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Heterobimetallic Transition Metal/Rare Earth Metal Bifunctional Catalysis: A Cu/Sm/Schiff Base Complex for *Syn*-Selective Catalytic Asymmetric Nitro-Mannich Reaction

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Abstract: The full details of a catalytic asymmetric *syn*-selective nitro-Mannich reaction promoted by heterobimetallic Cu/Sm/dinucleating Schiff base complexes are described, demonstrating the effectiveness of the heterobimetallic transition metal/rare earth metal bifunctional catalysis. The first-generation system prepared from $Cu(OAc)_2$/$Sm(O\text{-}i\text{Pr})_3$/Schiff base **1a** = 1:1:1 with an achiral phenol additive was partially successful for achieving the *syn*-selective catalytic asymmetric nitro-Mannich reaction. The substrate scope and limitations of the first-generation system remained problematic. After mechanistic studies on the catalyst prepared from $Sm(O\text{-}i\text{Pr})_3$, we reoptimized the catalyst preparation method, and a catalyst derived from $Sm_5O(O\text{-}i\text{Pr})_{13}$ showed broader substrate generality as well as higher reactivity and stereoselectivity compared to $Sm(O\text{-}i\text{Pr})_3$. The optimal system with $Sm_5O(O\text{-}i\text{Pr})_{13}$ was applicable to various aromatic, heteroaromatic, and isomerizable aliphatic *N*-Boc imines, giving products in 66−99% ee and *syn*/*anti* = >20:1−13:1. Catalytic asymmetric synthesis of nemonapride is also demonstrated using the catalyst derived from $Sm_5O(O\text{-}i\text{Pr})_{13}$.

Introduction

Catalytic asymmetric processes are potentially more economical and environmentally benign than those using stoichiometric amounts of chiral reagents.[1] To develop asymmetric catalysts that exhibit high activity, high stereoselectivity, and broad substrate generality, investigators often employ the concept of bifunctional asymmetric catalysis with both metallic catalysts and organocatalysts.[2] Dual activation of nucleophiles and electrophiles is key to developing bifunctional catalysts (Figure 1a). Since our first report on a lanthanum/lithium/binolate heterobimetallic complex in the early 1990s,[3] our group has been intensively working on the heterobimetallic Lewis acid/Brønsted base bifunctional catalysis of rare earth metal/alkali metal using BINOL and its derivatives as ligands (Figure 1b).[4] When designing bifunctional asymmetric catalysts, the construction of a suitable chiral environment for each targeted reaction is important. Optimization of enantioselectivity and reactivity requires a strategy for constructing a flexible and diverse chiral environment. To broaden the scope of heterobimetallic bifunctional rare earth metal asymmetric catalysis, it is desirable to develop a heterobimetallic system without using BINOLs or alkali metals. We believe that a new metal combination will lead to the new catalytic activity and selectivity.

Chiral Schiff base ligands, such as salens, are one of the privileged ligands in asymmetric catalysis. Various transition metal−salen complexes have been widely utilized for broad catalytic enantioselective transformations during the last two decades.[5] Trials to further expand the potential of Schiff base ligands by using them for heterobimetallic transition metal/alkali metal catalysts and transition metal/group 13 metal catalysts were recently reported by several groups.[6] Jacobsen and coworkers also reported intermolecular cooperative catalysis of group 13 metals and rare earth metals using a salen−Al catalyst

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(5) Reviews: (a) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421. (b) Katsuki, T. *Chem. Soc. Rev.* **2004**, *33*, 437. (c) Cozzi, P. G. *Chem. Soc. Rev.* **2004**, *33*, 410. (d) McGarrigle, E. M.; Gilheany, D. G. *Chem. Rev.* **2005**, *105*, 1563. (e) Baleizao, C.; Garcia, H. *Chem. Rev.* **2006**, *106*, 3987.

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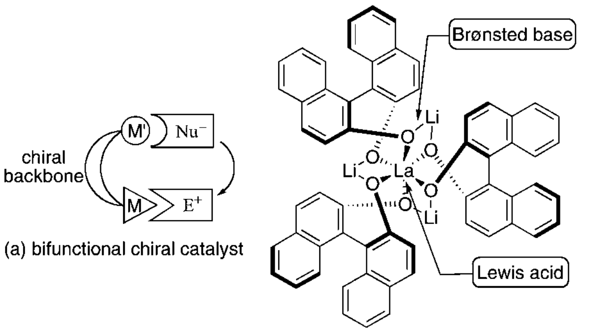


(a) bifunctional chiral catalyst

(b) bifunctional La/Li/BINOL catalyst

(c) dinucleating Schiff base **1**-H$_4$ and bimetallic M/RE/**1** complex

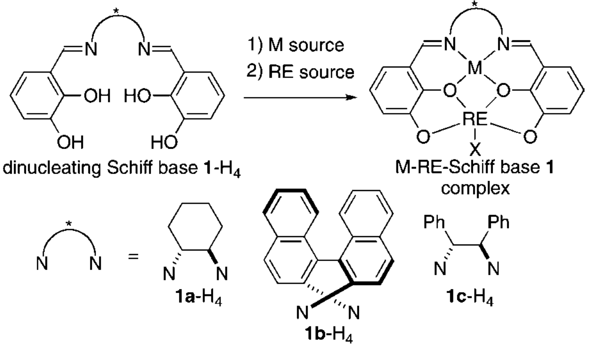
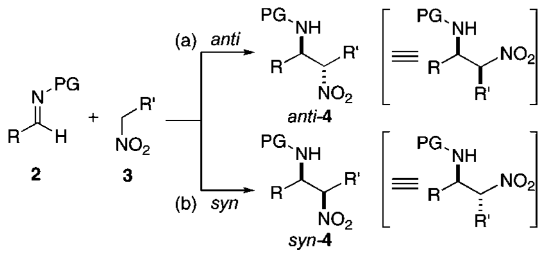


Figure 1. (a) Concept for bimetallic bifunctional catalysts, (b) a heterobimetallic La/Li/BINOL catalyst, and (c) dinucleating Schiff bases **1**-H$_4$ and a heterobimetallic transition metal(M)/rare earth metal (RE)/Schiff base **1** complex.

with an ErCl$_3$-pybox system.[7] However, the combination of transition metal/rare earth metal as chiral heterobimetallic Schiff base catalysts has not been investigated.

In this context, we launched a new investigation of transition metal/rare earth metal/Schiff base catalysts to expand the diversity of heterobimetallic rare earth metal asymmetric catalysts and communicated the utility of a dinucleating Schiff base **1a** (Figure 1c) in 2007.[8,9] The dinucleating Schiff base **1a** was suitable for incorporating both a transition metal and a rare earth metal. A Cu/Sm/Schiff base **1a** complex (M = Cu, RE = Sm) promoted the *syn*-selective catalytic asymmetric nitro-Mannich reaction. In the present paper, we report the complete details of the heterobimetallic Cu/Sm/Schiff base **1a** catalysis. Here, we describe the design of transition metal/rare earth metal heterobimetallic catalysts, the development of the first-generation Cu/Sm catalyst for the *syn*-selective catalytic asymmetric nitro-Mannich reaction, the mechanistic studies of the Cu/Sm catalyst, reoptimization toward the second generation Cu/Sm catalyst, and its application to catalytic asymmetric synthesis of pharmaceuticals.

Scheme 1. Catalytic Enantio- and Diastereoselective Nitro-Mannich Reaction



Results and Discussion

A. Development of the First-Generation Cu/Sm Schiff Base Catalyst and Its Application to the *Syn*-Selective Asymmetric Nitro-Mannich Reaction. The nitro-Mannich (aza-Henry) reaction[10] provides synthetically versatile β-nitroamines (Scheme 1) that can be converted to 1,2-diamines, α-aminocarbonyl compounds, and others.[11] Over the past decade, tremendous effort has been devoted to the development of catalytic enantioselective variants.[12−17] Since our reports using heterobimetallic metal−binolate complexes,[12] diastereo- and enanti-

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(8) For the preliminary communication of this article, see: Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 4900.

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(11) (a) For the utility of the nitro group in organic synthesis, see: *The Nitro Group in Organic Synthesis*; Ono, N., Ed.; Wiley-VCH: New York, 2002. (b) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017. (c) Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 612.

