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Direct Catalytic Asymmetric Mannich-Type Reaction of β-Keto Phosphonate Using a Dinuclear Ni_2−Schiff Base Complex

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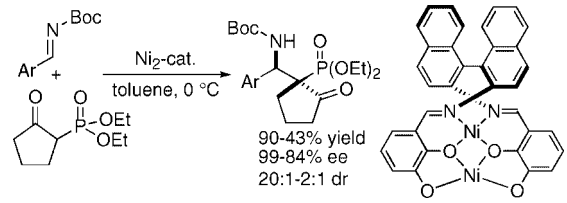
ABSTRACT



Direct catalytic asymmetric Mannich-type reactions of β-keto phosphonates are described. A homodinuclear Ni_2−Schiff base complex promoted the reaction at 0 °C, giving β-amino phosphonates in up to 90% yield, 20:1 dr, and 99% ee. Control experiments suggested that two Ni metals are important for achieving high yield and stereoselectivity.

The phosphonic acid functional group is regarded as a bioisostere of a carboxylic acid group. Aminophosphonic acid derivatives are useful structural motifs as haptens in catalytic antibody generation and as targets for enzyme inhibitors.[1] Several catalytic asymmetric methods for the synthesis of optically active α-amino phosphonic acid derivatives have been reported,[2] but catalytic asymmetric methods for β-amino phosphonic acid derivatives are limited.[3,4] Although catalytic asymmetric direct Mannich(-type) reactions for synthesizing β-amino acid derivatives have been intensively investigated over the past decade,[5,6] there are very few corresponding direct Mannich-type approaches for the synthesis of β-amino phosphonic acid derivatives, possibly due to the higher pK_a of the α-proton in phosphonic acid derivative donors than in carboxylic acid derivative donors.[7] Jørgensen et al. reported the first catalytic enantio- and diastereoselective direct Mannich-type reaction of β-keto

(1) *Review: Aminophosphonic and Aminophosphinic Acids, Chemistry and Biological Activity*; Kukhar, V. P., Hudson, H. R., Eds.; John Wiley & Sons: New York, 2000.

(2) Review: Gröger, H.; Hammer, B. *Chem.−Eur. J.* **2000**, *6*, 943. (a) For selected examples of catalytic asymmetric approaches, see also: Sawamura, M.; Ito, Y.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 2247. (b) Kitamura, M.; Tokunaga, M.; Pham, T.; Lubell, W. D.; Noyori, R. *Tetrahedron Lett.* **1995**, *36*, 5769. (c) Sasai, H.; Arai, S.; Tahara, Y.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 6656. (d) Kobayashi, S.; Kiyohara, H.; Nakamura, Y.; Matsubara, R. *J. Am. Chem. Soc.* **2004**, *126*, 6558. (e) Pawar, V. D.; Bettigeri, S.; Weng, S.-S.; Kao, J.-Q.; Chen, C.-T. *J. Am. Chem. Soc.* **2006**, *128*, 6308. (f) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102. (g) Saito, B.; Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 1978. For selected chiral auxiliary-based approaches, see: (h) Tager, K. M.; Taylor, C. M.; Smith, A. B., III *J. Am. Chem. Soc.* **1994**, *116*, 9377. (i) Davies, F. A.; Prasad, K. R. *J. Org. Chem.* **2003**, *68*, 7249, and references therein.

(3) Catalytic asymmetric Mannich-type approach: (a) Kjærsgaard, A.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 804. (b) Catalytic asymmetric aminohydroxylation approaches: Cravotto, G.; Giovenzana, G. B.; Pagliarin, R.; Palmisano, G.; Sisti, M. *Tetrahedron: Asymmetry* **1998**, *9*, 745. (c) Thomas, A. A.; Sharpless, K. B. *J. Org. Chem.* **1999**, *64*, 8379.

(4) General review on the synthesis of β-amino phosphonates: Palacios, F.; Alonso, C.; de los Santos, J. M. *Chem. Rev.* **2005**, *105*, 899.

