### Bifunctional Asymmetric Catalysis Based on Dinuclear Schiff Base Complexes

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Abstract: In this account, work in our group on the development and applications of a new family of bimetallic, bifunctional asymmetric catalysts based on dinucleating Schiff bases is described. Suitable design of the dinucleating Schiff bases led to the successful development of heterobimetallic transition metal/rare earth metal catalysts as well as homobimetallic transition metal/transition metal catalysts. The concepts involved in catalyst design, applications to asymmetric reactions, mechanistic insights into bimetallic catalysis as well as the catalytic asymmetric synthesis of biologically active compounds are introduced.

#### 1. Introduction

Catalytic asymmetric processes are potentially more economical and environmentally benign than those using stoichiometric amounts of chiral reagents.<sup>1</sup> The development of asymmetric catalysts that exhibit high activity, high stereoselectivity, and broad substrate generality is highly desirable, and is a major theme of modern organic synthesis. In approaches to this issue, the concept of bifunctional asymmetric catalysis, wherein both partners of a bimolecular reaction are simultaneously activated (dual activation, Figure 1), is often utilized for the design of metallic catalysts as well as organocatalysts.<sup>2</sup> Since our first report on a lanthanum/lithium/binolate heterobimetallic complex in the early 1990's,<sup>3</sup> our group has been working intensively on heterobimetallic Lewis acid/Brønsted base bifunctional catalysis by rare earth metal/alkali metal complexes using BINOL, Pybox, and their derivatives as ligands.<sup>4</sup> When designing bimetallic asymmetric catalysts, the construction of a suitable chiral environment for each targeted reaction is important for achieving the effective dual activation of nucleophiles and electrophiles through the cooperation of two metal centers. Optimization of enantioselectivity and reactivity requires a strategy for constructing a flexible and diverse chiral environment.<sup>5</sup> In order to broaden the scope of bimetallic bifunctional asymmetric catalysis, the development of a heterobimetallic system not using BINOLs or alkali metals is desirable. We believe that new metal combinations will lead to novel catalytic activity and selectivity.

Chiral Schiff base ligands, such as salens, are one class of privileged ligands in asymmetric catalysis. Over the last two



Figure 1. Dual activation with bifunctional bimetallic asymmetric catalysts.

decades, various transition metal-salen and group 13 metalsalen complexes have been widely utilized for a broad range of catalytic enantioselective transformations.<sup>6</sup> In the field of bifunctional catalysis, Jacobsen and coworkers have developed an elegant intramolecular cooperative catalysis using two metal-salen complexes.<sup>6a</sup> Attemps to further strengthen the catalytic activity by linking two salen complexes have also been reported.<sup>7</sup> In addition, several groups have nicely expanded the potential of Schiff base ligands by using them for heterobimetallic transition metal/alkali metal catalysts and transition metal/group 13 metal catalysts.8 However, the combination of transition metal and rare earth metal in chiral heterobimetallic Schiff base catalysts had not been investigated at the time we started our project. In this account, our own efforts toward the design and development of bifunctional heterodinuclear and homodinuclear Schiff base catalysts since 2007 are described. For reports from other groups, see a recent review article<sup>7</sup> and leading references.8

# 2. Heterobimetallic Schiff Base Catalysts Containing Rare Earth Metals

# 2.1 Heterobimetallic Cu/Sm/Schiff base Complex as a Lewis acid/Brønsted base Bifunctional Catalyst

When developing heterobimetallic complexes, the design of a suitable multidentate ligand is important for controlling the position of the two different metals in the complex. These positions have crucial effects on the reactivity as well as the stereoselectivity of the heterobimetallic complex. To realize bimetallic asymmetric catalysis using combinations of transition metal and rare earth metal, we utilized new dinucleating Schiff bases 1 with additional phenolic hydroxyl moieties compared to standard salens (Figure 2). Based on precedents in the field of coordination chemistry,<sup>9</sup> we hypothesized that the Schiff bases 1 would selectively incorporate a transition metal into the N<sub>2</sub>O<sub>2</sub> inner cavity, and an oxophilic rare earth metal with a large ionic radius into the O<sub>2</sub>O<sub>2</sub> outer cavity.

