

## A Bench-Stable Homodinuclear Ni<sub>2</sub>–Schiff Base Complex for Catalytic Asymmetric Synthesis of $\alpha$ -Tetrasubstituted *anti*- $\alpha$ , $\beta$ -Diamino Acid Surrogates

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Chiral  $\alpha,\beta$ -diamino acids are key structural components in many biologically active compounds.<sup>1</sup> Among methods for their synthesis, catalytic asymmetric direct Mannich-type reactions<sup>2</sup> of a glycine Schiff base are one of the most efficient and straightforward methods for producing chiral syn- $\alpha$ , $\beta$ -diamino acids.<sup>3</sup> Recently, Johnston<sup>4a</sup> and Willis<sup>4b</sup> reported alternative approaches for producing anti- $\alpha$ , $\beta$ -diamino acids via Mannich-type reactions of a nitroacetate and an  $\alpha$ -isothiocyanate acid derivative. Although high diastereo- and enantioselectivity were realized,  $\alpha$ , $\beta$ -diamino acids with an  $\alpha$ -tetrasubstituted carbon stereocenter cannot be produced using those reactions.<sup>3-5</sup> Jørgensen reported an exceptional example using an  $\alpha$ -methyl nitroacetate,<sup>6</sup> but only an  $\alpha$ -imino ester was utilized as an electrophile. Considering the importance of  $\alpha, \alpha$ disubstituted a-amino acids as chiral building blocks for pharmaceuticals and artificial peptides,<sup>7</sup> a new catalyst for chiral  $\alpha$ -tetrasubstituted  $\alpha,\beta$ -diamino acid synthesis with a broad substrate scope is in high demand. Herein, we report a new bench-stable homodinuclear Ni<sub>2</sub>-Schiff base 1b complex (Figure 1) that promoted Mannich-type reactions of N-Boc imines and  $\alpha$ -substituted nitroacetates to afford  $\alpha$ -tetrasubstituted anti- $\alpha,\beta$ -diamino acid surrogates in high ee (up to >99% ee). Ni<sub>2</sub>-1b was also applicable to asymmetric Mannich-type reactions of malonates and  $\beta$ -keto ester.

We recently reported the utility of the dinucleating Schiff base 1a-H<sub>4</sub> (Figure 1) in aza-Henry reactions of nitroethane and nitropropane.8 Schiff base 1a-H<sub>4</sub> selectively incorporated Cu into the N<sub>2</sub>O<sub>2</sub> inner cavity and oxophilic rare earth metal with a large ionic radius into the O<sub>2</sub>O<sub>2</sub> outer cavity. Cooperative functions of the two metals<sup>9</sup> in the heterobimetallic Cu-Sm-1a complex (Figure 1,  $M^1 = Cu$ ,  $M^2 = Sm$ ) were key to achieving high enantioselectivity in aza-Henry reactions. Thus, we initiated optimizations using Schiff base 1a, imine 2a, and nitroacetate 3a (Table 1). The Cu-Sm-1a complex, however, gave product 4aa in poor selectivity (entry 1, anti:syn = 49:51, 5% ee). Although we screened various heterobimetallic combinations of late transition metals and rare earth metals using Schiff base 1a, there were no promising results. During chiral ligand screening, we found that Schiff base 1b with a 1,1'binaphthyl-2,2'-diamine unit can incorporate metals with a smaller ionic radius than that of rare earth metals into the O<sub>2</sub>O<sub>2</sub> outer cavity, possibly due to conformational difference between 1a-H<sub>4</sub> and 1b- $H_4$ . After rescreening metal combinations using **1b** (entries 3–7), a homobimetallic Ni<sub>2</sub>-1b complex, prepared from Schiff base **1b**-H<sub>4</sub> and 2 equiv of Ni(OAc)<sub>2</sub>, gave the best result.<sup>10-12</sup> Ni<sub>2</sub>-**1b** (10 mol %) gave **4aa** in *anti:syn* = 90:10 and 98% ee (entry 5). Other metal combinations using **1b**, such as  $M_1 = Ni$ ,  $M_2 = Sm$ (entry 4, 59% ee),  $M_1$ ,  $M_2 = Cu$  (entry 6, 9% ee),  $M_1$ ,  $M_2 = Pd$ (entry 7), gave much less satisfactory results. The addition of MS 4Å improved reaction rate, giving 4aa in 95% isolated yield, anti: syn = 91:9, and 98% ee after 12 h (entry 8).

In contrast to the previously reported heterobimetallic Schiff base **1a** complex including rare earth metals, the present bimetallic  $Ni_2-1b$  complex was bench-stable and storable under air at room



**Figure 1.** Structures of dinucleating Schiff bases 1a-H<sub>4</sub> and 1b-H<sub>4</sub>, and postulated structures of bimetallic M<sup>1</sup>-M<sup>2</sup>-1 and (*R*)-Ni<sub>2</sub>-1b complexes.