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(13) For selected examples of enantioselective nitro-Mannich reactions with nitromethane, see: (a) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625. (b) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7975. (c) Bernardi, L.; Fini, F.; Herrera, R. P.; Ricci, A.; Sgarzani, V. *Tetrahedron* **2006**, *62*, 375. (d) Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; López, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 117. (e) Gao, F.; Zhu, J.; Tang, Y.; Deng, M.; Qian, C. *Chirality* **2006**, *18*, 741. (f) Zhou, H.; Peng, D.; Qin, B.; Hou, Z.; Liu, X.; Feng, X. *J. Org. Chem.* **2007**, *72*, 10302. (g) Chang, Y.-W.; Yang, J.-J.; Dang, J.-N.; Xue, Y.-X. *Synlett* **2007**, 2283. (h) Wang, C.; Zhou, Z.; Tang, C. *Org. Lett.* **2008**, *10*, 1707. (i) Tan, C.; Liu, X.; Wang, L.; Wang, J.; Feng, X. *Org. Lett.* **2008**, *10*, 5305. (j) Zhang, G.; Yashima, E.; Woggon, W.-D. *Adv. Synth. Catal.* **2009**, *351*, 1255. In refs 13a and 13h, nitroethane is also utilized in one example, giving *anti*-adducts.

(14) *Anti*-selective reactions with metal catalysts: (a) Yamada, K.-I.; Moll, G.; Shibasaki, M. *Synlett* **2001**, 980. (b) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992. (c) Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843. (d) Lee, A.; Kim, W.; Lee, J.; Hyeon, T.; Kim, B. M. *Tetrahedron: Asymmetry* **2004**, *15*, 2595. (e) Anderson, J. C.; Howell, G. P.; Lawrence, R. M.; Wilson, C. S. *J. Org. Chem.* **2005**, *70*, 5665. (f) Trost, B. M.; Lupton, D. W. *Org. Lett.* **2007**, *9*, 2023.

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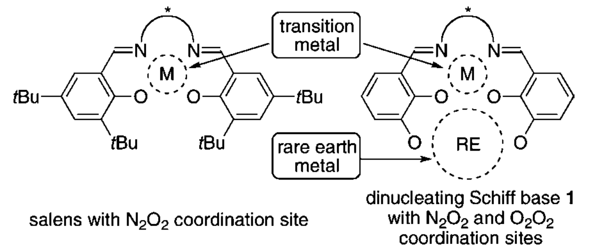


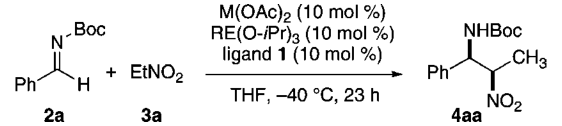
Figure 2. Ligand design for the formation of transition metal(M)/rare earth metal (RE) heterobimetallic complex.

oselective reactions with various nitroalkanes have been realized using metal catalysts[14] and organocatalysts, such as thioureas,[15] Brønsted acid catalysts,[16] and cinchona alkaloids.[17] Although those catalysts gave *anti*-**4** in good yield and high diastereo- and enantioselectivity (Scheme 1a),[18] there were no reports of a *syn*-selective catalytic asymmetric nitro-Mannich reaction when we started this project (Scheme 1b).[19] Thus, the development of a new catalyst for a complementary *syn*-selective nitro-Mannich reaction has been highly desirable. We initially investigated various metal−BINOLate complexes to achieve the *syn*-selective reaction, but all trials with BINOL and its derivatives failed. Therefore, we started investigations to design a new heterobimetallic transition metal/rare earth metal/Schiff base catalyst toward the development of the *syn*-selective nitro-Mannich reaction.

The ligand design is shown in Figure 2. We selected dinucleating Schiff base **1**, which has an additional phenolic OH functional group compared to classical salens. We speculated that the Schiff base **1** would incorporate a transition metal into the N$_2$O$_2$ inner cavity in a similar manner as salens and would also incorporate an oxophilic rare earth metal with a large ionic radius into the O$_2$O$_2$ outer cavity. On the basis of previous studies in the field of coordination chemistry,[20] the selection of a diamine backbone is thought to be important to selectively form heterobimetallic transition metal/rare earth metal complexes.

The initial optimization studies are summarized in Table 1. After screening various metal combinations using the dinucleating Schiff base **1a** for the reaction of *N*-Boc imine **2a** and nitroalkane **3a**, the combination of Cu(OAc)$_2$ and La(O-*i*Pr)$_3$ with **1a** afforded product **4aa** slightly in favor of the *syn*-isomer (entry 1, *syn*/*anti* = 3:1), despite poor enantioselectivity (5% ee). Because enantio- and diastereoselectivity are often affected by the size of rare earth metals,[21] other rare earth metals were examined in entries 2−9. Of these, Sm(O-*i*Pr)$_3$ gave the best selectivity (entry 4, *syn*/*anti* = >20:1, 80% ee). Metals with larger ionic radii (entries 1−3) and metals with smaller ionic radii (entries 5−9) afforded lower selectivity than samarium. Samarium would have a suitable size to induce high *syn*-selectivity as well as good enantioselectivity. In entries 10−13, other inner metals were investigated using Sm(O-*i*Pr)$_3$ as an outer metal. Zn(OAc)$_2$, Mg(OAc)$_2$, and Ni(OAc)$_2$ resulted in no reaction (entries 10−12). Rh(OAc)$_2$ in entry 13 gave product **4aa** in 90% yield, but with poor diastereo- and enantioselectivity. Thus, Cu(II) was also essential for realizing high selectivity and good reactivity. The effects of chiral ligands were investigated in entries 14 and 15, but neither Schiff base **1b**[22] nor **1c** afforded the desired product (0% yield), possibly because the distance between the Cu and Sm metal centers was not suitable to cooperatively promote the desired reaction.

Table 1. Optimization Studies: Metal and Ligand Effects



entry	metal sources M	 RE	ligand	yield[a] (%)	dr[a] (*syn*/*anti*)	% ee (*syn*)
1	Cu(OAc)$_2$	La(O-*i*Pr)$_3$	**1a**	73	3:1	5
2	Cu(OAc)$_2$	Pr(O-*i*Pr)$_3$	**1a**	82	1:1	9
3	Cu(OAc)$_2$	Nd(O-*i*Pr)$_3$	**1a**	71	>20:1	58
4	Cu(OAc)$_2$	Sm(O-*i*Pr)$_3$	**1a**	96	>20:1	80
5	Cu(OAc)$_2$	Eu(O-*i*Pr)$_3$	**1a**	93	>20:1	64
6	Cu(OAc)$_2$	Gd(O-*i*Pr)$_3$	**1a**	84	13:1	25
7	Cu(OAc)$_2$	Dy(O-*i*Pr)$_3$	**1a**	89	7:1	48
8	Cu(OAc)$_2$	Er(O-*i*Pr)$_3$	**1a**	71	11:1	36
9	Cu(OAc)$_2$	Yb(O-*i*Pr)$_3$	**1a**	63	4:1	6
10	Zn(OAc)$_2$	Sm(O-*i*Pr)$_3$	**1a**	0		
11	Mg(OAc)$_2$	Sm(O-*i*Pr)$_3$	**1a**	0		
12	Ni(OAc)$_2$	Sm(O-*i*Pr)$_3$	**1a**	0		
13	Rh(OAc)$_2$	Sm(O-*i*Pr)$_3$	**1a**	90	1:3	1[b]
14	Cu(OAc)$_2$	Sm(O-*i*Pr)$_3$	**1b**	0		
15	Cu(OAc)$_2$	Sm(O-*i*Pr)$_3$	**1c**	0		

[a] Determined by ^{1}H NMR analysis. [b] Enantiomeric excess of the *anti*-isomer.

The results in Table 1 suggested that both Cu and Sm are important for high *syn*-selectivity (>20:1), good enantioselectivity (80% ee), and good reactivity. To confirm the utility of the Cu/Sm combination, several control experiments were performed (Table 2). Neither Cu(OAc)$_2$ nor Sm(O-*i*Pr)$_3$ alone gave good results (entries 2 and 5). A Cu(II)−Lewis acid in

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(16) *Anti*-selective reactions with Brønsted acids: (a) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418. (b) Rueping, M.; Antonchick, A. P. *Org. Lett.* **2007**, *10*, 1731.

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(18) In this manuscript, *anti*-nitro-Mannich adduct and *syn*-nitro-Mannich adduct are defined as shown in Scheme 1. In refs 14−17, diastereomers are sometimes defined in the opposite way.

(19) After our preliminary communication on the first *syn*-selective reaction in ref 8, an organocatalytic *syn*-selective method using nitroethane was reported very recently: Jiang, X.; Zhang, Y.; Wu, L.; Zhang, G.; Liu, X.; Zhang, H.; Fu, D.; Wang, R. *Adv. Synth. Catal* **2009**, *351*, 2096.