As expected, the selection of a suitable metal combination for each targeted reaction was important for achieving high stereoselectivity. For the *syn*-selective nitro–Mannich-type reaction,<sup>10</sup> a heterobimetallic complex prepared from  $Cu(OAc)_2$ ,  $Sm(O-iPr)_3$ , and dinucleating Schiff base **1a** was



Figure 2. Ligand design and working hypothesis for the formation of a heterobimetallic transition metal(M)/rare earth metal (RE)/Schiff base 1 complex.

the best (Table 1, entry 3). Other metal combinations resulted in much lower selectivity and/or reactivity. As shown in entries 9 and 10, either Cu or Sm alone also resulted in poor reactivity and selectivity. Thus, both metals are essential for high catalytic activity and selectivity. The addition of an achiral phenol source further increased the effectiveness of the reaction (entry 11), giving the product in 94% ee. When reducing the catalyst loading to 5 mol % based on **1a**, the use of oxosamarium alkoxide,  $Sm_5O(O-iPr)_{13}$ , which has a well-ordered structure,<sup>11</sup> gave superior enantioselectivity (entry 12 vs.

**Table 1.** Effects of metal combination and achiral phenol in<br/>asymmetric nitro–Mannich-type reaction.

N <sup>Boc</sup>		M'/M = 1:	$M^{1}/M^{2}/ligand 1a/ArOH = 1:1:1:1 (x mol %)$		Boc	IH	
	Ph∕H <sup>+</sup>		=,4	0 °C, 23 h	Ph		
ent	ry met M <sup>1</sup>	al sources M <sup>2</sup> (	1a mol 9	<sub>%)</sub> ArOH	yield (%) (	dr <i>syn/anti</i> j	% ee ) ( <i>syn</i> )
1	Cu(OAc) <sub>2</sub>	La(O- <i>I</i> Pr) <sub>3</sub>	10	none	73	3:1	5
2	Cu(OAc) <sub>2</sub>	Pr(O- <i>i</i> Pr) <sub>3</sub>	10	none	82	1:1	9
3	Cu(OAc) <sub>2</sub>	Sm(O- <i>i</i> Pr) <sub>3</sub>	10	none	96	>20:1	80
4	Cu(OAc) <sub>2</sub>	Eu(O- <i>i</i> Pr) <sub>3</sub>	10	none	93	>20:1	64
5	Cu(OAc) <sub>2</sub>	Dy(O- <i>i</i> Pr) <sub>3</sub>	10	none	89	7:1	48
6	Zn(OAc) <sub>2</sub>	Sm(O- <i>i</i> Pr) <sub>3</sub>	10	none	0		
7	Mg(OAc) <sub>2</sub>	Sm(O- <i>i</i> Pr) <sub>3</sub>	10	none	0	-	_
8	Ni(OAc) <sub>2</sub>	Sm(O- <i>i</i> Pr) <sub>3</sub>	10	none	0	_	_
9	Cu(OAc) <sub>2</sub>	none	10	none	0	—	
10	none	Sm(O- <i>I</i> Pr) <sub>3</sub>	10	none	14	2:1	29 <sup>a</sup>
11	Cu(OAc) <sub>2</sub>	Sm(O- <i>i</i> Pr) <sub>3</sub>	10	4- <i>t</i> Bu-phenol	96	>20:1	94
12	Cu(OAc) <sub>2</sub>	Sm(O- <i>I</i> Pr) <sub>3</sub>	5	4- <i>t</i> Bu-phenol	94	>20:1	87
13	<sup>b</sup> Cu(OAc) <sub>2</sub>	Sm5(O)(O-1Pr)1	<sub>3</sub> 5	4- <i>t</i> Bu-phenol	97	>20:1	94
14	<sup>b</sup> Cu(OAc) <sub>2</sub>	Sm <sub>5</sub> (O)(O- <i>i</i> Pr) <sub>1</sub>	з 5	4-MeO-pheno	ol 93	>20:1	95
15	<sup>c</sup> Cu(OAc) <sub>2</sub>	Sm <sub>5</sub> (O)(O- <i>I</i> Pr) <sub>1</sub>	3 2	4-MeO-pheno	91	>20:1	91

