ORGANIC LETTERS

2010
Vol. 12, No. 14
3246−3249

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

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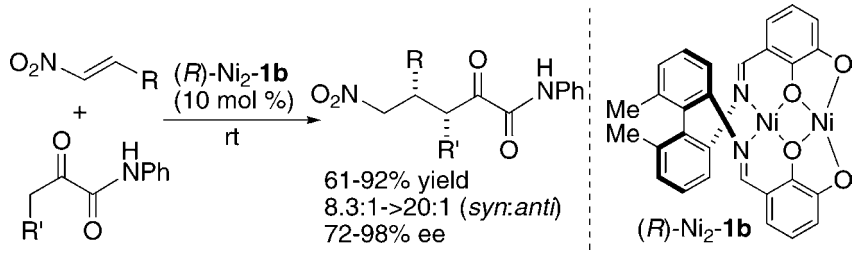
Received May 24, 2010

ABSTRACT



A *syn*-selective catalytic asymmetric 1,4-addition of α-ketoanilides to nitroalkenes is described. The homodinuclear Ni_2-Schiff base 1b complex was suitable for the reaction, and products were obtained in 61−92% yield, 8.3:1 → 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. Jørgensen[2] and our group[3] 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.

10.1021/ol101185p
Published on Web 06/15/2010

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.

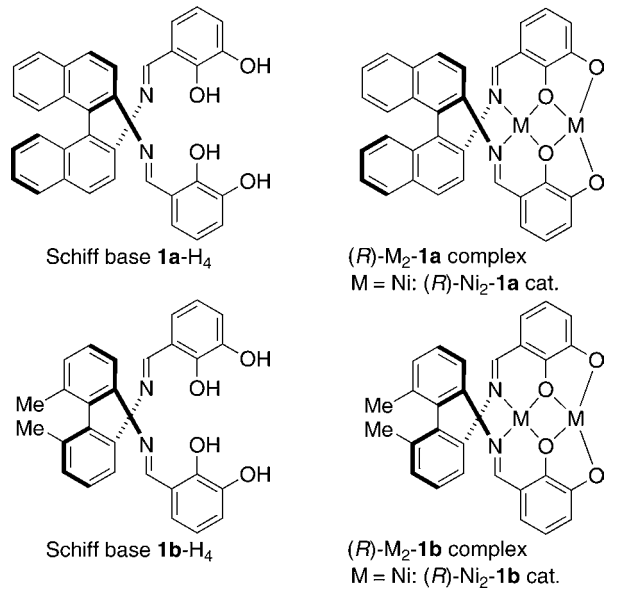
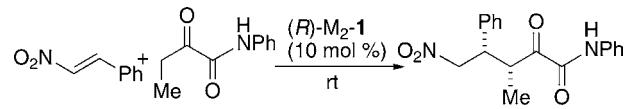


Figure 1. Structures of dinucleating Schiff bases **1a**-H_4 and **1b**-H_4 and homodinculear Ni_2-**1a** and -**1b** complexes.

Because dinuclear Ni_2-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 Ni_2-**1a** complex *syn*-selectively promoted the reaction, and product **4aa** was obtained in 20% yield and 34% ee (entry 1). A $Co_2(OAc)_2$-**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 Ni_2-**1a**, but the yield was poor (entry 2, 4% yield, 73% ee). The Ni_2-**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, 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).

Table 1. Optimization Studies



entry	M	1	solvent	additive	% yield[a]	dr[a] (*syn*/*anti*)	% 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.

The substrate scope and limitations of the reaction are summarized in Table 2. The Ni_2-**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-

(5) The utility of Ni_2-**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.

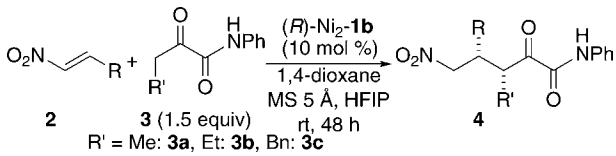
(6) For selected other examples of bimetallic Schiff base catalysts from our group, see the following. Cu-Sm cat.: (a) Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 4900. (b) Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **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.

