

syn-Selective Catalytic Asymmetric 1,4-Addition of α -Ketoanilides to Nitroalkenes under Dinuclear Nickel Catalysis

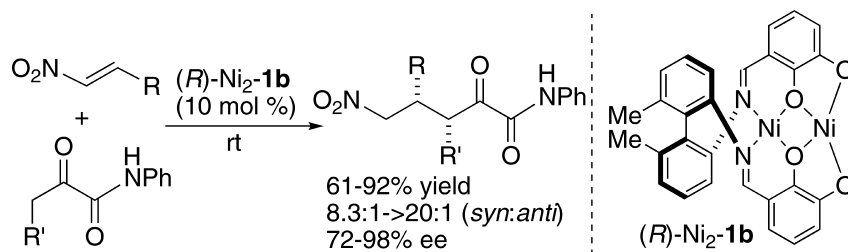
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ABSTRACT



A *syn*-selective catalytic asymmetric 1,4-addition of α -ketoanilides to nitroalkenes is described. The homodinuclear Ni₂-Schiff base 1b complex was suitable for the reaction, and products were obtained in 61–92% yield, 8.3:1 $\rightarrow$ 20:1 *syn*-selectivity, and 72–98% ee. Stereoselective transformation of the 1,4-adduct to a trisubstituted pyrrolidine was also performed.

Catalytic asymmetric Michael reactions to nitroalkenes provide versatile building blocks. Various chiral catalysts have been developed for these reactions using aldehydes, ketones, and 1,3-dicarbonyl compounds as nucleophiles.¹ In biosynthesis, pyruvic acid, a representative 1,2-dicarbonyl compound, is utilized as a key C2 and C3 donor unit. The use of related 1,2-dicarbonyl compounds such as α -ketoesters and α -ketoanilides as nucleophiles in catalytic asymmetric synthesis, however, is rather limited^{2–4} due to their high reactivity as electrophiles. Chemoselective activation of 1,2-

dicarbonyl compounds as nucleophiles is required to avoid undesired self-condensation reactions of 1,2-dicarbonyl compounds. Jørgensen² and our group³ independently reported direct catalytic asymmetric Mannich-type reactions using α -ketoesters and/or α -ketoanilides as donors, but applications of 1,2-dicarbonyl compounds as donors in asymmetric Michael reactions remained unsolved until a very recent report by Sodeoka and co-workers.⁴ In their first successful report, a mono-Ni chiral diamine complex promoted *anti*-selective catalytic asymmetric 1,4-addition of α -ketoesters to nitroalkenes, giving products in excellent *anti*-selectivity and enantioselectivity. The results prompted us

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(1) Reviews on asymmetric 1,4-addition to nitroalkenes: (a) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. Organocatalysis: (b) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. Metal catalysis: (c) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279.

(2) (a) Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, 40, 2995. (b) Juhl, K.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, 124, 2420.

(3) (a) Lu, G.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2008**, 47, 6847. (b) Xu, Y.; Lu, G.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, 48, 3353.

(4) (a) Nakamura, A.; Lectard, S.; Hashizume, D.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2010**, 132, 4036. For non-enantioselective 1,4-addition of α -ketoesters to nitroalkenes with a stoichiometric amount of base, see: Maeda, H.; Kraus, G. A. *J. Org. Chem.* **1997**, 62, 2314.

to report our preliminary efforts on this issue. Under dinuclear nickel-Schiff base **1** (Figure 1) catalysis,^{5–7} complementary *syn*-selectivity was accomplished, and products were obtained in up to 92% yield, >20:1 *syn*-selectivity, and 98% ee.