<sup>*a*</sup>The major product had the (S,S)-configuration. <sup>*b*</sup>1 mol % of Sm<sub>5</sub>O(O-*i*Pr)<sub>13</sub> was used. <sup>*c*</sup>0.4 mol % of Sm<sub>5</sub>O(O-*i*Pr)<sub>13</sub> was used. Reaction time was 39 h.

entry 13). Under the optimized reaction conditions, high *syn*-selectivity and enantioselectivity were achieved with only 2 mol % catalyst (entry 15). Selected examples of the substrate scope of this asymmetric nitro-Mannich-type reaction are shown in Table 2. The Cu/Sm/1a system was applicable to aryl, heteroaryl, and isomerizable alkyl imines, giving the products with high *syn*-selectivity and good enantioselectivity (Table 2).<sup>12</sup> Its applicability to functionalized aliphatic imines was demonstrated by a catalytic asymmetric synthesis of nemonapride (eq. 1), which is used clinically as an antipsychotic agent.

Table 2.	Heterodinuclear Cu/Sm/1a-catalyzed syn-selective
	catalytic asymmetric nitro-Mannich-type reaction.

R N	,Boc + R'CH₂NG H	Ci Sm <sub>5</sub> O Schi D <sub>2</sub> <u>4-M</u> é TI	u(OAc) <sub>2</sub> (x (O- <i>i</i> Pr) <sub>13</sub> ( ff base <b>1a</b> eO-phenol HF, –40 or	c mol 9 0.2x r (x mo (x mo (x mo 7 –50 9	%) mol %) ol %) ol %) ℃		Y <sup>R'</sup> NO₂
entry	imine (R) al	nitro- kane (R')	<b>1a</b> (x mol %)	time (h)	yield (%)	dr ( <i>syn/anti</i> )	% ee )( <i>syn</i> )
1	C <sub>6</sub> H <sub>5</sub>	-CH <sub>3</sub>	5	27	93	>20:1	95
2	4-Me-C <sub>6</sub> H <sub>4</sub>	-CH <sub>3</sub>	5	40	99	>20:1	98
3	3-Me-C <sub>6</sub> H <sub>4</sub>	-CH <sub>3</sub>	5	24	81	>20:1	97
4	2-Me-C <sub>6</sub> H <sub>4</sub>	-CH <sub>3</sub>	5	48	87	>20:1	92
5	4-MeO-C <sub>6</sub> H <sub>4</sub>	-CH <sub>3</sub>	5	39	87	>20:1	96
6	4-CI-C <sub>6</sub> H <sub>4</sub>	-CH <sub>3</sub>	10	23	81	>20:1	92
7	2-naphthyl	-CH <sub>3</sub>	5	24	98	>20:1	96
8	2-furyl	-CH <sub>3</sub>	5	27	86	>20:1	90
9	2-thienyl	-CH <sub>3</sub>	5	48	87	>20:1	88
10	$\mathrm{C_6H_5CH_2CH_2}\text{-}$	-CH <sub>3</sub>	8	39	74	>20:1	80
11	isobutyl	-CH <sub>3</sub>	10	46	72	>20:1	81
12	n-pentyl	-CH <sub>3</sub>	8	39	77	13:1	66
13	C <sub>6</sub> H <sub>5</sub>	-CH <sub>2</sub> CH <sub>3</sub>	5	48	85	>20:1	96
14	4-Me-C <sub>6</sub> H <sub>4</sub>	-CH <sub>2</sub> CH <sub>3</sub>	5	40	88	>20:1	97
15	2-naphtyl	-CH <sub>2</sub> OBr	10	21	86	>20:1	81