Table 1. Optimization of Reaction Conditions

Ph He CC Ph 2a 3a		D₂ <i>t</i> Bu − D₂	catalyst (5 mol % (M <sup>1</sup> /M <sup>2</sup> / <b>1</b> =1:1:1) THF, 0 °C		→ Ph → CO <sub>2</sub> tBu Me NO <sub>2</sub> 4aa			
	metal sources		Schiff		time	yield <sup>b</sup>	dr <sup>c</sup>	% ee
entry	M <sup>1a</sup>	M <sup>2a</sup>	base	additive	(h)	(%)	(anti/syn)	(anti)
1	Cu	Sm	1a	none	18	75	49:51	5
2	Ni	Sm	1a	none	18	36	50:50	15
3	Cu	Sm	1b	none	18	33	34:66	17
4	Ni	Sm	1b	none	18	42	61:39	59
5	Ni	Ni	1b	none	18	92	90:10	98
6	Cu	Cu	1b	none	18	95	34:66	9
7	Pd	Pd	1b	none	18	trace	ND	ND
8	Ni	Ni	1b	MS 4Å	12	95 <sup>d</sup>	91:9	98

<sup>*a*</sup> Cu(OAc)<sub>2</sub>, Ni(OAc)<sub>2</sub>, Pd(OAc)<sub>2</sub>, and Sm(O-*i*Pr)<sub>3</sub> were used as metal sources. <sup>*b*</sup> Conversion yield determined by <sup>1</sup>H NMR analysis (entries 1–6). <sup>*c*</sup> Diastereomeric ratio was determined by <sup>1</sup>H NMR analysis. <sup>*d*</sup> Isolated yield.

temperature for at least 3 months without loss of activity. Substrate scope in Table 2 was investigated using the Ni<sub>2</sub>-1b complex stored under air for more than 3 months.<sup>13</sup> The optimized reaction conditions were applicable to non-isomerizable aryl and heteroaryl imines, giving products in 91–99% ee (entries 1–6). Nitroacetates **3b**-**3d** also gave high diastereo- and enantioselectivity (entries 7–9, 94:6–88:12, >99–94% ee). For isomerizable aliphatic imines, the reactions were performed at a lower temperature to prevent the undesired isomerization of imines to enamides, giving products in 85–67% yield and 95–91% ee (entries 10–12). Reaction proceeded without problem in 2 mmol scale (entry 13). Catalyst loading was successfully reduced to 1 mol %, while maintaining high enantio-selectivity (entry 14, 98% ee). The NO<sub>2</sub> moiety in product **4aa** was readily reduced with NaBH<sub>4</sub>/NiCl<sub>2</sub> at room temperature, giving  $\alpha$ -tetrasubstituted *anti-* $\alpha$ , $\beta$ -diamino ester **5aa** in 94% yield (eq 1).

**Table 2.** Catalytic Asymmetric Mannich-Type Reaction of Nitroacetates **3** and *N*-Boc Imines<sup>a</sup>



<sup>*a*</sup> Reaction was performed in THF (0.4 M on imines **2**, 0.2–0.3 mmol scale) with MS 4Å using the Ni<sub>2</sub>–**1b** complex stored over 3 months under air at room temperature; 1.1 equiv of **3** was utilized unless otherwise noted. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> Determined by <sup>1</sup>H NMR analysis of crude mixture. <sup>*d*</sup> Two equivalents of **3a** were utilized. <sup>*e*</sup> Reaction was run in 2.0 mmol scale.



The utility of the Ni<sub>2</sub>-1b complex was further demonstrated in the Mannich-type reactions of other donors, such as malonates and  $\beta$ -keto ester (eqs 2 and 3).<sup>14</sup> High diastereo- and enantioselectivities were achieved at room temperature using 2.5 mol % of Ni<sub>2</sub>-1b (99-91% ee).<sup>15</sup>

Control experiments (Scheme 1) indicated that neither a mononuclear Ni-1b-H<sub>2</sub> complex nor Ni-salen 10a-10c complexes are effective for the present reaction, resulting in poor reactivity, diastereoselectivity, and enantioselectivity. We assume that cooperative functions of the two Ni metal centers in the Ni<sub>2</sub>-1b complex would be important for achieving high stereoselectivity as well as reactivity. Further mechanistic studies to elucidate the precise role of the two Ni centers are ongoing.

In summary, we developed a bench-stable homodinuclear  $Ni_2-1b$  complex for direct Mannich-type reactions of nitroacetates, giving  $\alpha$ -tetrasubstituted *anti*- $\alpha$ , $\beta$ -diamino acid surrogates in >99–91% ee. The Ni<sub>2</sub>-1b complex was also applicable to Mannich-type reactions of malonates and  $\beta$ -keto ester. Preliminary mechanistic experiments suggested the importance of the two Ni centers in the catalyst. Further mechanistic studies as well as applications of the Ni<sub>2</sub>-1b complex in other asymmetric reactions are ongoing.