(5) A general review on catalytic asymmetric Mannich(-type) reactions: (a) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541. For recent reviews on direct catalytic asymmetric Mannich(-type) reactions affording β-amino carbonyl compounds, see: (b) Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348. (c) Shibasaki, M.; Matsunaga, S. *J. Organomet. Chem.* **2006**, *691*, 2089. (d) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797. (e) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29.

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phosphonates, giving β-amino phosphonates in up to 84−43% ee.[3a] The imine in their studies was, however, limited to an *N*-Ts-imino ester. Thus, the development of a new complementary method applicable to imines with various substituents is highly desirable to broaden the availability of diverse optically active β-amino phosphonates. Herein, we report the utility of a homodinuclear Ni_2−Schiff base **1a** complex (Figure 1) to address this issue. The bimetallic Ni complex

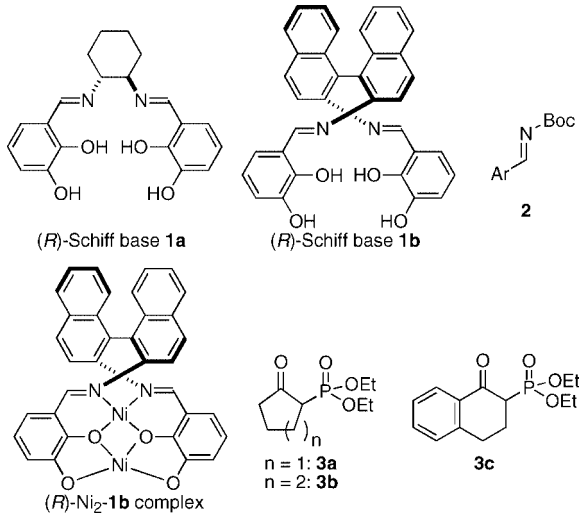
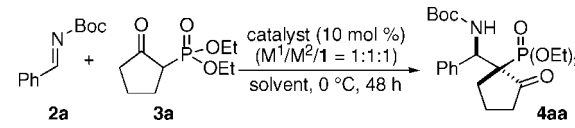


Figure 1. Structures of dinucleating Schiff bases **1a** and **1b**, *N*-Boc imines **2**, and β-keto phosphonates **3** and a proposed structure of a homodinuclear Ni_2−Schiff base **1b** complex.

promoted the Mannich-type reaction of various aryl and heteroaryl *N*-Boc imines **2** with β-keto phosphonates **3** at 0 °C, giving products in 90−43% yield, 20:1−2:1 dr, and 99−47% ee.

Initially, we screened various Lewis acid/Brønsted base bifunctional chiral metal catalysts[8] developed for direct Mannich-type reactions of other donors in our group[9] and found bimetallic Schiff base **1** complexes[10,11] to be promising candidates. Optimization studies are summarized in Table 1. In entries 1 and 2, Cu−Sm−Schiff base **1a**[10a] or **1b** complexes promoted the Mannich-type reaction of imine **2a**

Table 1. Optimization of Reaction Conditions



entry	metal sources M^{1a}	metal sources M^{2a}	Schiff base	solvent (× M)	additive	yield (%)	dr[b]	% ee (*anti*)
1	Cu	Sm	**1a**	THF (0.2)	none	91	20:1	1
2	Cu	Sm	**1b**	THF (0.2)	none	95	20:1	2
3	Ni	Sm	**1b**	THF (0.2)	none	95	18:1	1[c]
4	Cu	Cu	**1b**	THF (0.2)	none	95	20:1	28[c]
5	Ni	Ni	**1b**	THF (0.2)	none	92	10:1	80
6	Ni	Ni	**1b**	EtOAc (0.2)	none	43	10:1	77
7	Ni	Ni	**1b**	CH_2Cl_2 (0.2)	none	22	10:1	70
8	Ni	Ni	**1b**	toluene (0.2)	none	65	33:1	98
9	Ni	Ni	**1b**	toluene (0.2)	13X MS	75	5:1	93
10	Ni	Ni	**1b**	toluene (0.8)	none	83	15:1	96