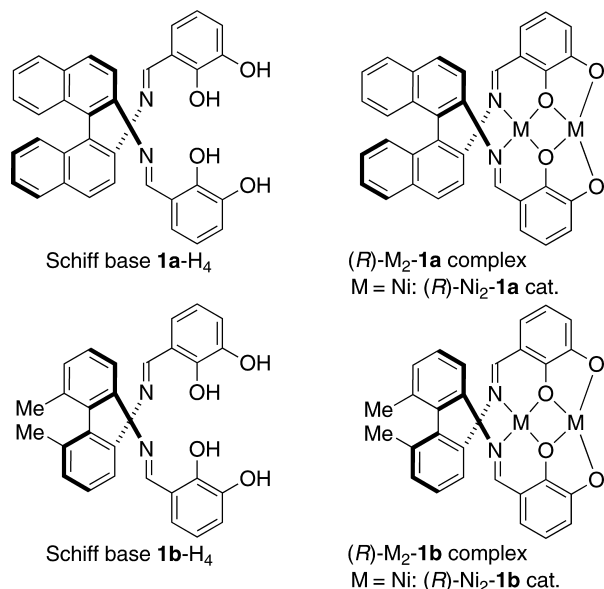


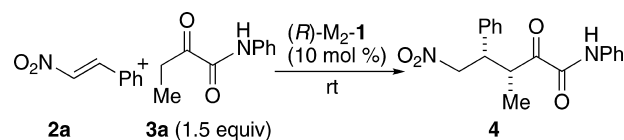
Figure 1. Structures of dinucleating Schiff bases **1a-H₄** and **1b-H₄** and homodinuclear Ni₂-**1a** and -**1b** complexes.

Because dinuclear Ni₂-Schiff base **1a** and **1b** catalysts (Figure 1) gave high selectivity in the asymmetric Mannich-type reaction of α -ketoanilides,^{3b} we performed optimization studies on the reaction of nitroalkene **2a** and α -ketoanilide **3a** using dinuclear Schiff base **1** complexes (Table 1).⁵ The Ni₂-**1a** complex *syn*-selectively promoted the reaction, and product **4aa** was obtained in 20% yield and 34% ee (entry 1). A Co₂(OAc)₂-**1a** complex (M = Co^{III}OAc),^{8a} which was developed for asymmetric Michael reaction of 1,3-dicarbonyl compounds to nitroalkenes, gave better enantioselectivity than the Ni₂-**1a**, but the yield was poor (entry 2, 4% yield, 73% ee). The Ni₂-**1b** complex derived from biphenyldiamine gave product **4aa** in good *syn*-selectivity (14:1) and 77% ee, but only 9% yield after 48 h at 0 °C (entry 3). Reactivity was slightly improved at rt, while maintaining similar enantioselectivity (entry 4, 21% yield,

(5) The utility of Ni₂-**1** in other reactions: (a) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170. (b) Chen, Z.; Yakura, K.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 3239. (c) Mouri, S.; Chen, Z.; Matsunaga, S.; Shibasaki, M. *Chem. Commun.* **2009**, 5138. (d) Mouri, S.; Chen, Z.; Mitsunuma, H.; Furutachi, M.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 1255. (e) Shepherd, N. E.; Tanabe, H.; Xu, Y.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 3666.

(6) For selected other examples of bimetallic Schiff base catalysts from our group, see the following. Cu-Sm cat.: (a) Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 4900. (b) Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 4925. Pd-La cat.: (c) Handa, S.; Nagawa, K.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3230. Ga-Yb cat.: (d) Mihara, H.; Xu, Y.; Shepherd, N. E.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 8384.

Table 1. Optimization Studies



entry	M	1	solvent	additive	% yield ^a	dr ^a (<i>syn</i> / <i>anti</i>)	% ee ^b
1 ^c	Ni	1a	THF	none	20	6.8:1	34
2 ^c	Co(OAc)	1a	THF	none	4	3.0:1	73
3 ^c	Ni	1b	THF	none	9	14:1	77
4	Ni	1b	THF	none	21	8.2:1	76
5	Co(OAc)	1b	THF	none	trace	ND	ND
6	Mn(OAc)	1b	THF	none	trace	ND	ND
7	Ni	1b	EtOH	none	33	3.0:1	52
8	Ni	1b	1,4-dioxane	none	18	6.2:1	90
9	Ni	1b	1,4-dioxane	MS 5 Å	50	5.6:1	87
10	Ni	1b	1,4-dioxane	MS 5 Å/HFIP ^d	71 ^e	14:1	90

^a Determined by crude ¹H NMR analysis. ^b Determined by chiral HPLC analysis. ^c Reactions were run at 0 °C in entries 1–3. ^d 5 equiv of HFIP was added. ^e Isolated yield after purification by silica gel column chromatography.

