dicarbonyl compounds as a pronucleophile, a slight modification of the chiral environment of the dinuclear Ni-catalyst was effective. The best selectivity was achieved with



Scheme 11 Negative control experiments using heterodinuclear **1b** complexes and mononuclear Ni-Schiff base complexes.

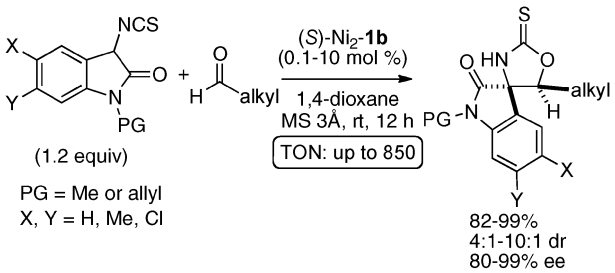


Scheme 12 Biphenyldiamine-based homodinuclear Ni_2–**1d**-catalyzed asymmetric Mannich-type reaction of 1,2-dicarbonyl compounds, and its application to azetidine-2-amide synthesis.

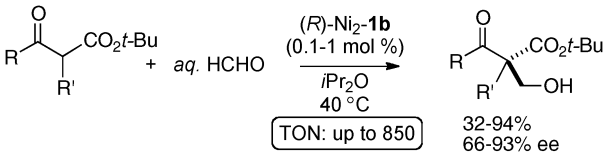
the Schiff base **1d** derived from biphenyldiamine, and the Ni_2–**1d** catalyst gave products in 91–95% ee and 10 : 1 → 50 : 1 dr at 0 °C (Scheme 12).[42] The Mannich adducts in Scheme 12 were useful precursors for the synthesis of fully substituted azetidine carboxylic acid derivatives as unnatural α-amino acids. Stereoselective reduction of Mannich adducts with K-Selectride, followed by intramolecular Mitsunobu cyclization, gave azetidine-2-amides.

The homodinuclear Ni_2–**1b** catalyst was also applicable to electrophiles other than imines. For example, the aldol-type reaction also proceeded under simple proton transfer conditions. As shown in Scheme 13, direct catalytic asymmetric aldol reaction of 3-isothiocyanato oxindoles[43] proceeded smoothly to give spiro-oxindoles in 80–99% ee and 4 : 1–10 : 1 dr from aliphatic aldehydes.[44,45] It is noteworthy that the reaction proceeded smoothly even when using as little as 0.1 mol% of Ni_2–**1b** catalyst (TON = 850). The Ni_2–**1b** catalyst gave, however, poor selectivity in the case of aromatic aldehydes. For the aromatic aldehydes, a $Sr(O\text{-}iPr)_2$/**3b** was used alternatively.[46] Because the Ni_2–**1b** catalyst was bench-stable and tolerant towards water, aqueous formaldehyde was utilized as an electrophile in catalytic asymmetric hydroxymethylation of β-keto esters, giving products in 66–94% ee. A high catalyst turnover number, up to 940, was also observed in the hydroxymethylation (Scheme 14).[47]

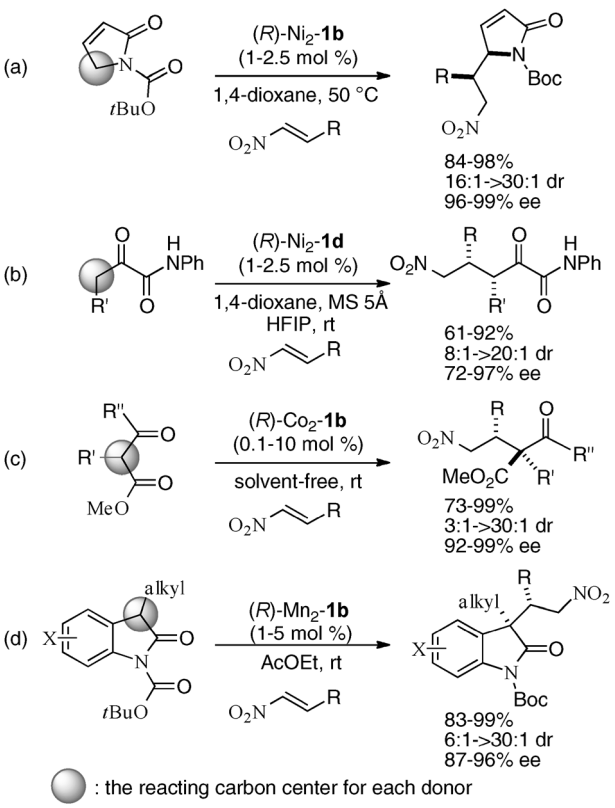
For the catalytic asymmetric Michael reaction to nitroalkenes,[48] the selection of a suitable metal source was important



Scheme 13 Catalytic asymmetric aldol-type reaction of 3-isothiocyanato oxindoles to aldehydes.