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  $\mu$ -oxotrimer [Cu<sub>3</sub>Sm<sub>3</sub>O(ligand 1a)<sub>3</sub>]<sup>+</sup>, a hexamer, a heptamer, an octamer, and a decamer, were observed. In the presence of an achiral phenol, the peak due to  $\mu$ -oxo-trimer [Cu<sub>3</sub>Sm<sub>3</sub>O(ligand 1a)<sub>3</sub>]<sup>+</sup>(m/z = 1,710) 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  $\mu$ -oxo- $\mu$ -aryloxy trimer in the presence of an achiral phenol (Figure 3). On the basis of these ESI-MS observations as well as the positive non-linear-effects seen in this system, we speculated that the  $\mu$ -oxo- $\mu$ -aryloxy trimer complex is the most enantioselective active species. Based on the initial rate kinetic studies and kinetic isotope effect studies, the catalytic cycle shown in Figure 4 was postulated for this reaction. In 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 is important to achieve this *syn*-selective catalytic asymmetric



µ-oxo-µ-aryloxy-trimer Cu/Sm/1a complex

Figure 3. Postulated role of the achiral phenol additive and structure of the  $\mu$ -oxo- $\mu$ -aryloxy-trimer Cu/Sm/1a putative active species.



Figure 4. Catalytic cycle proposed for the Cu/Sm-catalyzed nitro-Mannich-type reaction.

nitro–Mannich–type 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. Of the possible transition states, the sterically less hindered TS–1 is more favorable. Thus, the stereoselective C–C bond–formation via TS–1 followed by protonation by the phenolic proton affords *syn*–product and regenerates the catalyst.

### 2.2 Heterobimetallic Pd/La/Schiff base Complex

In section 2.1, our development of a dinucleating Schiff base to realize heterobimetallic catalysis incorporating a rare earth metal was introduced. The results we obtained suggested that the choice of transition metal (M)/rare earth metal (RE) combination and phenolic additive drastically affect the chiral environment. We assumed that the system could be used to create diverse chiral spaces simply by changing each component of the complex, M, RE and additive phenol. To demonstrate further the utility of the present heterobimetallic system, we applied the dinucleating Schiff base 1a to the anti-selective catalytic asymmetric nitroaldol reaction.<sup>13</sup> As shown in Scheme 1, the Cu-Sm-Schiff base complex suitable for nitro-Mannich-type reactions gave poor results in the nitroaldol reaction, giving product in only 33% yield, anti/syn ratio = 2.3:1, and 1% ee. Screening of the transition metal, rare earth metal, phenolic additive, and other reaction conditions finally revealed that use of the Pd/La/Schiff base 1a with 4bromophenol system was optimum, giving 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 enables optimization of targeted asymmetric reactions by appropriate selection of each catalyst component. With the optimized Pd/ La/1a system, the anti-selective catalytic asymmetric nitroaldol reaction of various aldehydes proceeded in up to 92% ee and 22:1 anti-selectivity (Scheme 2).<sup>14</sup> This reaction was applied to the short syntheses of some  $\beta$ -adrenoceptor agonists.

Scheme 1. Catalyst tuning for the catalytic asymmetric *anti*-selective nitroaldol reaction and postulated structure of the Pd/La/1a complex.

$$Ph H^{+} EtNO_2 \xrightarrow{(R,R)-cat.} Ph \xrightarrow{OH} Ph \xrightarrow{OH} CH_3$$

Cu/Sm/1a/4-tert-Bu-phenol: 33% yield, 1% ee, anti/syn = 2.3:1

(catalyst tuning) inner metal, outer metal, ArOH etc

Pd/La/1a/4-Br-phenol: 92% yield, 84% ee, anti/syn = 19:1



postulated structure of μ-oxo-μ-aryloxy-trimer Pd/La/**1a** complex





## 2.3 Heterobimetallic Ga/cationic Yb/Schiff base Complex as a Lewis acid/Lewis acid Bifunctional Catalyst

In sections 2.1 and 2.2, heterobimetallic transition metal/ rare earth metal systems were described. In both cases, the rare earth metal aryloxide moiety functioned as a Brønsted base. In rare earth metal catalysis, the use of cationic rare earth metal sources as a Lewis acid has also been widely studied.<sup>15</sup> If bimetallic Schiff base complexes with cationic rare earth metals could be incorporated into the outer  $O_2O_2$  cavity of dinucleating Schiff bases, we should be able to use the resulting bimetallic complexes as Lewis acid/Lewis acid cooperative catalysts.<sup>16</sup>