[a] $Cu(OAc)_2$, $Sm(O\text{-}iPr)_3$, and $Ni(OAc)_2$ were used as metal sources. [b] Determined by ^1H NMR analysis. [c] *ent*-**4aa** was obtained in major.

and β-keto phosphonate **3a** in high yield (95−91%) and diastereoselectivity (20:1) at 0 °C, but with poor enantioselectivity (entry 1, 1% ee, and entry 2, 0% ee). A homodinuclear Ni_2−Schiff base **1b** complex,[10b] which was recently developed for the Mannich-type reaction of nitroacetates and related active methylene compounds, gave promising results. When the reaction was performed in THF (0.2 M) at 0 °C, product **4aa** was obtained in 92% yield, 10:1 diastereoselectivity, and 80% ee after 48 h (entry 5). In contrast, other dinuclear Schiff base **1b** complexes gave poor enantioselectivity (entries 2−4). Changing the solvent to toluene improved the diastereo- and enantioselectivity to 33:1 and 98% ee, respectively, but the reactivity decreased (entry 8, 65% yield). The addition of 13X MS improved the yield to 75%, but the diastereo- and enantioselectivity decreased

(6) For selected examples of direct catalytic asymmetric Mannich-type reactions using 1,3-dicarbonyl and related active methylene compounds as donors: (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) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191. (g) Yamaoka, Y.; Miyabe, H.; Yasui, Y.; Takemoto, Y. *Synthesis* **2007**, 2571. (h) Nojiri, A.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 5630. (i) Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866, and references therein. See also ref 10b. For other examples, see reviews in ref 5.

(7) For example, pK_a of diethyl malonate is 16.4 (in DMSO), while that of triethyl phosphonoacetate is 18.6 (in DMSO).

(8) Recent reviews on bifunctional Lewis acid/Brønsted base asymmetric metal catalysis: (a) Matsunaga, S.; Shibasaki, M. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 60. (b) Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev.* **2006**, *35*, 269.

(9) La catalyst: (a) Morimoto, H.; Lu, G.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 9588. Zn catalysts: (b) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777, and references therein. (c) Yoshida, T.; Morimoto, H.; Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3470. In catalyst: (d) Harada, S.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4365. Ba catalyst: (e) Yamaguchi, A.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 3387. Y catalyst: (f) Sugita, M.; Yamaguchi, A.; Yamagiwa, N.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 5339.

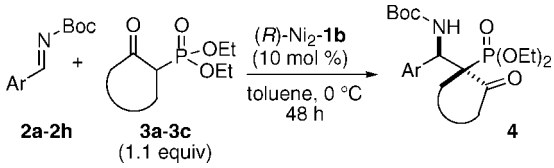
(10) (a) Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 4900. (b) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170. (c) Handa, S.; Nagawa, K.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3230.

(11) For selected examples of related bifunctional bimetallic Schiff base complexes in asymmetric catalysis, see: (a) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 1641. (b) Annamalai, V.; DiMauro, E. F.; Carroll, P. J.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *68*, 1973, and references therein. (c) Sammis, G. M.; Danjo, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 9928. (d) Li, W.; Thakur, S. S.; Chen, S.-W.; Shin, C.-K.; Kawthekar, R. B.; Kim, G.-J. *Tetrahedron Lett.* **2006**, *47*, 3453 references therein. For related early studies with dinuclear Ni_2−Schiff base complexes as epoxidation catalysts, see also: (e) Oda, T.; Irie, R.; Katsuki, T.; Okawa, H. *Synlett* **1992**, 641.

(entry 9, dr = 5:1, 93% ee).[12] Under concentrated reaction conditions (toluene, 0.8 M) in the absence of 13X MS, complete conversion was observed. Product **4aa** was obtained in 83% yield, and good diastereo- and enantioselectivity were maintained (entry 10, dr = 15:1, 96% ee).