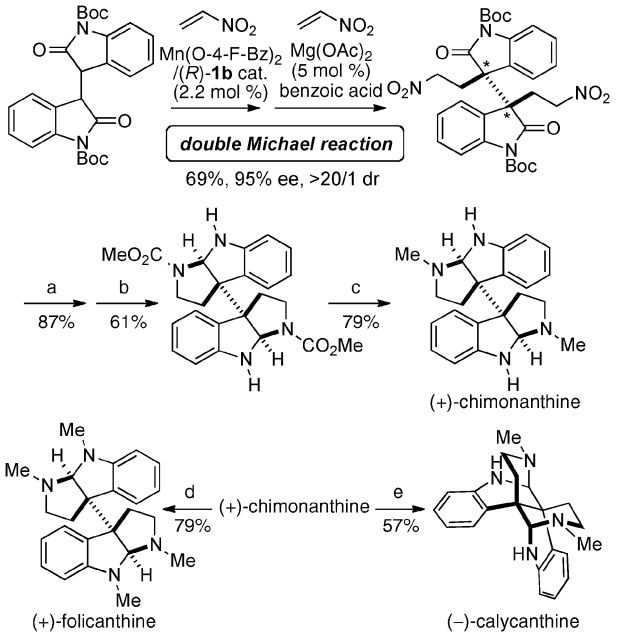


Scheme 14 Catalytic asymmetric aldol reaction of β-keto esters with aqueous formaldehyde.

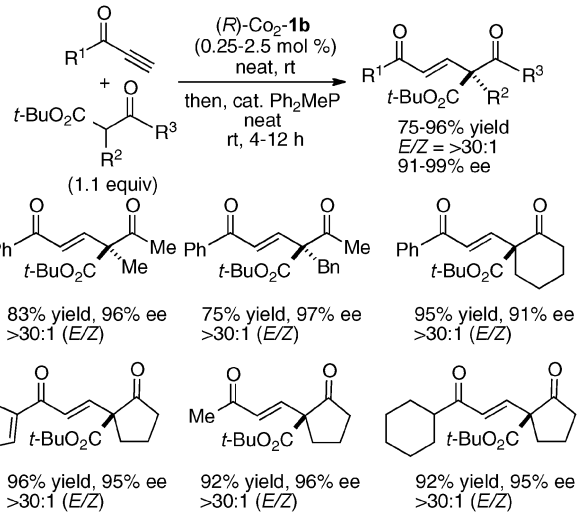


Scheme 15 Catalytic asymmetric Michael reactions of various bidentate donors to nitroalkenes under homodinuclear Schiff base catalysis.

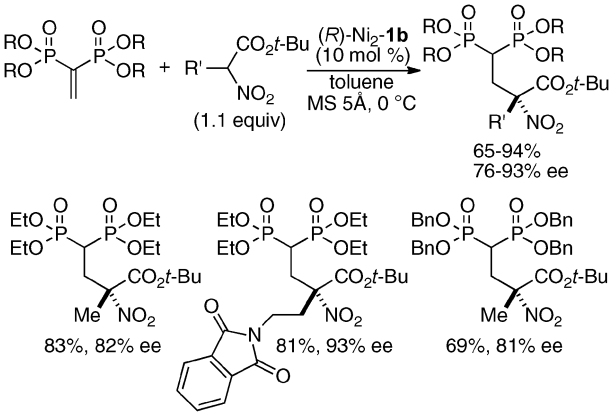
in the control of catalyst sites-substrates arrangement. Ni_2–**1b** smoothly promoted asymmetric vinylogous Michael reaction with the α,β-unsaturated γ-butyrolactam, giving products in high enantio- and diastereoselectivity (Scheme 15a).[41,49] When using 1,2-dicarbonyl compounds as donors, Ni_2–**1d** gave much better stereoselectivity than Ni_2–**1b** (Scheme 15b).[50] On the other hand, homodinuclear Ni-catalysts gave poor to moderate enantio- and diastereoselectivity for other donors, such as β-keto esters and *N*-Boc oxindoles. After optimization studies, Co_2–**1b** was found to be the best for asymmetric Michael reaction with β-keto esters (Scheme 15c),[36,51] while Mn_2–**1b** was required in the reaction with *N*-Boc oxindoles as donors (Scheme 15d).[37] The related enantio- and diastereoselective double Michael reaction of *N*-Boc bisoxindole was applied for a concise catalytic enantioselective total synthesis of hexahydropyrrolo-indole alkaloids, such as (+)-chimonanthine, (+)-folicanthine, and (−)-calycanthine (Scheme 16).[52–54] In the double Michael reaction of *N*-Boc bisoxindole, $Mn(O\text{-}4\text{-}F\text{-}benzoate)_2$ was utilized instead of $Mn(OAc)_2$