To incorporate a cationic rare earth metal into the outer cavity of a dinucleating Schiff base, we utilized Schiff base **2** derived from *o*-vanillin (Figure 5). We selected  $\alpha$ -additions of  $\alpha$ -isocyanoacetamides to aldehydes as a model reaction because for this transformation a salen-Al catalyst gave only modest enantioselectivity and reactivity.<sup>17</sup> Our working hypothesis for bimetallic Schiff base catalysis is shown in Figure 6. We assumed that the bimetallic Schiff base complex would not only activate the aldehyde with one metal, but might also interact with the  $\alpha$ -isocyanoacetamide through the other metal to effectively control the orientation of the two substrates in the enantio-discriminating step (Figure 6, TS-(A)). After screening suitable metal combinations for Schiff base **2**, Ga(O*i*Pr)<sub>3</sub>/Yb(OTf)<sub>3</sub> was found to afford promising results. The



Figure 5. Design of Schiff bases  $2-H_2$  for the preparation of heterobimetallic complexes incorporating cationic rare earth metals (RE<sup>3+</sup>).

chiral diamine backbone affected both the reactivity and enantioselectivity (Table 3, entries 1-3). Schiff base 2a gave unsatisfactory results, but 2b containing a binaphthyl diamine unit gave 78% ee (entry 2). The best reactivity and selectivity were achieved using Schiff base 2c with an anthracene-derived diamine unit (entry 3, 67% yield, 94% ee). After optimization of the Ga/Yb ratio (1:0.95), product was obtained in > 95%conversion and 96% ee after 24 h (entry 4). To confirm the utility of the Ga(O-iPr)<sub>3</sub>/Yb (OTf)<sub>3</sub> combination, several control experiments were performed with the best ligand 2c (entries 5-13). Neither Ga-2c alone nor Yb-2c alone efficiently promoted the reaction (entries 5-6). For Ga(O-iPr)<sub>3</sub> and other rare earth metal triflates, the reactivity decreased in correlation with the Lewis acidity of the rare earth metal (Yb > Gd > Nd > La),<sup>18</sup> while good to excellent enantioselectivity was maintained in entries 7-9 (89-96% ee). We investigated Et<sub>2</sub>AlCl, Al(O-iPr)<sub>3</sub>, and In(O-iPr)<sub>3</sub> as other sources of group 13 metals for the inner cavity (entries 10-12), but the results were less satisfactory than that of entry 4. In entry 13, Schiff base 1c was utilized instead of Schiff base 2c, but no reaction occurred. The results described in entries 5-13 indi-



Figure 6. Working hypothesis for bimetallic Lewis acid/Lewis acid catalysis of  $\alpha$ -additions of  $\alpha$ -isocyanoacetamides to aldehydes.