The optimized reaction conditions were applied to various aryl and heteroaryl *N*-Boc imines **2** (Table 2). The reaction

Table 2. Substrate Scope and Limitation in Mannich-Type Reaction of *N*-Boc Imines with β-Keto Phosphonates[a]



entry	imine	Ar	3	additive	product	yield[b] (%)	dr[c]	% ee v(*anti*)
1	Ph	**2a**	**3a**	none	**4aa**	83	15:1	96
2[d]	Ph	**2a**	**3a**	none	**4aa**	85	17:1	98
3[e]	Ph	**2a**	**3a**	none	**4aa**	78	9:1	93
4	3-thienyl	**2b**	**3a**	none	**4ba**	90	17:1	98
5	3-furyl	**2c**	**3a**	none	**4ca**	82	13:1	99
6	2-furyl	**2d**	**3a**	none	**4da**	75	6:1	98
7	4-Me-C_6H_4	**2e**	**3a**	13X MS	**4ea**	63	10:1	95
8	4-MeO-C_6H_4	**2f**	**3a**	13X MS	**4fa**	86	7:1	87
9	4-F-C_6H_4	**2g**	**3a**	13X MS	**4ga**	64	6:1	85
10	4-Cl-C_6H_4	**2h**	**3a**	13X MS	**4ha**	43	11:1	84
11	3-MeO-C_6H_4	**2i**	**3a**	none	**4ia**	73	2:1	92
12	2-naphthyl	**2j**	**3a**	none	**4ja**	71	20:1	84
13[f]	Ph	**2a**	**3b**	none	**4ab**	51	6:1	47
14	Ph	**2a**	**3c**	none	**4ac**	47	8:1	55

[a] Reactions were run using imines **2** (0.4 mmol scale) and 1.1 equiv of **3a** in toluene (0.8 M) at 0 °C for 48 h unless otherwise noted. [b] Isolated yield after purification by column chromatography. [c] Determined by ^{1}H NMR analysis. [d] Reaction was run in 2.0 mmol scale. [e] Reaction was run using 5 mol % of Ni_2-**1b** catalyst for 72 h. [f] Reaction was run at 25 °C.

of *N*-Boc imine **2a** proceeded smoothly both in 0.4 and 2.0 mmol scale (entries 1 and 2). With 5 mol % catalyst loading, product was obtained in 78% yield and 93% ee after 72 h (entry 3). The reaction proceeded smoothly with heteroaryl imines **2b**−**2d**, giving the products in 90−75% yield, 17:1−6:1 dr, and 99−98% ee (entries 4−6).[13] With aryl imines **2e**−**2j** with substituents, the reactivity was much lower than with imine **2a** (entries 7−12). Thus, in entries 7−10, the reactions were performed in the presence of 13X MS to improve the yield of the products at the expense of stereoselectivity, giving products in 86−43% yield, 11:1−6:1 dr, and 95−84% ee. Although the present Ni_2−Schiff base **1b** complex afforded good reactivity and enantioselectivity with various aryl and heteroaryl imines (entries 1−12), there still remained limitations on β-keto phosphonate donors. When using other β-keto phosphonates **3b** and **3c**, only modest reactivity and enantioselectivity were observed (entries 13−14). With isomerizable alkyl *N*-Boc imines, yield was poor (<20%), possibly due to competitive isomerization to enecarbamates. Further studies to broaden the generality of the β-keto phosphonate donors are ongoing. The relative and absolute configuration of product **4ha** was unequivocally determined by single-crystal X-ray analysis (Figure 2).