Scheme 16 Concise catalytic asymmetric total synthesis of (+)-chimonanthine, (+)-folicanthine, and (−)-calycanthine *via* double Michael reaction; reagents and conditions: (a) $NiCl_2$, $NaBH_4$, dimethyl dicarbonate, MeOH, 87% yield; (b) $LiEt_3BH$, toluene, −78 °C to −40 °C, 1 h; 4 M HCl in AcOEt, rt, 5 h; TFA, rt, 15 h, 61% yield; (c) sodium bis-(2-methoxyethoxy) aluminum hydride, toluene, reflux, 4.5 h, 79% yield; (d) aq. HCHO, $NaBH(OAc)_3$, MeCN, rt, 0.5 h, 79% yield; (e) AcOH, H_2O, 95 °C, 48 h, 57% yield.



Scheme 17 Asymmetric Michael addition of β-keto esters to alkynones under homodinuclear Co_2–**1b** catalysis.

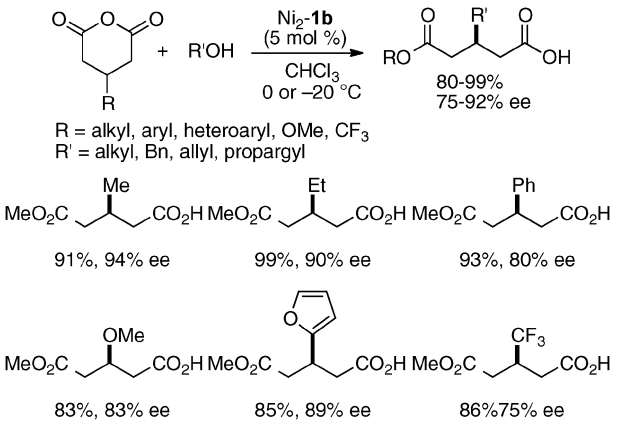


Scheme 18 Asymmetric Michael addition of nitroacetates to vinylidene-bisphosphonates under homodinuclear Ni_2–**1b** catalysis.

as a metal source in the first Michael reaction. For the second Michael reaction, the chiral Mn–**1b** catalyst gave the double Michael product in excellent enantioselectivity *via* chiral amplification (99% ee), but only in moderate yield (44%) possibly due to the steric hindrance of vicinal quaternary carbon stereocenters;[55] thus, the diastereoselectivity in the second Michael reaction was controlled by a catalytic amount of less hindered achiral $Mg(OAc)_2$, giving the double Michael adduct in 69% yield (in two steps), 95% ee, and >20 : 1 dr. Reduction of the nitro groups in the double Michael adduct (87% yield), followed by reductive cyclization gave a known key intermediate in 61% yield. Enantioselective total synthesis of (+)-chimonanthine was thus achieved in overall 25% yield (5 steps from *N*-Boc bisoxindole). (+)-Folicanthine and (−)-calycanthine were also synthesized from (+)-chimonanthine using the reported procedure.[52]

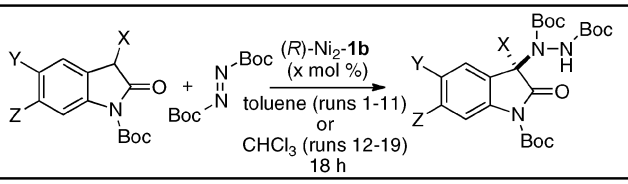
Asymmetric Michael reactions with other acceptors were also achieved under homodinuclear Schiff base catalysis, such as alkynones (Scheme 17)[36] and vinylidenebisphosphonates (Scheme 18).[56] In the catalytic asymmetric Michael addition to alkynones, Co_2–**1b** catalyst gave the best results under solvent-free conditions. Because the *E*/Z ratio was moderate after the Co_2–**1b**-catalyzed addition/protonation process, the crude reaction mixture was directly treated with a catalytic amount of Ph_2MeP to afford the thermodynamically more favorable *E*-isomer predominantly (>30 : 1). In the catalytic asymmetric 1,4-addition of nitroacetates to vinylidenebisphosphonates, Ni_2–**1b** catalyst gave the best enantioselectivity. Products in Scheme 18 can be key synthetic intermediates for biologically important bisphosphonates with an α-amino acid unit.