Ph	CN H + Bn	N 0 -20	I or 2 DI %) F AÅ °C	°h∕	N Bn	N
entry	M source	RE source (x mol %)	ligand	time (h)	% yield	% ee
1	Ga(O- <i>i</i> Pr) <sub>3</sub>	Yb(OTf) <sub>3</sub> (10)	2a	74	55	29
2	Ga(O- <i>i</i> Pr) <sub>3</sub>	Yb(OTf) <sub>3</sub> (10)	2b	71	27	78
З	Ga(O- <i>I</i> Pr) <sub>3</sub>	Yb(OTf) <sub>3</sub> (10)	2c	74	67	94
4	Ga(O- <i>I</i> Pr) <sub>3</sub>	Yb(OTf) <sub>3</sub> (9.5)	2c	24	>95	96
5	Ga(O- <i>i</i> Pr) <sub>3</sub>	none	2c	24	trace	-
6	none	Yb(OTf) <sub>3</sub> (10)	2c	24	trace	-
7	Ga(O- <i>i</i> Pr) <sub>3</sub>	Gd(OTf) <sub>3</sub> (9.5)	2c	24	62	96
8	Ga(O- <i>I</i> Pr) <sub>3</sub>	Nd(OTf) <sub>3</sub> (9.5)	2c	24	33	95
9	Ga(O- <i>I</i> Pr) <sub>3</sub>	La(OTf) <sub>3</sub> (9.5)	2c	24	11	89
10	Et <sub>2</sub> AICI	Yb(OTf) <sub>3</sub> (9.5)	2c	48	68	37
11	Al(O- <i>i</i> Pr) <sub>3</sub>	Yb(OTf) <sub>3</sub> (9.5)	2c	24	>95	79
12	In(O- <i>i</i> Pr) <sub>3</sub>	Yb(OTf) <sub>3</sub> (9.5)	2c	24	55	80
13	Ga(O- <i>i</i> Pr) <sub>3</sub>	Yb(OTf) <sub>3</sub> (9.5)	1c	24	trace	-

Table 3.Screening of heterobimetallic M/cationic RE/Schiff base<br/>complexes for  $\alpha$ -addition of isocyanide to benzaldehyde.

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cated that the Ga(O-*i*Pr)<sub>3</sub>/Yb(OTf)<sub>3</sub> combination as well as Schiff base **2c** were essential for obtaining high reactivity and enantioselectivity in the present reaction. The optimized Lewis acid/Lewis acid bifunctional system was applicable to a broad range of aryl, heteroaryl, alkenyl, and alkyl aldehydes, giving products in 88–98% ee (Scheme 3).<sup>19</sup>



# 3. Homobimetallic Transition Metal/Schiff base Complex as a Lewis acid/Brønsted base Bifunctional Catalyst

In section 2, the dinucleating Schiff bases 1a and 2c selectively incorporating a transition metal or a group 13 metal into the N2O2 inner cavity, and an oxophilic rare earth metal with a large ionic radius into the O<sub>2</sub>O<sub>2</sub> outer cavity were described. To further expand the utility and diversity of dinuclear Schiff base catalysis, we next decided to develop a new system that would incorporate metals with a smaller ionic radius than the rare earth metals into the O<sub>2</sub>O<sub>2</sub> outer cavity. On the basis of molecular modeling, we speculated that the Schiff base 1b derived from 1,1'-binaphthyl-2,2'-diamine would be suitable because of the conformational difference between trans-1,2diaminocyclohexane and 1,1'-binaphthyl-2,2'-diamine. In fact, treatment of the Schiff base 1b with 2 equiv of Ni(OAc)<sub>2</sub>·4H<sub>2</sub>O afforded a homodinuclear Ni/Schiff base 1b complex in 93% yield (Scheme 4).<sup>20</sup> This complex was stable and storable under air at room temperature for more than three months without any loss of activity. Using it, Mannich-

**Scheme 4.** Preparation of bench–stable Ni<sub>2</sub>–**1b**, Co<sub>2</sub>–**1b**, and Mn<sub>2</sub>– **1b** catalysts from dinucleating Schiff base **1b**–H<sub>4</sub>.



type reactions of aryl, heteroaryl, and isomerizable alkyl N-Boc imines and  $\alpha$ -substituted nitroacetates gave products in 91 - >99% ee and good *anti*-selectivity (Table 4),<sup>20</sup> which were successfully converted into  $\alpha, \beta$ -diamino acids with an  $\alpha$ tetrasubstituted stereocenter. Catalyst loading was successfully reduced to 1 mol %, while maintaining high enantioselectivity. As shown by the control experiments outlined in Scheme 5, monometallic Ni-salen complexes gave poor reactivity, diastereoselectivity, and enantioselectivity. Thus, the cooperative functioning of the two Ni centers must be important. The postulated catalytic cycle is shown in Figure 7. <sup>1</sup>H NMR analysis of the bimetallic Ni<sub>2</sub>-1b complex does not show any peaks due to the paramagneticity, suggesting that at least one of the Ni metal centers has a non-planar coordination mode. Based on molecular modeling, we believe that the outer Ni center adopts the  $cis-\beta$  configuration due to the strain present in the bimetallic complex. In other words, we speculate that one of the Ni–O bonds of the Ni in the outer  $O_2O_2$  cavity is in apical position. This Ni-O bond could work as a Brønsted base to deprotonate  $\alpha$ -nitroacetates giving the Ni-enolate intermediate in situ. The other Ni in the inner N<sub>2</sub>O<sub>2</sub> cavity then functions in a similar way to conventional metal-salen Lewis acid