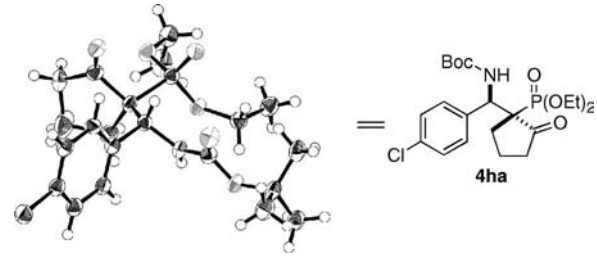
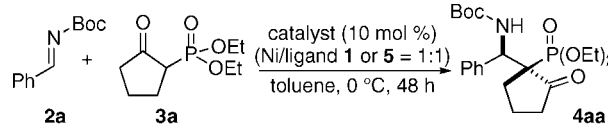
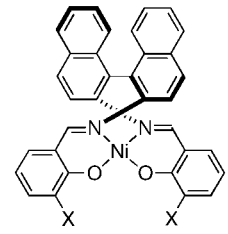


Figure 2. ORTEP plot of β-amino phosphonate **4ha**.

Control experiments (Scheme 1) demonstrated that neither a mononuclear Ni−Schiff base **1b** complex nor Ni−salen **5a**−**5c** complexes were effective for the present reaction, resulting in poor reactivity and enantioselectivity (65−21% yield, 53−1% ee). We assume that cooperative functions of the two Ni metal centers in the Ni_2−**1b** complex are important for achieving good enantioselectivity as well as reactivity. We speculate that the Ni−aryloxide moiety in the Ni_2−**1b** complex may function as a Brønsted base to generate a Ni−enolate from β-keto phosphonate **3**,[14] which would react with *N*-Boc imines **2** that are nicely fixed by the other Lewis acidic Ni metal center. The postulated transition state

Scheme 1. Negative Control Experiments Using Mononuclear Ni−Schiff Base **1b** and Ni−Salen **5a**−**5c** Complexes





ligand (X)	yield (%)	dr (*anti*/*syn*)	% ee (*anti*)
1b: X = OH	21	8:1	53
5a: X = OMe	35	10:1	2
5b: X = H	65	10:1	1
5c: X = *t*-Bu	31	7:1	2

(12) Molecular sieves type 13X (13X MS) purchased from Fluka were utilized after flame-drying activation under reduced pressure (ca. 1.0 kPa). Other molecular sieves such as 4 Å molecular sieves and 5 Å molecular sieves gave less satisfactory results.

(13) In contrast to furyl and thienyl imines, the use of pyridyl imines was unsuccessful, giving products in only poor enantioselectivity.

(14) For recent other examples of bifunctional chiral mono-Ni(II) catalyst for activation of 1,3-dicarbonyl and related compounds to form Ni−enolates as key intermediates, 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. (c) Suzuki, T.; Hamashima, Y.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 5435.

model to afford *anti*-**4** as a major adduct is shown in Figure 3. Mechanistic studies to elucidate the precise reaction mechanism are ongoing.

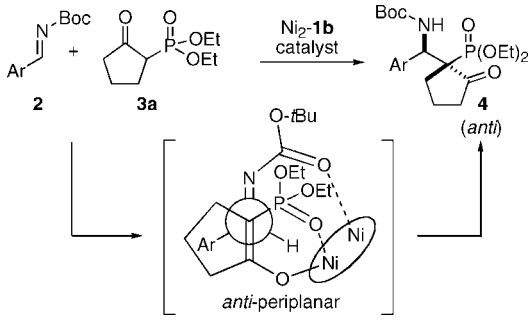


Figure 3. Hypothetical transition state model of direct Mannich-type reaction with β-keto phosphonate using the Ni_2−**1b** catalyst.

In summary, we developed direct catalytic asymmetric Mannich-type reactions of β-keto phosphonates with aryl and heteroaryl *N*-Boc imines **2** promoted by a homodinuclear Ni_2−Schiff base **1b** complex. The reaction proceeded at 0 °C, and β-amino phosphonates were obtained in 90−43% yield, 20:1−2:1 dr, and 99−47% ee. Further studies to broaden the substrate scope, especially β-keto phosphonate donors **3**, by tuning the dinuclear Ni_2−Schiff base **1** complex are ongoing.

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Supporting Information Available: Detailed experimental procedures, spectral data for new compounds, and X-ray crystallography data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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