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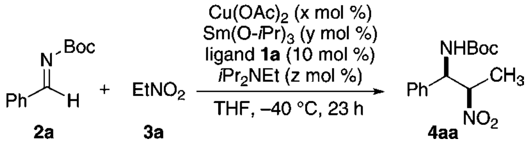
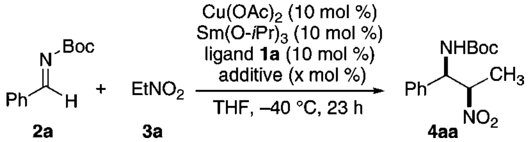
Table 2. Control Experiments



entry	$Cu(OAc)_2$ (*x* mol %)	Sm(O-*i*Pr)$_3$ (*y* mol %)	*i*Pr$_2$NEt (*z* mol %)	yield[a] (%)	dr[a] (*syn*/*anti*)	% ee (*syn*)
1	10	10	0	96	>20:1	80
2	10	0	0	0		
3	10	0	20	0		
4	10	0	100	24	2:1	1[b]
5	0	10	0	14	2:1	29[b]
6	10	5	0	14	16:1	3
7	10	20	0	90	7:1	3

[a] Determined by ^{1}H NMR analysis. [b] *ent*-**4aa** was the major product.

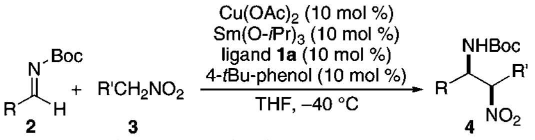
Table 3. Additive Screening To Improve Enantioselectivity



entry	additive (*x* mol %)	yield[a] (%)	dr[a] (*syn*/*anti*)	% ee (*syn*)
1	none	96	>20:1	80
2	$Ph_3P{=}O$ (30)	97	10:1	67
3	DMSO (30)	94	13:1	71
4	NMO (30)	73	>20:1	73
5	$Ph_3P{=}S$ (30)	92	10:1	72
6	*i*PrOH (30)	79	>20:1	62
7	*i*PrOH (100)	87	>20:1	87
8	phenol (10)	81	>20:1	85
9	4-*t*Bu-phenol (10)	96	>20:1	94
10	4-nitrophenol (10)	0		
11	2,6-di-Me-phenol (10)	90	>20:1	89
12	2,6-di-*t*Bu-phenol (10)	91	>20:1	76
13	4-*t*Bu-phenol (5)	88	>20:1	86
14	4-*t*Bu-phenol (15)	94	>20:1	92
15	4-*t*Bu-phenol (20)	87	>20:1	92

[a] Determined by ^{1}H NMR analysis.

Table 4. Substrate Scope and Limitations[a]



3a: R' = CH_3; **3b**: R' = CH_3CH_2-
3c: R' = $BnOCH_2$-

entry	imine (R)	nitroalkane 2	3	4	time (h)	yield[b] (%)	dr[c] (*syn*/*anti*)	% ee (*syn*)
1	C_6H_5	**2a**	**3a**	**4aa**	23	96	>20:1	94
2	4-CH_3-C_6H_4	**2b**	**3a**	**4ab**	48	90	>20:1	98
3	3-CH_3-C_6H_4	**2c**	**3a**	**4ca**	48	77	>20:1	96
4	2-CH_3-C_6H_4	**2d**	**3a**	**4da**	48	25	N.D.	N.D.
5	4-CH_3O-C_6H_4	**2e**	**3a**	**4ea**	48	87	>20:1	94
6	4-Cl-C_6H_4	**2f**	**3a**	**4fa**	48	81	>20:1	90
7[d]	2-naphthyl	**2g**	**3a**	**4ga**	48	87	>20:1	93
8[d]	2-furyl	**2h**	**3a**	**4ha**	48	71	>20:1	91
9	2-thienyl	**2i**	**3a**	**4ia**	27	91	>20:1	65
10	$C_6H_5(CH_2)_2$	**2j**	**3a**	**4ja**	48	62	>20:1	83
11	isobutyl	**2k**	**3a**	**4ka**	52	51	7:1	39
12[d]	*n*-pentyl	**2l**	**3a**	**4la**	52	63	10:1	43
13	C_6H_5	**2a**	**3b**	**4ab**	48	84	>20:1	88
14	4-CH_3-C_6H_4	**2b**	**3b**	**4bb**	48	68	>20:1	95
15	4-CH_3O-C_6H_4	**2e**	**3b**	**4eb**	48	64	>20:1	91
16	4-Cl-C_6H_4	**2f**	**3b**	**4fb**	27	97	>20:1	57
17[d]	C_6H_5	**2a**	**3c**	**4ac**	27	49	8:1	51

[a] The reaction was performed in THF (0.2 M on imines **2**) at −40 °C using 10 mol % of $Cu(OAc)_2$/Sm(O-*i*Pr)$_3$/**1a**/4-*t*Bu-phenol unless otherwise noted. [b] Isolated yield of **4** after purification by silica gel column chromatography. [c] Determined by ^{1}H NMR analysis of crude mixture. [d] The reaction was run at −50 °C.

the presence of an amine base resulted in poor reactivity (entry 3, 20 mol % amine, 0% yield) and selectivity (entry 4, 1 equiv of amine, 24% yield, 1% ee, *syn*/*anti* = 2/1), implying the importance of Brønsted basic Sm(O-*i*Pr)$_3$. The ratio of $Cu(OAc)_2$/Sm(O-*i*Pr)$_3$:ligand **1a** was also critical for good selectivity (entry 1 vs entries 6 and 7), and a complex prepared in a ratio of 1:1:1 performed the best.

To further improve the enantioselectivity, achiral additives were screened (Table 3). Because Lewis basic additives sometimes had positive effects in rare earth metal-catalyzed reactions for modifying the chiral environment around the rare earth metal center,[23] several Lewis bases were examined in entries 2−5. Lewis base additives, however, resulted in worse selectivity than obtained in entry 1. Instead, the addition of a proton source was found to have positive effects for the present reaction. When 2-propanol (1 equiv) was added, enantioselectivity increased to 87% (entry 7). In the case of phenol, a catalytic amount was sufficient to improve enantioselectivity (entry 8, 85% ee). Among phenol derivatives, electron-rich 4-*t*Bu-phenol gave product **4aa** in 94% ee (entry 9). In contrast, more acidic 4-nitrophenol diminished the catalytic activity (entry 10, 0% yield). Sterically hindered 2,6-di-*t*Bu-phenol was not effective at all (entry 12), suggesting that phenols would act as a ligand to the metal rather than as a proton source. In contrast to 2,6-di-*t*Bu-phenol, 2,6-dimethylphenol gave positive effects (entry 11). We assume that 2,6-dimethylphenol is sterically demanding but still can interact with the Sm-metal center. The role of phenolic additives will be further discussed in the section of mechanistic studies. In entries 13−15, the effects of the amount of 4-*t*Bu-phenol (5−20 mol %) were investigated, and Cu/Sm/**1a**/4-*t*Bu-phenol in a 1:1:1:1 ratio gave slightly better enantioselectivity than the others (entry 9 vs entries 13−15).

The substrate scope and limitations of the optimized reaction conditions of the $Cu(OAc)_2$/Sm(O-*i*Pr)$_3$/ligand **1a**/4-*t*-Bu-phenol = 1:1:1:1 system are summarized in Table 4. With *para*- and *meta*-substituted aromatic imines **2b** and **2c**, the reaction proceeded smoothly to give products in good yield, high *syn*-selectivity and high enantioselectivity (entries 2 and 3). *Ortho*-substituted imine **2d**, however, had poor reactivity, presumably due to the steric hindrance (entry 4, 25% yield). Aryl imines **2e** and **2f** with either an electron-donating substituent or an electron-withdrawing substituent gave *syn*-adducts with high enantioselectivity (entries 5 and 6). 2-Furyl imine **2h** gave good selectivity (entry 8, *syn*/*anti* = >20:1, 91% ee), but 2-thienyl imine **2i** afforded product **4ia** with moderate enantioselectivity (entry 9, 65% ee). The use of aliphatic *N*-Boc imines in direct Mannich-type reactions is generally difficult due to competitive isomerization to ena-

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[23] (a) Kino, R.; Daikai, K.; Kawanami, T.; Furuno, H.; Inanaga, J. *Org. Biomol. Chem.* **2004**, *2*, 1822, and references therein. (b) Yamagiwa, N.; Tian, J.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 3413. (c) Hara, K.; Park, S.-Y.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Chem. Asian J* **2008**, *3*, 1500, and references therein.

mides.[24] With the Cu(OAc)$_2$/Sm(O-*i*Pr)$_3$/ligand **1a**/4-*t*-Bu-phenol = 1:1:1:1 system, the reaction of aliphatic imines **2j**−**l** gave products in modest yield (entries 10−12, 51−62% yield). *Syn*-selectivity and enantioselectivity strongly depended on the structure of the aliphatic imines. Imine **2j** gave **4ja** in 83% ee and >20:1 *syn*-selectivity (entry 10), but imines **2k** and **2l** resulted in poor enantioselectivity and somewhat lower *syn*-selectivity (**4ka**: 39% ee and 7:1 *syn*-selectivity; **4la**: 43% ee and 10:1 *syn*-selectivity). The results with other nitroalkanes are summarized in entries 13−17. Nitropropane (**3b**) was applicable for imines **2a**, **2b**, and **2e** to give products with high *syn*-selectivity and good enantioselectivity (entries 13−15, 88−95% ee). In contrast, imine **2f** with an electron-withdrawing group gave product **4fb** with moderate ee (entry 16, 57% ee). The use of 2-benzyloxynitroethane (**3c**) afforded the corresponding product **4ac** in moderate yield and enantioselectivity (entry 17, 49% yield and 51% ee).

