

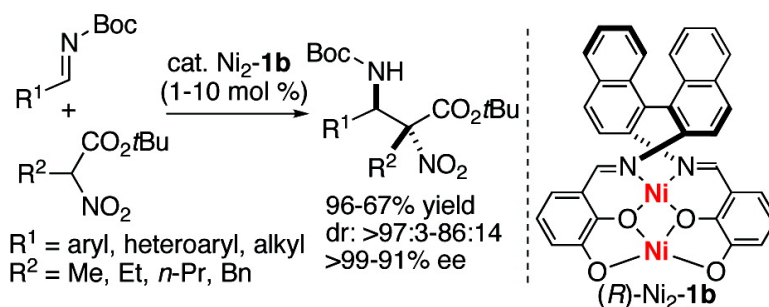
Communication

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A Bench-Stable Homodinuclear Ni₂–Schiff Base Complex for Catalytic Asymmetric Synthesis of α -Tetrasubstituted *anti*- α,β -Diamino Acid Surrogates

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Chiral α,β -diamino acids are key structural components in many biologically active compounds.¹ Among methods for their synthesis, catalytic asymmetric direct Mannich-type reactions² of a glycine Schiff base are one of the most efficient and straightforward methods for producing chiral *syn*- α,β -diamino acids.³ Recently, Johnston^{4a} and Willis^{4b} reported alternative approaches for producing *anti*- α,β -diamino acids via Mannich-type reactions of a nitroacetate and an α -isothiocyanate acid derivative. Although high diastereo- and enantioselectivity were realized, α,β -diamino acids with an α -tetrasubstituted carbon stereocenter cannot be produced using those reactions.^{3–5} Jørgensen reported an exceptional example using an α -methyl nitroacetate,⁶ but only an α -imino ester was utilized as an electrophile. Considering the importance of α,α -disubstituted α -amino acids as chiral building blocks for pharmaceuticals and artificial peptides,⁷ a new catalyst for chiral α -tetrasubstituted α,β -diamino acid synthesis with a broad substrate scope is in high demand. Herein, we report a new bench-stable homodinuclear Ni₂–Schiff base **1b** complex (Figure 1) that promoted Mannich-type reactions of *N*-Boc imines and α -substituted nitroacetates to afford α -tetrasubstituted *anti*- α,β -diamino acid surrogates in high ee (up to >99% ee). Ni₂–**1b** was also applicable to asymmetric Mannich-type reactions of malonates and β -keto ester.

We recently reported the utility of the dinucleating Schiff base **1a**-H₄ (Figure 1) in aza-Henry reactions of nitroethane and nitropropane.⁸ Schiff base **1a**-H₄ selectively incorporated Cu into the N₂O₂ inner cavity and oxophilic rare earth metal with a large ionic radius into the O₂O₂ outer cavity. Cooperative functions of the two metals⁹ in the heterobimetallic Cu–Sm–**1a** complex (Figure 1, M¹ = Cu, M² = 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 O₂O₂ outer cavity, possibly due to conformational difference between **1a**-H₄ and **1b**-H₄. After rescreening metal combinations using **1b** (entries 3–7), a homobimetallic Ni₂–**1b** complex, prepared from Schiff base **1b**-H₄ and 2 equiv of Ni(OAc)₂, gave the best result.^{10–12} Ni₂–**1b** (10 mol %) gave **4aa** in *anti:syn* = 90:10 and 98% ee (entry 5). Other metal combinations using **1b**, such as M₁ = Ni, M₂ = Sm (entry 4, 59% ee), M₁, M₂ = Cu (entry 6, 9% ee), M₁, M₂ = 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 Ni₂–**1b** complex was bench-stable and storable under air at room

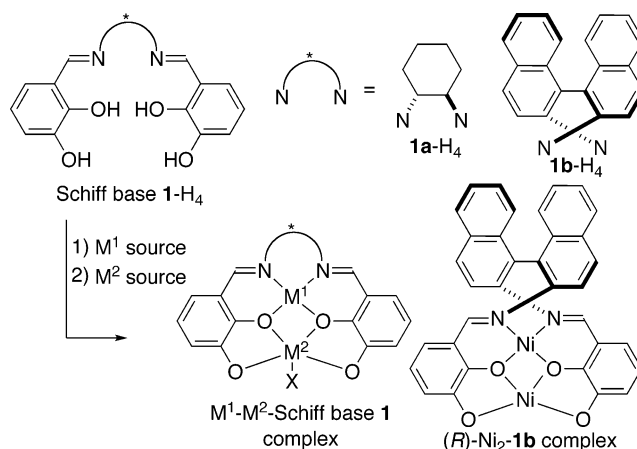


Figure 1. Structures of dinucleating Schiff bases **1a**-H₄ and **1b**-H₄, and postulated structures of bimetallic M¹–M²–**1** and (R)-Ni₂–**1b** complexes.