(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) Co_2-**1a**: (a) Chen, Z.; Furutachi, M.; Kato, Y.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2218. Mn_2-**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]



entry	R	2	cat. (mol %)	3	% yield[b]	4	dr[c] (*syn*/*anti*)	% ee[d]
1	Ph	**2a**	10	**3a**	71	**4aa**	14:1	90
2	4-Cl-C_6H_4	**2b**	10	**3a**	87	**4ba**	19:1	86 (96)[e]
3	4-Br-C_6H_4	**2c**	10	**3a**	86	**4ca**	8.4:1	86
4	3-Br-C_6H_4	**2d**	10	**3a**	77	**4da**	8.3:1	82
5	4-MeO-C_6H_4	**2e**	10	**3a**	92	**4ea**	>20:1	98
6[f]	4-MeO-C_6H_4	**2e**	5	**3a**	83	**4ea**	>20:1	97
7[f]	4-MeO-C_6H_4	**2e**	2.5	**3a**	68	**4ea**	>20:1	97
8	3-MeO-C_6H_4	**2f**	10	**3a**	63	**4fa**	10:1	85
9	4-Me-C_6H_4	**2g**	10	**3a**	83	**4ga**	11:1	89
10	2-thienyl	**2h**	10	**3a**	82	**4ha**	11:1	72
11	(*E*)-PhCH=CH	**2i**	10	**3a**	70	**4ia**	>20:1	90
12	$PhCH_2CH_2$	**2j**	10	**3a**	60	**4ja**	10:1	92
13	4-MeO-C_6H_4	**2e**	10	**3b**	74	**4eb**	>20:1	92
14	4-MeO-C_6H_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 ^{1}H 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**

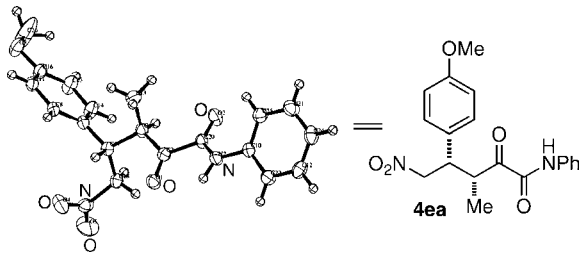
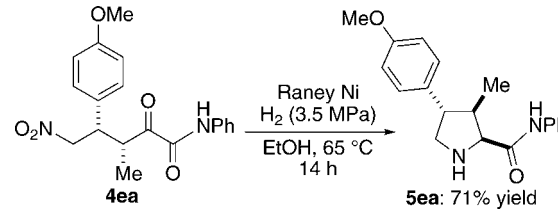


Figure 2. ORTEP plot of product **4ea**.

also had good *syn*-selectivity, but its enantioselectivity was somewhat decreased (entry 10, 72% ee). Nitrodiene **2i** 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). Ni_2-**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 Ni_2−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 O_2O_2 cavity is speculated to work as a Brønsted base to generate Ni-enolate in situ.[13] The other Ni in the inner N_2O_2 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

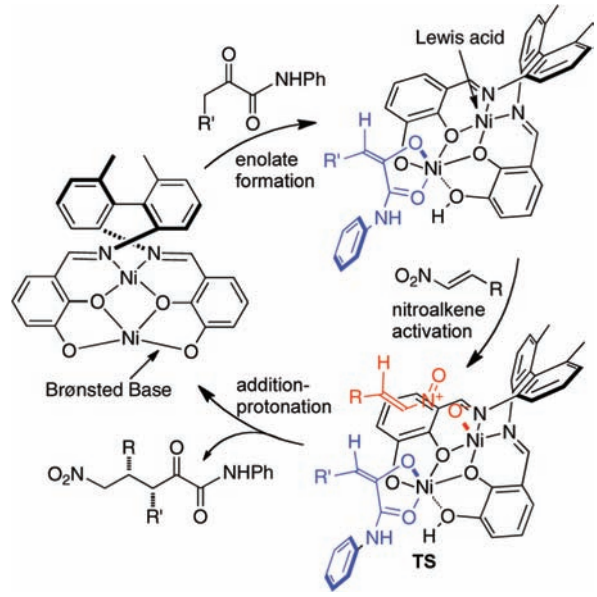


Figure 3. Postulated catalytic cycle of Ni_2-**1b**-catalyzed asymmetric 1,4-addition.

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

via the transition state (TS in Figure 3), followed by protonation, affords the *syn*-adduct and regenerates the Ni_2-**1b** catalyst.

In summary, we succeeded in a catalytic asymmetric 1,4-addition of α-ketoanilides to nitroalkenes under dinuclear nickel catalysis. The homodinuclear Ni_2−Schiff base **1b** complex promoted the reaction at rt, and products were obtained in 60−92% yield, 8.3:1 → 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 coworkers. Further studies to improve the reactivity of dinuclear nickel catalysis are ongoing.

Acknowledgment. This work was supported by Grant-in-Aid for Scientific Research (S), Takeda Science foundation (for S.M.), and Grant-in-Aid for Young Scientist (A). Y.X. is thankful for a JSPS fellowship. We thank Dr. M. Shiro at RIGAKU for his generous help and advice on X-ray crystallographic analysis of **4ea**. S.M. and Y.X. thank Prof. M. Kanai at the University of Tokyo for his generous support of this project.

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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(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) ^{1}H NMR analysis of the bimetallic Ni_2-**1a** and Ni_2-**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.