B. Mechanistic Studies. We developed the first *syn*-selective catalytic asymmetric nitro-Mannich reaction using the heterobimetallic Cu(OAc)$_2$/Sm(O-*i*Pr)$_3$/ligand **1a**/4-*t*-Bu-phenol = 1:1:1:1 system.[8,19] Improvements in terms of the substrate scope and limitations, however, were needed. Detailed information of the present catalyst should be useful toward further improvement. Mechanistic studies on the first-generation Cu(OAc)$_2$/Sm(O-*i*Pr)$_3$/ligand **1a**/4-*t*-Bu-phenol = 1:1:1:1 system are described in this section.

The results in Table 2 clearly indicate that Cu(OAc)$_2$/Sm(O-*i*Pr)$_3$/Schiff base **1a** in a 1:1:1 ratio is important for realizing high reactivity, high *syn*-selectivity, and good enantioselectivity. We speculated that Cu(OAc)$_2$/Sm(O-*i*Pr)$_3$/Schiff base **1a** made a complex with a 1:1:1 ratio. Because the structure of the Cu(II)/Schiff base **1a** = 1:1 complex was unequivocally determined by Constable, Housecroft, and co-workers by X-ray crystallographic analysis,[25] we believe that Cu is in the N$_2$O$_2$ inner cavity of **1a** and Sm is in the O$_2$O$_2$ outer cavity of **1a**. The results from some previous studies on related heterobimetallic transition metal/rare earth metal/Schiff base complexes in the field of coordination chemistry also support our assumption.[20] Mohanta and co-workers reported the X-ray single-crystal structure of a monomeric heterobimetallic [Cu^{II}(OH$_2$)(Schiff base)Gd^{III}(NO$_3$)$_3$] complex prepared from Cu(OAc)$_2$, Gd(NO)$_3$, and *N*,*N*-bis(3-ethoxysalicylidene)cyclohexanediamine.[20b] Because of the similarities between Mohanta's Cu/Gd(NO)$_3$ complex and our Cu/Sm(O-*i*Pr)$_3$/Schiff base **1a** complex, we initially speculated that a similar monomeric species was formed in our system. Some differences between Mohanta's monomeric complex and our Cu/Sm/**1a** catalyst, however, should be carefully considered. (1) The number of phenolic OH groups: Schiff base **1a** has two additional phenolic OH groups compared to *N*,*N*-bis(3-ethoxysalicylidene)cyclohexanediamine. (2) Counteranions of rare earth metal: rare earth metal alkoxides form several oligomeric species and the properties of rare earth metal isopropoxides are largely different from those of the corresponding rare earth metal nitrates. (3) The phenol additive effect: the reason for the positive effects of 4-*t*Bu-phenol on enantioselectivity has not yet been clarified.

To obtain insight into the active species of the present reaction, the relationship between the optical purity of ligand **1a** and product **4aa** was investigated. A weak positive nonlinear effect was observed (Figure 3). To exclude the possibility that a reservoir model induced the observed nonlinear effect,[26] we repeated the experiments by changing either the reaction temperature (at −40 and −50 °C, Figure 3a) or the catalyst concentration (10, 20, and 40 mM, Figure 3b). No significant difference was observed by altering either temperature or concentration, suggesting that the active species is not a monomer.

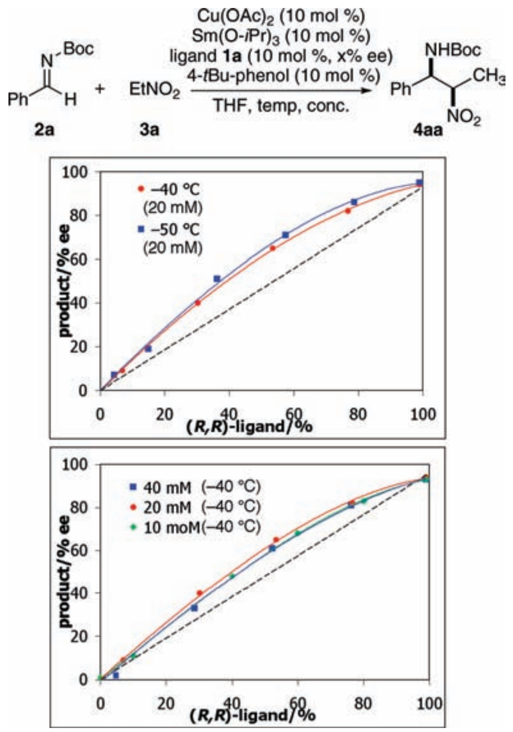

Figure 3. Nonlinear effect examination with various enantiomeric excesses of Schiff base **1a**: (a) reaction temperature effects on nonlinear effect; (b) catalyst concentration effects on nonlinear effect.

ESI-MS analysis also supported the idea that the active species is not a monomer. To obtain insight into the role of 4-*t*Bu-phenol, a mixture of the Cu(OAc)$_2$/Sm(O-*i*Pr)$_3$/ligand **1a** = 1:1:1 system was analyzed with and without 4-*t*Bu-phenol. In the absence of 4-*t*Bu-phenol (Figure 4a), no peak corresponding to a monomeric Cu/Sm/ligand **1a** = 1:1:1 complex was detected. Instead, several peaks corresponding to oligomeric species, such as *m*/*z* = 1710, 2001, 2280, 2651, and 2854, were observed together with a fragment peak (*m*/*z* = 438), which was assigned as [CuNa(ligand **1a**)]$^+$. The strongest peak, *m*/*z* = 1710, was assigned to μ-oxo-trimer [Cu$_3$Sm$_3$O(ligand **1a**)$_3$]$^+$ and/or hexamer [Cu$_6$Sm$_6$O$_2$(ligand **1a**)$_6$]$^{2+}$.[27,28] The postulated structure of the μ-oxo-trimer complex and other assignments are summarized in Figure 4a. The ESI-MS spectrum suggested that several oligomeric species exist in a mixture of Cu(OAc)$_2$/

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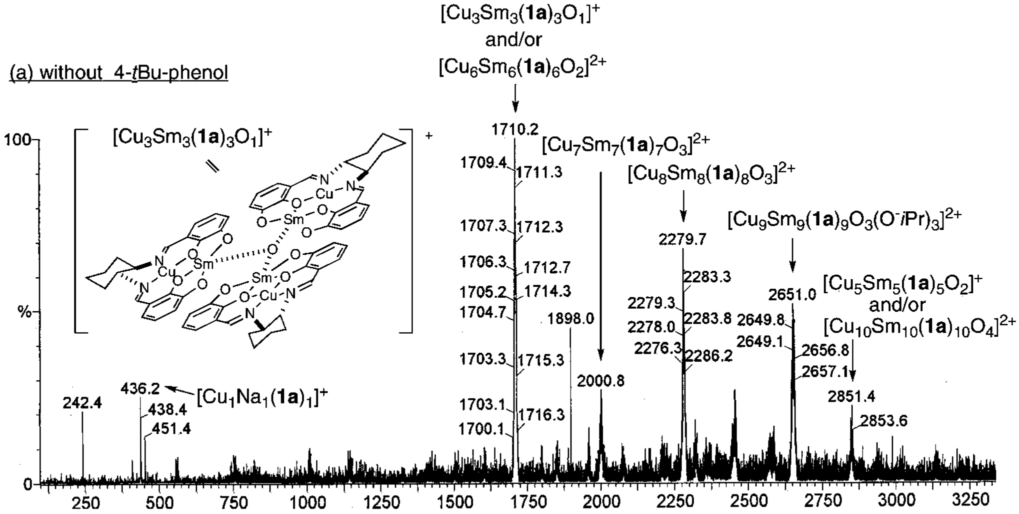
(24) For the successful use of aliphatic imines in nitro-Mannich reaction via in situ generation of aliphatic imines from α-amido sulfones, see refs 13b and 17.

(25) Constable, E. C.; Zhang, G.; Housecroft, C. E.; Neuburger, M.; Schaffner, S.; Woggon, W.-D. *New J. Chem.* **2009**, *33*, 1064.

(26) Reviews: (a) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922. (b) Satyanarayana, T.; Abraham, S.; Kagan, H. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 456.

(27) For recent examples of chiral μ-oxo or μ-hydroxide multi-rare earth metal complexes, see: (a) Kato, N.; Mita, T.; Kanai, M.; Therrien, B.; Kawano, M.; Yamaguchi, K.; Danjo, H.; Sei, Y.; Sato, A.; Furusho, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6768. (b) Fujimori, I.; Mita, T.; Maki, K.; Shiro, M.; Sato, A.; Furusho, S.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 16438. (c) Wooten, A. J.; Salvi, L.; Carroll, P. J.; Walsh, P. J. *Adv. Synth. Catal.* **2007**, *349*, 561.