The utility of the homodinuclear Ni_2–**1b** catalyst was further expanded to reactions other than C–C bond-forming reactions. Catalytic desymmetrization of 3-methylglutaric anhydride and its derivatives with alcohols gave hemi-esters in 80–99% yield and 75–92% ee (Scheme 19).[57] The product of the desymmetrization reaction was utilized as a key building block in the synthetic studies of caprazamycin B.[58] Ni_2–**1b** also promoted asymmetric C–N bond-forming reaction.[59] As shown in Table 5, 1 mol% of Ni_2–**1b** was sufficient to promote asymmetric amination of 3-alkyl-substituted *N*-Boc oxindoles,[60] giving products in high yield with 87–99% ee (runs 1–11). On the other hand, 3-aryl-substituted *N*-Boc oxindoles required much higher catalyst loading (10 mol%) to induce moderate to good enantioselectivity (runs 12–19), because the background racemic reaction competed in the case of 3-aryl-substituted donors.[61] Amination adducts were readily converted into 3-amino-oxindoles *via*

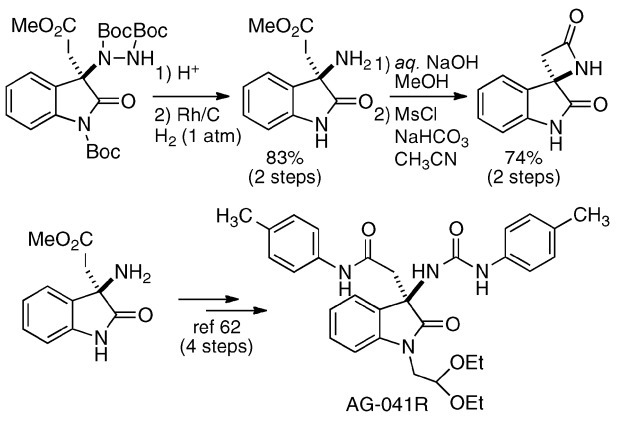


Scheme 19 Ni_2–**1b**-catalyzed desymmetrization of 3-substituted-glutaric anhydrides.

Table 5 Ni_2–**1b**-catalyzed asymmetric amination of oxindoles



Run	X	Y	Z	x	Temp (°C)	Yield (%)	ee (%)
1	Me	H	H	1	50	99	99
2	Allyl	H	H	1	50	99	97
3	(*E*)-Cinnamyl	H	H	1	50	86	91
4	Bn	H	H	1	50	93	99
5	Me	MeO	H	1	50	91	94
6	Me	F	H	1	50	95	96
7	Allyl	F	H	1	50	90	98
8	Allyl	Cl	H	1	50	93	95
9	Bn	H	Cl	1	50	98	99
10	$-CH_2CO_2Me$	H	H	1	50	98	96
11	$-CH_2CN$	H	H	1	50	89	87
12	Ph	H	H	10	30	94	90
13	4-F–C_6H_4	H	H	10	30	91	82
14	3-MeO–C_6H_4	H	H	10	30	93	86
15	2-MeO–C_6H_4	H	H	10	30	75	98
16	Ph	Me	H	10	30	72	74
17	Ph	MeO	H	10	30	86	82
18	4-F–C_6H_4	MeO	H	10	30	72	73
19	3-MeO–C_6H_4	MeO	H	10	30	78	66



Scheme 20 Transformation of the amination adduct.

Boc-removal under acidic conditions, followed by Rh–C catalyzed N–N bond cleavage. A suitably functionalized amination product was, thus, successfully converted into an optically active oxindole bearing a spiro-β-lactam unit and a known intermediate for AG-041R synthesis (Scheme 20).[62]

Conclusions

In summary, a new family of bimetallic cooperative asymmetric catalysts based on dinucleating Schiff bases has been developed. Dinucleating Schiff bases enabled the new metal combinations in bimetallic catalysis, which were impossible in our early studies with BINOL-based chiral ligands. The new either hetero- or homo-bimetallic combinations, such as transition metal/rare earth metal, group 13 metal/rare earth metal, Lewis acidic rare earth metal/Brønsted basic rare earth metal, and transition metal/transition metal led to much improved catalytic activity and selectivity. Readily tunable chiral environments were successfully achieved in the bimetallic Schiff base system, and its utility was demonstrated in a variety of catalytic asymmetric C–C and C–N bond-forming reactions under simple proton transfer conditions. High selectivity and catalytic activity have been realized through unique intramolecular cooperative functions of two metal centers in distinct cavities. Further applications of these bimetallic Schiff base cooperative catalysis are actively ongoing in our group.

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