76% ee). With the Schiff base **1b**, other metals, Co and Mn,^{8b} were also investigated (entries 5 and 6), but only trace, if any, product was obtained. Among the solvents screened, 1,4-dioxane produced the best enantioselectivity (entry 8, 90% ee). Achiral additives to improve the reactivity were investigated, and the addition of MS 5 Å (entry 9) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP, entry 10) was effective,⁹ giving **4aa** in 71% isolated yield, 14:1 *syn*-selectivity, and 90% ee (entry 10).

The substrate scope and limitations of the reaction are summarized in Table 2. The Ni₂-**1b** catalyst was applicable to a broad range of nitroalkenes. Various nitrostyrene derivatives **2b–2g** with either an electron-withdrawing or electron-donating substituent on the aromatic ring gave products with good to excellent *syn*-selectivity and enanti-

(7) For selected examples of related bifunctional bimetallic Schiff base catalysis in asymmetric synthesis, see: (a) Annamalai, V.; DiMauro, E. F.; Carroll, P. J.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *68*, 1973. (b) Yang, M.; Zhu, C.; Yuan, F.; Huang, Y.; Pan, Y. *Org. Lett.* **2005**, *7*, 1927. (c) Gao, J.; Woolley, F. R.; Zingaro, R. A. *Org. Biomol. Chem.* **2005**, *3*, 2126. (d) Li, W.; Thakur, S. S.; Chen, S.-W.; Shin, C.-K.; Kawthekar, R. B.; Kim, G.-J. *Tetrahedron Lett.* **2006**, *47*, 3453. (e) Mazet, C.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2008**, *47*, 1762. (f) Hirahata, W.; Thomas, R. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2008**, *130*, 17658. (g) Sun, J.; Yuan, F.; Yang, M.; Pan, Y.; Zhu, C. *Tetrahedron Lett.* **2009**, *50*, 548. (h) Wu, B.; Gallucci, J. C.; Parquette, J. R.; RajanBabu, T. V. *Angew. Chem., Int. Ed.* **2009**, *48*, 1126. See also a review: (i) Haak, R. M.; Wezenberg, S. J.; Kleij, A. W. *Chem. Commun.* **2010**, 46, 2713.

(8) Co₂-**1a**: (a) Chen, Z.; Furutachi, M.; Kato, Y.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2218. Mn₂-**1a**: (b) Kato, Y.; Furutachi, M.; Chen, Z.; Mitsunuma, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 9168.

(9) We assume that HFIP had positive effects as a proton source to accelerate product dissociation step (catalyst turnover step). For selected examples of HFIP effects in asymmetric reactions, see: (a) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134, and references therein. (b) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015. (c) Kawara, A.; Taguchi, T. *Tetrahedron Lett.* **1994**, *35*, 8805. (d) Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030. (e) Takita, R.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 4661.

Table 2. *syn*-Selective Catalytic Asymmetric 1,4-Addition of α -Ketoanilides to Nitroalkenes^a