(a) without 4-*t*Bu-phenol



(b) with 4-*t*Bu-phenol

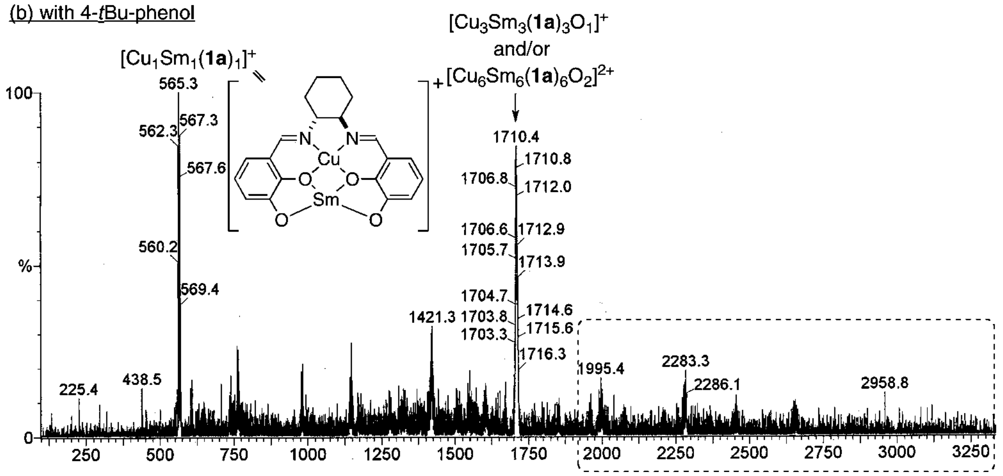


Figure 4. ESI-MS spectra of Cu/Sm/Schiff base **1a** = 1:1:1 mixture (a) without 4-*t*Bu-phenol and (b) with 4-*t*Bu-phenol.

$Sm(O\text{-}i\text{Pr})_3$/ligand **1a** = 1:1:1 without 4-*t*Bu-phenol. In the presence of 4-*t*Bu-phenol, the peak of $m/z = 1710$ was similarly observed. Peaks for higher m/z, however, such as 2280, 2651, and 2854, became much weaker (compare Figure 4b with Figure 4a). Instead, a new peak of $m/z = 565$ was observed, which was assigned as a $[Cu_1Sm_1(\text{ligand } \mathbf{1a})]^+$ monomer.

As described above, the nonlinear effect experiments excluded the possibility of a reservoir model. Thus, the $[Cu_1Sm_1(\text{ligand } \mathbf{1a})]^+$ monomer observed in the presence of 4-*t*Bu-phenol in Figure 4b cannot be an active species in the present system. We assume that the peak of $m/z = 565$ would be a fragment peak of the μ-oxo-trimer $[Cu_3Sm_3O(\text{ligand } \mathbf{1a})_3]^+$ (or hexamer) under mass analysis conditions. The postulated role of 4-*t*Bu-phenol is shown in Figure 5. The mixture of Cu/Sm/ligand **1a** = 1:1:1 would afford several oligomeric species, including the μ-oxo-trimer, hexamer, and higher order oligomers, such as a heptamer, a octamer, a nonamer, and a decamer. The addition of 4-*t*Bu-phenol would diminish the higher order oligomers and μ-oxo-μ-aryloxy trimer (or hexamer) would become a major species, as observed in Figure 4b. The improved enantiomeric

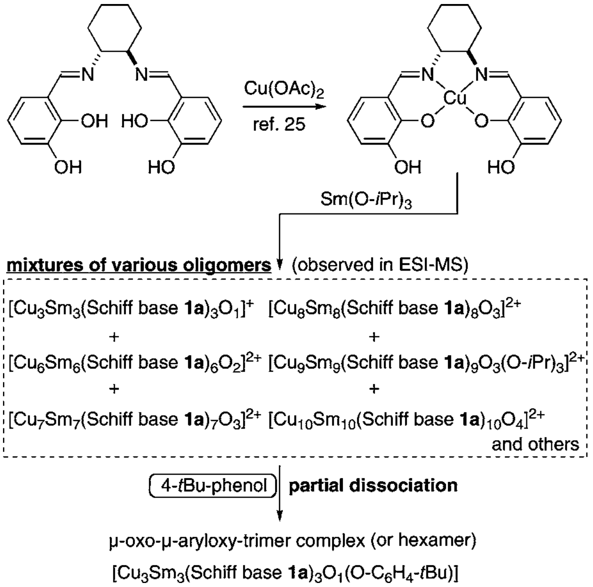


Figure 5. Proposed role of phenol additive to generate the μ-oxo-μ-aryloxy trimer complex.

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(28) In ESI-MS charts in Figure 4, peaks were observed depending on the Sm natural isotope distribution pattern: ^{144}Sm: 3.1%, ^{147}Sm: 15.0%, ^{148}Sm: 11.3%, ^{149}Sm: 13.8%, ^{150}Sm: 7.4%, ^{152}Sm: 26.7%, ^{154}Sm: 22.7%. The peaks at m/z 1710 were 0.5 mass units apart in ESI-TOF-MS analysis. Judging from the peak distribution patterns, the peak at m/z 1710 was speculated to be composed of a mixture of a dicationic hexamer as well as a monocationic trimer. Other peaks were assigned in analogy based on m/z as well as the peak distribution pattern. See the Supporting Information for the ESI-TOF-MS spectra.

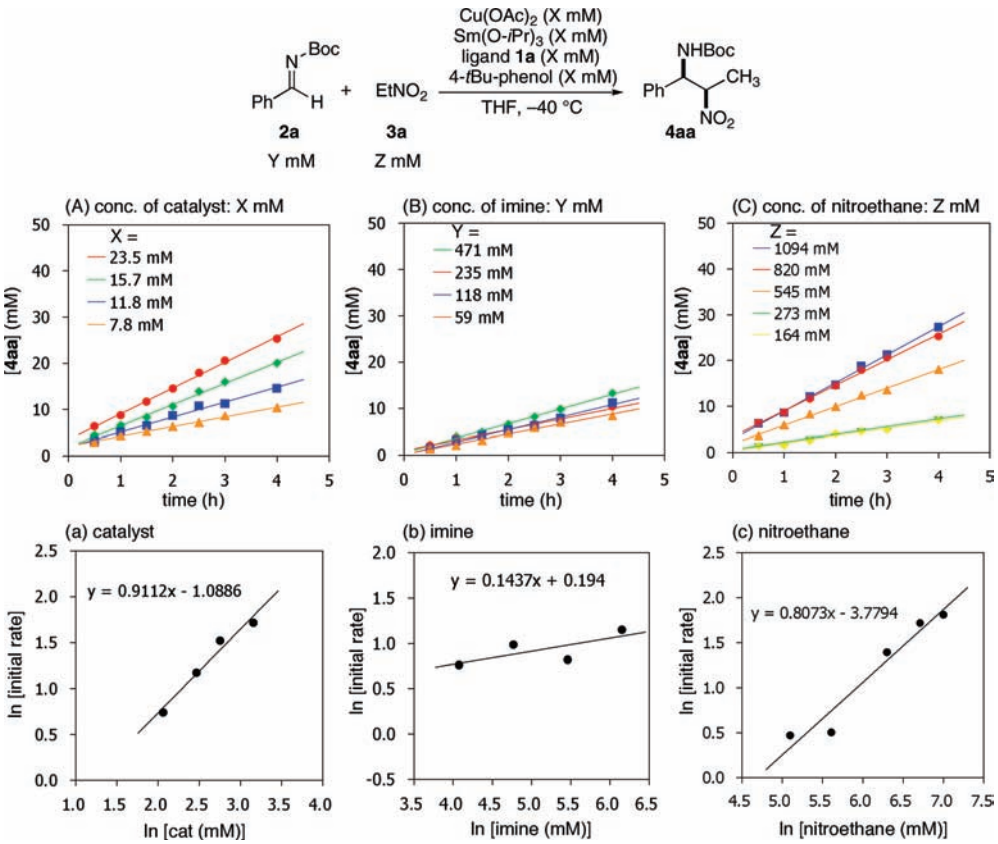

Figure 6. (A−C): Reaction profiles of *syn*-selective catalytic asymmetric nitro-Mannich reactions; (a−c) the rate-dependency on each component.

excess in the presence of 4-*t*Bu-phenol (Table 3, entry 1 vs entry 9) can be explained as follows. In the absence of 4-*t*Bu-phenol, several oligomeric species competitively promoted the nitro Mannich-type reaction, resulting in 80% ee (Table 3, entry 1). In the presence of 4-*t*Bu-phenol, 4-*t*Bu-phenol would act as a ligand to samarium, and higher order oligomer species, which were less enantioselective for the present reaction, partially dissociated to form more enantioselective μ-oxo-μ-aryloxy trimer (or hexamer) as a major species.[29] Thus, the enantioselectivity of the reaction improved to 94% ee (Table 3, entry 9). The negative data using sterically hindered 2,6-di-*t*Bu-phenol (Table 3, entry 12) also support the assumption that 4-*t*Bu-phenol acts as a ligand to samarium. In Table 3, entries 9 and 13−15, the amount of 4-*t*Bu-phenol slightly affected enantioselectivity. We assume that excess 4-*t*Bu-phenol, that is, 1 equiv to Cu/Sm, had beneficial effects to effectively promote the partial dissociation.