 
 Table 4.
 Catalytic asymmetric direct Mannich-type reaction under homodinuclear Ni Schiff base catalysis.

	N <sup>-Boc</sup> II + B'-		(/ 0₂ <i>t</i> Bu(	₽)-Ni <sub>2</sub> -1 x mol %	<b>b</b>	Boc、	NH	_
F	R <sup>M</sup> H <sup>T</sup> <sup>T</sup>	NC	) <sub>2</sub> TH	IF, MS temp	4Å	R		₂tBu
entr	y imine: R	Nu: R'	cat (x mol 9	temp %) (°C)	time (h)	yield (%)	dr ( <i>anti/syn</i>	% ee ) ( <i>anti</i> )
1	Ph	Ме	5	0	12	95	91:9	98
2	4-MeO-C <sub>6</sub> H <sub>4</sub>	Me	5	0	12	92	87:13	98
3	4-Me-C <sub>6</sub> H <sub>4</sub>	Me	5	0	12	90	89:11	97
4	4-CI-C <sub>6</sub> H <sub>4</sub>	Me	5	0	12	87	86:14	97
5	4-F-C <sub>6</sub> H <sub>4</sub>	Me	5	0	12	91	90:10	91
6	3-thienyl	Me	5	0	12	96	91:9	99
7	Ph	Et	5	0	12	91	94:6	99
8	Ph	<i>n</i> Pr	5	0	12	92	92:8	>99
9	Ph	Bn	5	0	12	94	88:12	94
10	PhCH <sub>2</sub> CH <sub>2</sub> -	Me	10	-40	36	73	>97:3	95
11	<i>n</i> -butyl	Me	10	-40	36	67	>97:3	93
12	<i>i</i> -butyl	Me	10	-20	24	85	>97:3	91
13	Ph	Me	1	rt	12	93	88:12	98





95% yield, 91:9 dr, 98% ee

X = OMe: 22% yield, 57:43 dr, 4% ee X = H: 17% yield, 68:32 dr, 3% ee X = *t*Bu: 58% yield, 77:23 dr, 2% ee



Figure 7. Catalytic cycle postulated for the Ni<sub>2</sub>-1b-catalyzed asymmetric direct Mannich-type reaction.

catalysis to control the orientation of the imine component. C-C bond-formation via the transition state (TS in Figure 7), followed by protonation, affords the *syn*-adduct and regenerates the  $Ni_2$ -1b catalyst.

As shown in Figure 8, the  $Ni_2$ -1b complex was applicable to a broad range of direct catalytic asymmetric C-C bondforming reactions under simple proton transfer conditions. As



Figure 8. Representative examples of direct asymmetric C-C bondforming reactions under homodinuclear bifunctional Schiff base catalysis.