		R'	3 (1.5 equiv)	4	R'	3	4
		R' = Me: 3a , Et: 3b , Bn: 3c					
entry	R	cat. (mol %)	2 (%)	3 (%)	4 (%)	dr ^c (syn/anti)	% ee ^d
1	Ph	2a 10	3a 71	4aa 14:1	90		
2	4-Cl-C ₆ H ₄	2b 10	3a 87	4ba 19:1	86 (96) ^e		
3	4-Br-C ₆ H ₄	2c 10	3a 86	4ca 8.4:1	86		
4	3-Br-C ₆ H ₄	2d 10	3a 77	4da 8.3:1	82		
5	4-MeO-C ₆ H ₄	2e 10	3a 92	4ea >20:1	98		
6 ^f	4-MeO-C ₆ H ₄	2e 5	3a 83	4ea >20:1	97		
7 ^f	4-MeO-C ₆ H ₄	2e 2.5	3a 68	4ea >20:1	97		
8	3-MeO-C ₆ H ₄	2f 10	3a 63	4fa 10:1	85		
9	4-Me-C ₆ H ₄	2g 10	3a 83	4ga 11:1	89		
10	2-thienyl	2h 10	3a 82	4ha 11:1	72		
11	(<i>E</i>)-PhCH=CH	2i 10	3a 70	4ia >20:1	90		
12	PhCH ₂ CH ₂	2j 10	3a 60	4ja 10:1	92		
13	4-MeO-C ₆ H ₄	2e 10	3b 74	4eb >20:1	92		
14	4-MeO-C ₆ H ₄	2e 10	3c 61	4ec >20:1	83		

^a Reaction was run using 1.5 equiv of **3**, 5 equiv of HFIP (1,1,1,3,3,3-hexafluoroisopropanol), and MS 5 Å (20 mg for 0.2 mmol of **2**) in anhydrous 1,4-dioxane (1.0 M) at room temperature. ^b Isolated yield after purification by silica gel column chromatography. ^c Determined by crude ¹H NMR analysis. ^d Determined by chiral HPLC analysis. ^e Number in parentheses is the value after enantioenrichment by recrystallization from hexane/ethyl acetate (entry 2, 81% yield). ^f Reaction was run for 72 h at rt.

oselectivity (entries 2–9, 8.3:1 → 20:1, 82–98% ee). Good *syn*-selectivity and enantioselectivity were maintained even with reduced catalyst loading (entry 6: 5 mol %, entry 7: 2.5 mol %), although longer reaction time was required and yield of **4ea** decreased. The absolute and relative configuration of **4ea** was determined by X-ray crystallographic analysis (Figure 2).¹⁰ 2-Thienyl-substituted nitroalkene **2h**

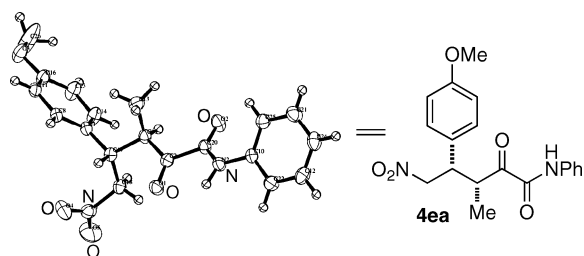


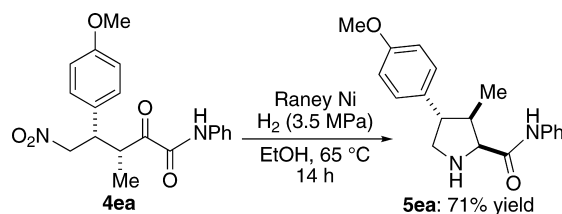
Figure 2. ORTEP plot of product **4ea**.

also had good *syn*-selectivity, but its enantioselectivity was somewhat decreased (entry 10, 72% ee). Nitrodiene **2i**

(10) Flack parameter was –0.14. CIF file is available as Supporting Information.

predominantly afforded the 1,4-adduct **4ia** in high *syn*-selectivity and enantioselectivity (entry 11, >20:1 and 90% ee). β -Alkyl-substituted nitroalkene **2j** was also applicable, and the product was obtained in 10:1 *syn*-selectivity and 92% ee (entry 12). Ni₂-**1b** was applicable to other α -ketoanilides **3b** and **3c**, giving products in >20:1 *syn*-selectivity and 92–83% ee (entries 13 and 14). To demonstrate the synthetic utility of the reaction, transformation of the product to a trisubstituted pyrrolidine was performed (Scheme 1). Reduction of **4ea** with Raney-Ni in EtOH directly gave the cyclized adduct **5ea** in 71% yield.^{11,12}