To obtain information on the catalytic cycle, we performed initial rate kinetic and kinetic isotope effect studies (Figure 6 and Figure 7). The reaction profile of the *syn*-selective catalytic asymmetric nitro-Mannich reaction and the rate dependency on each component are summarized in Figure 6. The reaction rate had a 0.9th-order dependency on the catalyst (Figure 6a),[30] almost a zeroth-order dependency on imine (Figure 6b), and a 0.8th-order dependency on nitroethane (Figure 6c). These results implied that the rate-determining step would be the deprotonation of nitroalkane. The kinetic isotope effect examination using deuterated nitroethane ($CH_3CD_2NO_2$) resulted in $k_H/k_D = 5.72$, clearly supporting the assumption (Figure 7).

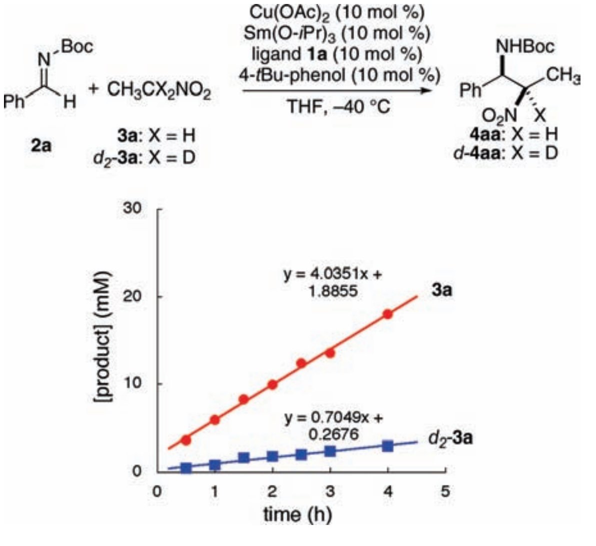

Figure 7. Kinetic isotope effect study using deuterated nitroethane d_2-**3a**.

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(29) The difference in the reaction rate with and without 4-*t*Bu-phenol additive also supported our assumption. The reaction rate in the absence of 4-*t*Bu-phenol was 3.6-fold faster than that with 4-*t*Bu-phenol. See the Supporting Information for detailed experimental data.

(30) Kinetic data of the order in catalyst also matched well with ESI-MS analysis. In the presence of 4-*t*Bu-phenol additive, the order was slightly lower than 1st (0.9th order, Figure 6), suggesting that trimer and higher order aggregates would exist in equilibrium and the trimer complex would be the active species. In contrast, the order in catalyst was greater than 1st (2.0nd order, see the Supporting Information) in the absence of 4-*t*Bu-phenol additive. The data implied that trimer and higher order aggregates would exist in equilibrium and higher order aggregates would participate in the reaction in the absence of 4-*t*Bu-phenol.

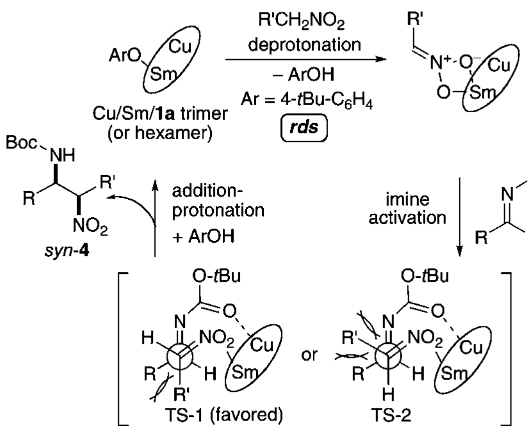


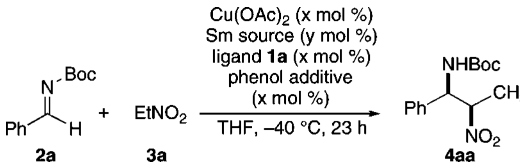
Figure 8. Plausible catalytic cycle.

The proposed catalytic cycle is shown in Figure 8. In this catalyst system, both Cu and Sm are essential as confirmed in Tables 1 and 2. We assume that the cooperative dual activation of nitroalkanes and imines with Cu and Sm would be important to realize the *syn*-selective catalytic asymmetric nitro-Mannich-type reaction. The Sm-aryl oxide moiety in the catalyst (either 4-*t*Bu-phenoxide or a part of Schiff base) would act as a Brønsted base to generate Sm-nitronate. On the other hand, Cu(II) would act as a Lewis acid to control the position of *N*-Boc-imine.[31] Among possible transition states, the sterically less hindered TS-1 would be more favorable. Thus, the stereoselective C−C bond-formation via TS-1 followed by protonation with 4-*t*Bu-phenol (or the phenolic proton in the catalyst) affords *syn*-**4** and regenerates the catalyst.

C. Condition Reoptimization toward the Second-Generation Heterobimetallic Schiff Base Complex. The observed nonlinear effect shown in Figure 3 suggested that the heterobimetallic Cu(OAc)$_2$/Sm(O-*i*Pr)$_3$/ligand **1a**/4-*t*-Bu-phenol = 1:1:1:1 system exists as an oligomeric species. ESI-MS analysis also implied that the present system exists as mixtures of oligomeric species in the absence of 4-*t*-Bu-phenol. Mechanistic studies suggested that 4-*t*-Bu-phenol has beneficial effects by partially dissociating less enantioselective higher order oligomers. Even after the addition of 4-*t*-Bu-phenol, however, higher order oligomers were observed as a minor species (Figure 4b). We hypothesized that catalyst efficiency and enantioselectivity would improve if well-ordered species of the Cu/Sm/Schiff base complex could be more selectively prepared. Because the complexation of Cu(OAc)$_2$ with ligand **1a** affords a monomeric Cu/**1a** complex,[25] we investigated various samarium sources to change the degree of oligomerization (Table 5). Lewis acidic Sm(OTf)$_3$, SmCl$_3$, and Sm(NO$_3$)$_3$ as metal sources gave product **4aa** in low yield (entries 3−5). With Brønsted basic Sm(HMDS)$_3$, which has a monomeric structure, the reaction proceeded in high yield, but diastereo- and enantioselectivity were poor (entry 6). The addition of 2-propanol (30 mol % = 3 equiv to Sm source) to monomeric Sm(HMDS)$_3$ (10 mol %) to generate Sm(O-*i*Pr)$_3$ in situ also gave poor diastereo- and enantioselectivity (entry 7). The results in entries 6 and 7 suggested that the monomeric samarium source has negative effects on catalyst stereoselectivity. Therefore, we investigated oxo-rare earth metal alkoxide, Sm$_5$O(O-*i*Pr)$_{13}$, with a well-ordered structure[32] and achieved good reactivity and sufficient stereoselectivity (entry 8). The advantage of Sm$_5$O(O-*i*Pr)$_{13}$ over Sm(O-*i*Pr)$_3$ was clearly observed when the catalyst loading was reduced to 5 mol % (based on Schiff base **1a**).[33] With the complex derived from Sm$_5$O(O-*i*Pr)$_{13}$, the reaction proceeded smoothly using 5 mol % of ligand **1a** without loss of enantioselectivity (entry 9, 94% ee), while enantioselectivity decreased to 87% ee in entry 2 using Sm(O-*i*Pr)$_3$. Reoptimization of phenolic additives (entries 9−11) revealed that 4-MeO-phenol gave slightly better enantioselectivity than 4-*t*Bu-phenol, although a longer reaction time was required (entry 11, 95% ee, 27 h).