donors in direct Mannich-type reactions, not only nitroacetates, but also malonates,<sup>20</sup>  $\beta$ -keto esters,<sup>20</sup> and  $\beta$ -keto phosphonates<sup>21</sup> gave excellent enantioselectivity and diastreoselectivity. For the chemoselective activation of 1,2-dicarbonyl compounds as donors, the use of Schiff base 1d (Figure 2) derived from biphenyl diamine gave superior selectivity.<sup>22</sup> It is noteworthy that the Ni<sub>2</sub>-1b complex also promoted the vinylogous direct catalytic asymmetric Mannich-type reaction of an  $\alpha,\beta$ -unsaturated  $\gamma$ -butyrolactam,<sup>23</sup> giving synthetically versatile functionalized  $\alpha, \beta$ -unsaturated  $\gamma$ -butyrolactams in 99% ee. Because the Ni<sub>2</sub>-1b complex is bench-stable and can be used without regard to exposure to air or moisture, hydroxymethylation of  $\beta$ -keto esters using formalin as an electrophile can successfully be achieved.<sup>24</sup> The reaction proceeded with 0.1-1 mol % catalyst, and hydroxymethylated products were obtained in up to 94% ee and 94% yield (TON = up to 940). For asymmetric Michael reactions, the choice of metal was important, this depending on the combination of nucleophile and electrophile. Thus, while for Michael reactions of  $\alpha$ -nitroacetates to vinylbisphosphonates,<sup>25</sup>  $\alpha$ -ketoanilides to nitroalkenes,<sup>26</sup> and  $\alpha$ ,  $\beta$ -unsaturated  $\gamma$ -butyrolactam to nitroalkenes,<sup>23</sup> either the Ni<sub>2</sub>-1b or Ni<sub>2</sub>-1d was the best, for the asymmetric 1,4-addition of  $\beta$ -keto esters to alkynones,<sup>27</sup> Co<sub>2</sub>-1b catalyst was essential to achieve high enantioselectivity. The reaction then proceeded in up to 99% ee under solvent free conditions at room temperature. The Co<sub>2</sub>-1b catalyst was also effective for Michael reaction of  $\beta$ -keto esters to nitroalkenes, this reaction proceeding with as little as 0.1 mol% catalyst loading (TON = up to 980).<sup>28</sup> On the other hand, the  $Mn_2-1b$ catalyst was the best for asymmetric 1,4-addition of N-Boc oxindoles to nitroalkenes for chiral  $\beta$ -amino oxindole synthesis.<sup>29</sup> In all the cases shown in Figure 8, the homodinuclear Ni2-, Co2-, or Mn2-Schiff base complexes displayed much superior reactivity and stereoselectivity to mono-nuclear Ni-, Co-, or Mn-salen complexes. The Ni<sub>2</sub>-1b catalyst was also applicable to the catalytic asymmetric amination of 3substituted N-Boc oxindoles, for which 1 mol% of Ni<sub>2</sub>-1b gave products in 86-99% yield and 87-99% ee (Table 5).<sup>30</sup> A suitably substituted product was successfully converted into an optically active oxindole containing a spiro- $\beta$ -lactam unit and a known key intermediate for AG-041R synthesis (Scheme 6).<sup>31</sup>

 Table 5.
 Catalytic asymmetric amination of 3-substituted N-Boc oxindoles under dinuclear Ni-catalysis.

Y Z	X N Boc (1.1	N N 2 equiv)	c ( <i>R</i> )-Ni <sub>2</sub> -1 (1 mol % toluene 50 °C, 18	$b \\ (b) \\ (b) \\ (b) \\ (b) \\ (c) \\ $	N Boc
entry	х	Y	Z	% yield	% ee
1	Me	Н	Н	99	99
2	allyl	н	н	99	97
3	Ph~~\$	н	Н	86	91
4	Bn	н	Н	93	99
5	Me	MeO	н	91	94
6	Me	F	Н	95	96
7	allyl	F	Н	90	98
8	allyl	CI	н	93	95
9	-CH <sub>2</sub> CO <sub>2</sub> Me	н	Н	98	96
10	-CH <sub>2</sub> CN	н	н	89	87
11	Bn	Н	CI	98	99

Scheme 6. Transformation of amination adduct.



#### 4. Summary

In summary, a new family of bimetallic bifunctional asymmetric catalysts based on dinucleating Schiff bases has been developed by our group. Various asymmetric transformations have been realized via unique intramolecular cooperative functioning of two metal centers in these dinuclear Schiff base complexes. Because new metal combinations lead to novel catalytic activity and selectivity, further applications of these bimetallic Schiff base catalysis are rapidly expanding,<sup>32</sup> which will be reported in due course.

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#### PROFILE



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