Scheme 1. Transformations of Michael Adduct **4ea**



In the present reaction, we assume that the two Ni centers function cooperatively as observed in other related reactions using Ni₂–Schiff base **1a** and **1b** complexes.⁵ The postulated reaction mechanism is summarized in Figure 3. One of the Ni–O bonds in the outer O₂O₂ cavity is speculated to work as a Brønsted base to generate Ni-enolate in situ.¹³ The other Ni in the inner N₂O₂ cavity functions as a Lewis acid to control the position of the nitroalkene, similar to conventional metal-salen Lewis acid catalysis. The C–C bond formation

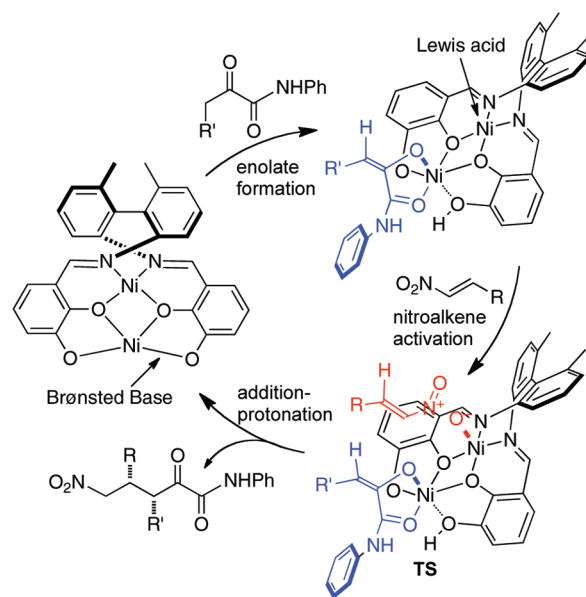


Figure 3. Postulated catalytic cycle of Ni₂-**1b**-catalyzed asymmetric 1,4-addition.

via the transition state (TS in Figure 3), followed by protonation, affords the *syn*-adduct and regenerates the Ni₂-**1b** catalyst.

In summary, we succeeded in a catalytic asymmetric 1,4-addition of α -ketoanilides to nitroalkenes under dinuclear nickel catalysis. The homodinuclear Ni₂-Schiff base **1b**

(11) Minor diastereomer was not detected under the reaction conditions.

(12) For transformations of anilide moiety into carboxylic acid, ester, amide, and alcohol under mild reaction conditions, see: (a) Evans, D. A.; Aye, Y.; Wu, J. *Org. Lett.* **2006**, 8, 2071. (b) Saito, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, 128, 8704. (c) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *Synlett* **2006**, 3529, and references therein.

(13) ¹H NMR analysis of the bimetallic Ni₂-**1a** and Ni₂-**1b** complexes does not show any peaks, suggesting that at least one of the Ni metal centers has non-planar coordination mode. On the basis of the molecular model, we assume that the outer Ni center has *cis*- β configuration due to strain of the bimetallic complexes. In other words, one of the Ni–O bonds of the outer Ni center is speculated to be in apical position. Thus, the Ni–O bond would work as a Brønsted base to deprotonate α -ketoanilide to give the Ni-enolate intermediate. Of course, the proposed mechanism in Figure 3 is too much speculative at the moment, and mechanistic studies, including trials to elucidate precise coordination modes of two Ni metal centers by X-ray single crystal analysis, are ongoing. For the utility of *cis*- β metal complexes of salens in asymmetric catalysis, see a review: Katsuki, T. *Chem. Soc. Rev.* **2004**, 33, 437.

complex promoted the reaction at rt, and products were obtained in 60–92% yield, 8.3:1 $\rightarrow$ 20:1 *syn*-selectivity, and 72–98% ee. The observed *syn*-selectivity was complementary to that previously reported for an *anti*-selective reaction under mono-Ni-diamine catalysis by Sodeoka and co-workers. Further studies to improve the reactivity of dinuclear nickel catalysis are ongoing.

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Supporting Information Available: Experimental procedures, spectral data of new compounds, and X-ray crystallography data of **4ea** in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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