The new Cu/Sm catalyst derived from Sm$_5$O(O-*i*Pr)$_{13}$ improved the substrate scope and limitations, as summarized in Table 6. The reactions with 10 mol % of ligand **1a** revealed that the reaction rate is generally better with Sm$_5$O(O-*i*Pr)$_{13}$. For example, the reaction of imines **2b**, **2c**, and **2e** with an electron-donating group was complete within 23 h (Table 6, entries 5, 7, and 10 vs Table 4, entries 2, 3, and 5). Therefore, the reaction proceeded well with 5 mol % catalyst loading (entries 6, 8, and 11). In entries 3 and 4, the reaction of imine **2a** proceeded in good yield with 1−2 mol % of catalyst, but a longer reaction time was required and enantioselectivity was slightly decreased. Not only the catalytic activity but also the

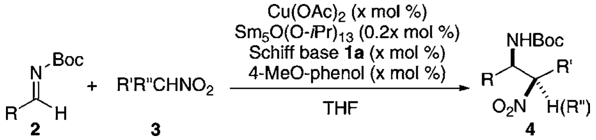
Table 5. Effects of Samarium Source


2a **3a** **4aa**

entry	Sm source (*y* mol %)	ligand **1a** (*x* mol %)	phenol additive	yield (%)	dr[a] (*syn*/*anti*)	% ee (*syn*)
1	Sm(O-*i*Pr)$_3$ (10)	10	4-*t*Bu-phenol	96	>20:1	94
2	Sm(O-*i*Pr)$_3$ (5)	5	4-*t*Bu-phenol	94	>20:1	87
3[b]	Sm(OTf)$_3$ (10)	10	4-*t*Bu-phenol	<10	N.D.	N.D.
4[b]	SmCl$_3$ (10)	10	4-*t*Bu-phenol	<10	N.D.	N.D.
5[b]	Sm(NO$_3$)$_3$·6H$_2$O (10)	10	4-*t*Bu-phenol	<10	N.D.	N.D.
6	Sm(HMDS)$_3$ (10)	10	4-*t*Bu-phenol	84	5:1	6
7[c]	Sm(HMDS)$_3$ (10)	10	4-*t*Bu-phenol	85	5:1	11
8	Sm$_5$O(O-*i*Pr)$_{13}$ (2)	10	4-*t*Bu-phenol	96	>20:1	94
9	Sm$_5$O(O-*i*Pr)$_{13}$ (1)	5	4-*t*Bu-phenol	97	>20:1	94
10	Sm$_5$O(O-*i*Pr)$_{13}$ (1)	5	4-Me-phenol	59	>20:1	95
11[d]	Sm$_5$O(O-*i*Pr)$_{13}$ (1)	5	4-MeO-phenol	93	>20:1	95

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Prior to complexation with Sm sources, BuLi was added to a Cu/**1a** complex to generate Li aryl oxide so as to facilitate counteranion exchange. [c] 2-Propanol [30 mol % = 3 equiv to Sm(HMDS)] was added. [d] Reaction time was 27 h.

Table 6. Catalytic Asymmetric Nitro-Mannich-Type Reaction Using the Second-Generation Cu/Sm Catalyst Prepared from $Sm_5O(O\text{-}i\text{Pr})_{13}$[a]



entry	R for imine 2		nitroalkane 3			Schiff base **1a** (mol %)	product	time (h)	temp (°C)	yield[b] (%)	dr[c] (*syn*/*anti*)	% ee (*syn*)
			R'	R″								
1	C_6H_5	**2a**	CH_3-	H-	**3a**	10	**4aa**	24	−40	98	>20:1	93
2	C_6H_5	**2a**	CH_3-	H-	**3a**	5	**4aa**	27	−40	93	>20:1	95
3	C_6H_5	**2a**	CH_3-	H-	**3a**	2	**4aa**	39	−40	91	>20:1	91
4	C_6H_5	**2a**	CH_3-	H-	**3a**	1	**4aa**	95	−40	81	>20:1	86
5	4-CH_3-C_6H_4	**2b**	CH_3-	H-	**3a**	10	**4ba**	22	−40	91	>20:1	98
6	4-CH_3-C_6H_4	**2b**	CH_3-	H-	**3a**	5	**4ba**	40	−40	99	>20:1	98
7	3-CH_3-C_6H_4	**2c**	CH_3-	H-	**3a**	10	**4ca**	23	−40	86	>20:1	97
8	3-CH_3-C_6H_4	**2c**	CH_3-	H-	**3a**	5	**4ca**	24	−40	81	>20:1	97
9	2-CH_3-C_6H_4	**2d**	CH_3-	H-	**3a**	5	**4da**	48	−40	87	>20:1	92
10	4-CH_3O-C_6H_4	**2e**	CH_3-	H-	**3a**	10	**4ea**	23	−40	93	>20:1	98
11	4-CH_3O-C_6H_4	**2e**	CH_3-	H-	**3a**	5	**4ea**	39	−40	87	>20:1	96
12	4-Cl-C_6H_4	**2f**	CH_3-	H-	**3a**	10	**4fa**	23	−40	81	>20:1	92
13	4-Cl-C_6H_4	**2f**	CH_3-	H-	**3a**	5	**4fa**	23	−40	93	>20:1	85
14	2-naphthyl	**2g**	CH_3-	H-	**3a**	10	**4ga**	24	−40	94	>20:1	98
15	2-naphthyl	**2g**	CH_3-	H-	**3a**	5	**4ga**	24	−40	98	>20:1	96
16	2-furyl	**2h**	CH_3-	H-	**3a**	10	**4ha**	23	−40	83	>20:1	92
17	2-furyl	**2h**	CH_3-	H-	**3a**	5	**4ha**	27	−40	86	>20:1	90
18	2-thienyl	**2i**	CH_3-	H-	**3a**	10	**4ia**	24	−40	94	>20:1	91
19	2-thienyl	**2i**	CH_3-	H-	**3a**	5	**4ia**	48	−40	87	>20:1	88
20	$C_6H_5(CH_2)_2$	**2j**	CH_3-	H-	**3a**	8	**4ja**	39	−50	74	>20:1	80
21	isobutyl	**2k**	CH_3-	H-	**3a**	10	**4ka**	46	−40	72	>20:1	81
22	*n*-pentyl	**2l**	CH_3-	H-	**3a**	8	**4la**	39	−50	77	13:1	66
23	*c*-hexyl	**2m**	CH_3-	H-	**3a**	10	**4ma**	48	−40	trace		
24	C_6H_5	**2a**	CH_3CH_2-	H-	**3b**	10	**4ab**	28	−40	85	>20:1	99
25	C_6H_5	**2a**	CH_3CH_2-	H-	**3b**	5	**4ab**	48	−40	85	>20:1	96
26	C_6H_5	**2a**	CH_3CH_2-	H-	**3b**	2	**4ab**	72	−40	78	>20:1	96
27	4-CH_3-C_6H_4	**2b**	CH_3CH_2-	H-	**3b**	10	**4bb**	48	−40	68	>20:1	95
28	4-CH_3-C_6H_4	**2b**	CH_3CH_2-	H-	**3b**	5	**4bb**	40	−40	88	>20:1	97
29	4-CH_3O-C_6H_4	**2e**	CH_3CH_2-	H-	**3b**	10	**4eb**	48	−40	64	>20:1	91
30	4-CH_3O-C_6H_4	**2e**	CH_3CH_2-	H-	**3b**	5	**4eb**	43	−40	69	>20:1	93
31	4-Cl-C_6H_4	**2f**	CH_3CH_2-	H-	**3b**	10	**4fb**	23	−40	93	>20:1	88
32	C_6H_5	**2a**	$BnOCH_2$-	H-	**3c**	10	**4ac**	21	−50	86	>20:1	76
33	4-CH_3-C_6H_4	**2b**	$BnOCH_2$-	H-	**3c**	10	**4bc**	24	−50	54	16:1	80
34	2-naphthyl	**2g**	$BnOCH_2$-	H-	**3c**	10	**4gc**	21	−40	86	>20:1	81
35	C_6H_5	**2a**	$CH_3(CH_2)_2$-	H-	**3d**	10	**4ad**	48	−40	trace		
36	C_6H_5	**2a**	CH_3-	CH_3-	**3e**	10	**4ae**	48	−40	trace		
37	C_6H_5	**2a**	$C_6H_5CH_2$-	H-	**3f**	10	**4af**	24	−40	80	>20:1	11

[a] The reaction was performed in THF (0.2 M on imines **2**) using *x* mol % of $Cu(OAc)_2$, 0.2*x* mol % of $Sm_5O(O\text{-}i\text{Pr})_{13}$, *x* mol % of Schiff base **1a**, and *x* mol % of 4-MeO-phenol. [b] Isolated yield. [c] Determined by ^1H NMR analysis of crude mixture.