Scheme 1. Control Experiments Using Mononuclear Ni–Schiff Base 1b-H<sub>2</sub> or Ni–Salen 10a–10c Complexes



Acknowledgment. This work was supported by Grant-in-Aid for Specially Promoted Research from MEXT. We thank Prof. S. Kobayashi, Dr. R. Matsubara (X-ray crystallographic analysis), and Prof. T. Ohwada, Dr. S. Uchiyama, and Mr. S. Handa (ESI-MS) at the University of Tokyo for their kind help.

**Supporting Information Available:** Experimental procedures, spectral data of new compounds, determination of relative and absolute configurations, ESI-MS data of Ni<sub>2</sub>-1b, and CIF of **4aa**. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

- A review on α,β-diamino acids: Viso, A.; Fernández de la Pradilla, R.; García, A.; Flores, A. Chem. Rev. 2005, 105, 3167.
- (2) For reviews on direct Mannich-type reactions, see: (a) Marques, M. M. B. Angew. Chem., Int. Ed. 2006, 45, 348. (b) Shibasaki, M.; Matsunaga, S. J. Organomet. Chem. 2006, 691, 2089.
- (3) With glycine Schiff base: (a) Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. J. Org. Chem. 2003, 68, 2583. (b) Ooi, T.; Kameda, M.; Fujii, J.-i.; Maruoka, K. Org. Lett. 2004, 6, 2397. (c) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Ohshima, T.; Shibasaki, M. Chem. Asian J. 2007, 2, 794 and references therein. See also: (d) Salter, M. M.; Kobayashi, J.; Shimizu, Y.; Kobayashi, S. Org. Lett. 2006, 8, 3533.
- (4) (a) Singh, A.; Yoder, R. A.; Shen, B.; Johnston, J. N. J. Am. Chem. Soc. 2007, 129, 3466. (b) Cutting, G. A.; Stainforth, N. E.; John, M. P.; Kociok-Köhn, G.; Willis, M. C. J. Am. Chem. Soc. 2007, 129, 10632.
- (5) For other catalytic asymmetric approaches to α,β-diamino acids using α-imino esters as electrophiles, see: (a) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992.
  (b) Chowdari, N. S.; Ahmad, M.; Albertshofer, K.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2006**, *8*, 2839. See also ref 1 for other examples.
- (6) Knudsen, K. R.; Jørgensen, K. A. Org. Biomol. Chem. 2005, 3, 1362.
- (7) Reviews: (a) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (b) Ohfune, Y.; Shinada, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1115.
- (8) Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. J. Am. Chem. Soc. 2007, 129, 4900.
- (9) Review of bifunctional metal catalysis: Shibasaki, M.; Matsunaga, S. Chem. Soc. Rev. 2006, 35, 269 and references therein.
- (10) ESI-MS analysis indicated that Schiff base 1b incorporated two Ni to afford homodinuclear Ni<sub>2</sub>-1b complex. See Supporting Information.
- (11) For a related bimetallic Ni-Cs<sub>2</sub>-salen complex in asymmetric Michael reaction of malonates, see: Annamalai, V.; DiMauro, E. F.; Carroll, P. J.; Kozlowski, M. C. J. Org. Chem. 2003, 68, 1973 and references therein.
- (12) For other recent examples of bifunctional chiral mono-Ni(II) catalyst for activation of 1,3-dicarbonyl compounds in Michael addition, see: (a) Evans, D. A.; Seidel, D. J. Am. Chem. Soc. 2005, 127, 9958. (b) Evans, D. A.; Mito, S.; Seidel, D. J. Am. Chem. Soc. 2007, 129, 11583.
- (13) Freshly prepared  $Ni_2-1b$  complex gave comparable results.
- (14) There are many excellent chiral catalysts for direct Mannich-type reactions with malonates, β-keto esters, and 1,3-diketones. For selected examples, see: (a) Marigo, M.; Kjærsgaard, A.; Juhl, K.; Gathergood, N.; Jørgensen, K. A. Chem.-Eur. J. 2003, 9, 2359. (b) Uraguchi, D.; Terada, M. J. Am. Chem. Soc. 2004, 126, 5356. (c) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. Angew. Chem., Int. Ed. 2005, 44, 1525. (d) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. J. Am. Chem. Soc. 2005, 127, 11256. (e) Song, J.; Wang, Y.; Deng, L. J. Am. Chem. Soc. 2006, 128, 6048. (f) Sasamoto, N.; Dubs, C.; Hamashima, Y.; Sodeoka, M. J. Am. Chem. Soc. 2006, 128, 6048. (f) Sasamoto, N.; Dubs, C.; Hamashima, Y.; Sodeoka, M. J. Am. Chem. Soc. 2006, 128, 14010. (g) Tillman, A. L.; Ye, J.; Dixon, D. J. Chem. Commun. 2006, 1191. For other examples, see reviews in ref 2.
- (15) For the determination of relative and absolute configurations of products4, 7, and 9, and ORTEP structure of 4aa, see Supporting Information.

JA710398Q