Table 1. Optimization of Reaction Conditions

entry	metal sources		Schiff base	additive	time (h)	yield ^b (%)	dr ^c (<i>anti/syn</i>)	% ee (<i>anti</i>)
	M ^{1a}	M ^{2a}						
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 ^d	91:9	98

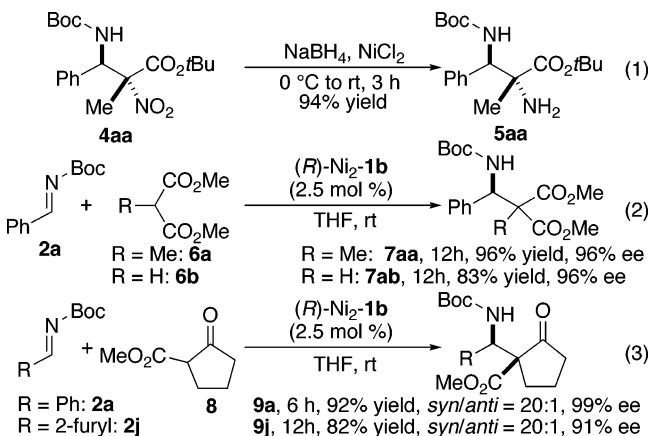
^a Cu(OAc)₂, Ni(OAc)₂, Pd(OAc)₂, and Sm(O-*i*Pr)₃ were used as metal sources. ^b Conversion yield determined by ¹H NMR analysis (entries 1–6). ^c Diastereomeric ratio was determined by ¹H NMR analysis. ^d Isolated yield.

temperature for at least 3 months without loss of activity. Substrate scope in Table 2 was investigated using the Ni₂–**1b** complex stored under air for more than 3 months.¹³ 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 enantioselectivity (entry 14, 98% ee). The NO₂ moiety in product **4aa** was readily reduced with NaBH₄/NiCl₂ at room temperature, giving α -tetrasubstituted *anti*- α,β -diamino ester **5aa** in 94% yield (eq 1).

Table 2. Catalytic Asymmetric Mannich-Type Reaction of Nitroacetates **3** and *N*-Boc Imines^a

entry	imine R ¹	Nu 3 (x mol %)	cat (x mol %)	temp (°C)	time (h)	yield ^b (%)	dr ^c (anti/syn)	% ee (anti)
1	Ph-	2a 3a	5	0	12	95	91:9	98
2	4-MeO-C ₆ H ₄ -	2b 3a	5	0	12	92	87:13	98
3	4-Me-C ₆ H ₄ -	2c 3a	5	0	12	90	89:11	97
4	4-Cl-C ₆ H ₄ -	2d 3a	5	0	12	87	86:14	97
5	4-F-C ₆ H ₄ -	2e 3a	5	0	12	91	90:10	91
6	3-thienyl	2f 3a	5	0	12	96	91:9	99
7	Ph-	2a 3b	5	0	12	91	94:6	99
8	Ph-	2a 3c	5	0	12	92	92:8	>99
9	Ph-	2a 3d	5	0	12	94	88:12	94
10 ^d	PhCH ₂ CH ₂ -	2g 3a	10	-40	36	73	>97:3	95
11 ^d	<i>n</i> -butyl	2h 3a	10	-40	36	67	>97:3	93
12 ^d	<i>i</i> -butyl	2i 3a	10	-20	24	85	>97:3	91
13 ^e	Ph-	2a 3a	5	0	13	91	90:10	98
14	Ph-	2a 3a	1	rt	12	93	88:12	98

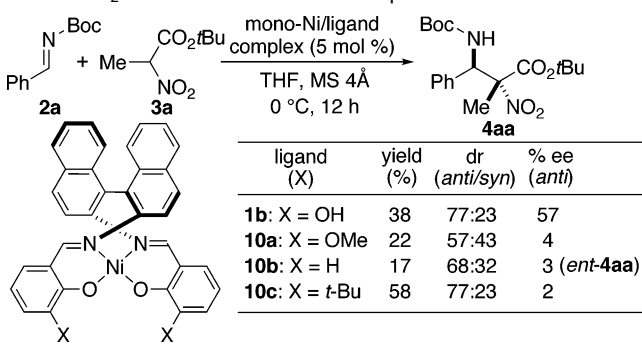
^a Reaction was performed in THF (0.4 M on imines **2**, 0.2–0.3 mmol scale) with MS 4Å using the Ni₂-**1b** complex stored over 3 months under air at room temperature; 1.1 equiv of **3** was utilized unless otherwise noted. ^b Isolated yield. ^c Determined by ¹H NMR analysis of crude mixture. ^d Two equivalents of **3a** were utilized. ^e Reaction was run in 2.0 mmol scale.



The utility of the Ni₂-**1b** complex was further demonstrated in the Mannich-type reactions of other donors, such as malonates and β-keto ester (eqs 2 and 3).¹⁴ High diastereo- and enantioselectivities were achieved at room temperature using 2.5 mol % of Ni₂-**1b** (99–91% ee).¹⁵

Control experiments (Scheme 1) indicated that neither a mononuclear Ni-**1b**-H₂ 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 Ni₂-**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 Ni₂-**1b** complex for direct Mannich-type reactions of nitroacetates, giving α-tetrasubstituted *anti*-α,β-diamino acid surrogates in >99–91% ee. The Ni₂-**1b** complex was also applicable to Mannich-type reactions of malonates and β-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 Ni₂-**1b** complex in other asymmetric reactions are ongoing.

Scheme 1. Control Experiments Using Mononuclear Ni–Schiff Base **1b**-H₂ or Ni–Salen **10a**–**10c** Complexes

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Supporting Information Available: Experimental procedures, spectral data of new compounds, determination of relative and absolute configurations, ESI-MS data of Ni₂-**1b**, and CIF of **4aa**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (15) For the determination of relative and absolute configurations of products **4**, **7**, and **9**, and ORTEP structure of **4aa**, see Supporting Information.

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