substrate generality was improved by $Sm_5O(O\text{-}i\text{Pr})_{13}$. Using *ortho*-substituted imine **2d**, which showed poor reactivity (Table 4, entry 4), the reaction proceeded smoothly to give **4da** in 87% yield, *syn*/*anti* = >20:1, and 92% ee (Table 6, entry 9). 2-Thienyl imine **2i**, which showed poor enantioselectivity in Table 4, entry 9 (65% ee), also afforded the product with sufficient enantioselectivity (entries 18 and 19, 91−88% ee). The isolated yield and diastereo- and enantioselectivity of the aliphatic imines were also improved with $Sm_5O(O\text{-}i\text{Pr})_{13}$ (Table 4, entries 10−12, vs Table 6, entries 20−22). With sterically hindered imine **2m**, however, the reactivity was poor even using the new system with $Sm_5O(O\text{-}i\text{Pr})_{13}$ (entry 23). The reactions also proceeded in good *syn*-selectivity with nitropropane **3b** (Table 6, entries 24−31). With imine **2a**, the amount of catalyst was successfully reduced to 2 mol % and **4ab** was obtained in >20:1 *syn*-selectivity and 96% ee (entry 26). Imines **2b** and **2e** with an electron-donating substituent gave comparable results using 5 mol % of catalyst (Table 6, entries 27−30, vs Table 4, entries 14 and 15). Imine **2f** gave the product with 57% ee in Table 4, entry 16, while **4fb** was obtained in 88% ee with $Sm_5O(O\text{-}i\text{Pr})_{13}$ (Table 6, entry 31). The results with nitroalkane **3c** were

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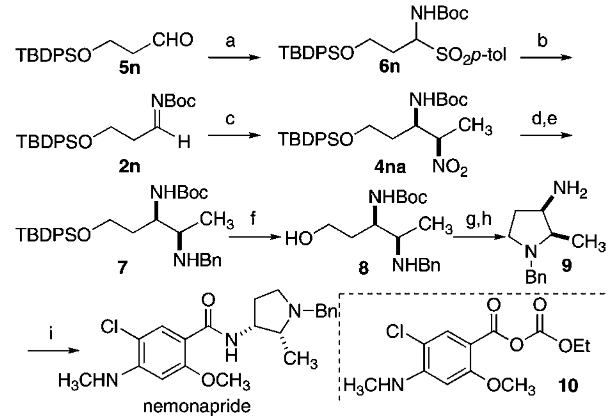
(31) The possibility that Sm acts as a Lewis acid and Cu-nitronate is generated cannot be excluded from the experimental data in this manuscript, but we assume that the roles of Cu and Sm shown in Figure 8 are more reasonable because more Lewis acidic Sm metal sources, such as $Sm(OTf)_3$, $SmCl_3$, and $Sm(NO_3)_3$, gave much less satisfactory reactivity. See Table 5, entries 3−5.

(32) (a) For the structures of oxo-rare earth metal alkoxides, see: Kritikos, M.; Moustiankimov, M.; Wijk, M.; Westin, G. *J. Chem. Soc., Dalton Trans.* **2001**, 1931. For the utility of oxo-Nd alkoxide in asymmetric catalysis, see: (b) Nitabaru, T.; Nojiri, A.; Kobayashi, M.; Kumagai, N.; Shibasaki, M *J. Am. Chem. Soc.* **2009**, *131*, 13860.

(33) In ESI-MS analysis, a clear difference between the catalyst from $Sm(O\text{-}i\text{Pr})_3$ and the catalyst from $Sm_5O(O\text{-}i\text{Pr})_{13}$ was not observed.

(34) (a) Takahashi, K.; Murakami, M.; Hirata, Y.; Takashima, M.; Iwanami, S.; Hasegawa, O.; Usuda, S. U.S. Patent 4097487, 1978. (b) Takashima, M.; Iwanami, S.; Usuda, S. U.S. Patent 4210660. (c) Iwanami, S.; Takashima, M.; Hirata, Y.; Hasegawa, O.; Usuda, S. *J. Med. Chem.* **1981**, *24*, 1224. (d) Furuya, T.; Iwanami, S.; Takenaka, A.; Sasada, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2321. (e) Yamamoto, M.; Usuda, S.; Tachikawa, S.; Maeno, H. *Neuropharmacology* **1982**, *21*, 945.

Scheme 2. Catalytic Asymmetric Synthesis of Nemonapride[a]



[a] Reagents and conditions: (a) $BocNH_2$, p-$tolSO_2Na$, HCO_2H, THF, H_2O, rt, 36 h, 92%; (b) Cs_2CO_3, CH_2Cl_2, 40 °C, 40 min, quant yield; (c) $Cu(OAc)_2$ (10 mol %)/$Sm_5O(O$-$i$$Pr)_{13}$ (2 mol %)/Schiff base **1a** (10 mol %), 4-MeO-phenol (10 mol %), THF, −40 °C, 48 h, 65% yield, *syn*/*anti* = >20:1, 80% ee; (d) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, MeOH, 0 °C, 15 min, 98% yield; (e) PhCHO, $MgSO_4$, THF, rt, 11 h; then $NaBH_4$, MeOH, 0 °C, 7 h, 82% yield; (f) TBAF, AcOH, THF, rt, 7 h, 99% yield; then recrystallization from 2-propanol/pentane, 77% yield, >99% ee; (g) MsCl, Et_3N, THF, 0 °C, 88% yield; (h) TFA, CH_2Cl_2, rt; (i) **10**, CH_2Cl_2, 0 °C, 74% yield (two steps).

also improved with $Sm_5O(O$-$i$$Pr)_{13}$ (Table 4, entry 17, vs Table 6, entries 32−34). With nitrobutane (**3d**) and sterically hindered 2-nitropropane (**3e**), however, poor reactivity was observed (entries 35 and 36). With 1-nitro-2-phenylethane (**3f**), the reactivity and *syn*-selectivity were good (>20:1), but enantioselectivity was poor (entry 37).

To demonstrate the utility of the present *syn*-selective nitro-Mannich reaction, we performed a catalytic asymmetric synthesis of nemonapride, which is used clinically as an antipsychotic agent.[34,35] Starting from aldehyde **5n**, α-amido sulfone **6n** was obtained in 92% yield. Imine **2n** was obtained in quantitative yield under a modified Deng's procedure[36] using Cs_2CO_3 and used immediately for the catalytic asymmetric nitro-Mannich reaction. The catalyst prepared from $Sm_5O(O$-$i$$Pr)_{13}$ produced the desired *syn*-β-nitroamine **4na** in 65% yield and 80% ee (>20:1 = *syn*/*anti*) (Scheme 2). No *anti*-isomer was detected with NMR analysis. With the first-generation catalyst prepared from $Sm(O$-$i$$Pr)_3$, both diastereo- and enantioselectivity were poor (4:1, 46% ee). The nitro moiety of **4na** was reduced to give 1,2-diamine in 98% yield, which was subsequently benzylated via reductive alkylation to afford **7** in 82% yield. After removal of the TBDPS group, optically pure **8** was obtained through recrystallization from 2-propanol/pentane (77% yield, >99% ee). Treatment of **8** with MsCl and Et_3N gave cyclized adduct in 88% yield. After removal of the Boc group, condensation of **9** with mixed anhydride **10** gave nemonapride in 74% yield (two steps).

Conclusion

We developed a new heterobimetallic transition metal/rare earth metal system with a dinucleating Schiff base **1a**. A mixture of $Cu(OAc)_2$/$Sm(O$-$i$$Pr)_3$/Schiff base **1a** complex with an achiral phenol additive was partially successful for achieving a *syn*-selective catalytic asymmetric nitro-Mannich reaction. The substrate generality of the first-generation system remained problematic. After mechanistic studies on the catalyst prepared from $Sm(O$-$i$$Pr)_3$, we reoptimized the catalyst preparation method, and the second-generation catalyst derived from $Sm_5O(O$$i$$Pr)_{13}$ showed broader substrate generality as well as higher reactivity and stereoselectivity compared to $Sm(O$-$i$$Pr)_3$. The optimal system with $Sm_5O(O$-$i$$Pr)_{13}$ was applicable to various aromatic, heteroaromatic, and isomerizable aliphatic *N*-Boc imines, giving products in 66−99% ee and *syn*/*anti* = >20:1−13:1. Catalytic asymmetric synthesis of nemonapride was also achieved using the catalyst derived from $Sm_5O(O$-$i$$Pr)_{13}$. Further studies to apply the heterobimetallic transition metal/rare earth metal catalysts with dinucleating Schiff bases **1** to other asymmetric reactions, especially ones in which the rare earth metal/alkali metal/BINOL systems were not suitable, are ongoing.

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Supporting Information Available: Experimental procedures, spectral data of new compounds, determination of absolute and relative configurations, ESI-MS charts, and detailed reaction profiles in kinetic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

JA100514Y

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(35) For examples of enantioselective syntheses of nemonapride, see: (a) Huang, P. Q.; Wang, S. L.; Zhen, H.; Fei, X. S. *Tetrahedron Lett.* **1997**, *38*, 271. (b) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Ohshima, T.; Shibasaki, M. *Chem. Asian J.* **2007**, *2*, 794. (c) Hoang, C. T.; Nguyen, V. H.; Alezra, V.; Kouklovsky, C. *J. Org. Chem.* **2008**, *73*, 1162.

(36) Song, J.; Wang, Y.; Deng, Li. *J. Am. Chem. Soc.* **2006**, *128*, 6048. See the Supporting Information for the modified procedure.