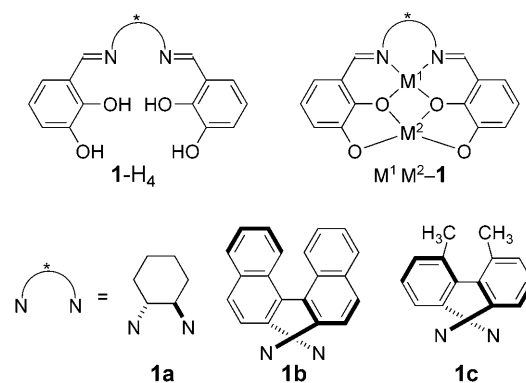


Direct *anti*-Selective Catalytic Asymmetric Mannich-Type Reactions of α -Ketoanilides for the Synthesis of γ -Amino Amides and Azetidine-2-amides**

Yingjie Xu, Gang Lu, Shigeki Matsunaga,* and Masakatsu Shibasaki*

Catalytic asymmetric Mannich(-type) reactions of aldehydes, ketones, esters, and other donors for the synthesis of β -amino carbonyl compounds have been investigated intensively over the past decade.^[1,2] In contrast, Mannich-type reactions of homoenolates or their synthetic equivalents for the production of γ -amino acids have not been studied as extensively.^[3–6] Recently, Scheidt and co-workers^[3a] and Bode and co-workers^[3b] reported the enantioselective addition of homoenolate equivalents to nitrones and a ketimine under the catalysis of *N*-heterocyclic carbenes to afford γ -amino esters with contiguous stereocenters at the β and γ positions. Jørgensen and co-workers reported a *syn*-selective asymmetric direct Mannich-type reaction with α -ketoester donors as homoenolate synthetic equivalents. After the stereoselective reduction of the α -keto unit in the Mannich adduct, a highly functionalized γ -amino ester with three contiguous stereocenters was obtained with excellent enantio- and diastereoselectivity.^[4] The method was limited, however, to reactions with an *N*-tosyl α -iminoester. Recently, we also reported *syn*-selective Mannich-type reactions of α -ketoanilide donors with aryl, heteroaryl, and alkyl *N*-thiophenesulfonyl imines in the presence of a heterobimetallic lanthanum aryl oxide/lithium aryl oxide/pyridine-2,6-bisoxazoline (pybox) catalyst.^[5] Owing to the stereodiversity of γ -amino acids, a complementary *anti*-selective reaction is in high demand. Herein, we describe an *anti*-selective direct catalytic asymmetric Mannich-type reaction of α -ketoanilide donors and its application to the stereoselective synthesis of γ -amino amides and azetidine-2-amides. A homodinuclear nickel complex prepared from a new biphenyldiamine-based dinucleating Schiff base **1c** (Scheme 1) promoted the reaction of α -ketoanilides **2** with *o*-nitrobenzenesulfonyl (*o*-Ns) imines **3** to afford the



Scheme 1. Structures of the dinucleating Schiff bases **1a-H₄**, **1b-H₄**, and **1c-H₄** and dinuclear complexes M^1M^2-1 .

products in up to 99% yield with an *anti/syn* ratio of more than 50:1 and 95% *ee*.

To develop the *anti*-selective reaction, we initially screened several chiral catalysts for the reaction of the α -ketoanilide **2a** with the *N*-thiophenesulfonyl imine **3a**. These compounds were found to be the best substrates for a previously reported *syn*-selective Mannich-type reaction.^[5,7] Among the Lewis acid/Brønsted base bifunctional catalysts^[8] developed by our research group for other direct Mannich-type reactions,^[9] dinuclear Schiff base complexes^[10,11] gave promising results in terms of *anti* selectivity (Table 1). Originally developed for a nitro-Mannich-type reaction,^[10a] a heterobimetallic Cu/Sm(OAr) (Ar = 4-*t*BuC₆H₄) complex with the Schiff base **1a** gave the product **4aa** in 93% yield with good *anti* selectivity (*anti/syn* = 9.5:1) at –40°C, but with poor enantioselectivity (1% *ee*; Table 1, entry 1). The homodinuclear complex Ni₂-**1b** that was developed for a Mannich-type reaction of nitroacetates and other active methylene compounds^[10c] promoted the reaction at 0°C to give **4aa** in 88% yield (*anti/syn* > 20:1) and with 82% *ee* (Table 1, entry 2). Other homodinuclear complexes of Schiff base **1b** were not suitable for this reaction (Table 1, entries 3–5). The protecting group on the imine affected the *anti* selectivity as well as the enantioselectivity (Table 1, entries 6–11).^[12] The *o*-Ns-protected imine^[13] **3g** gave the best result: The Ni₂-**1b** complex promoted the reaction of **3g** with α -ketoanilide **2a** to afford the product **4ag** (*anti/syn* > 20:1) in 93% yield with 88% *ee* (Table 1, entry 11). Ligand tuning revealed that the new biphenyldiamine-based Schiff base **1c**^[14] gave better enantioselectivity (91% *ee*; Table 1, entry 12), possibly as a result of a slight change in the dihedral angle of the biaryl moiety. When the solvent was changed from THF to THF/

[*] Y. Xu, G. Lu, Dr. S. Matsunaga, Prof. Dr. M. Shibasaki
Graduate School of Pharmaceutical Sciences
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
Fax: (+81) 3-5684-5206
E-mail: smatsuna@mol.f.u-tokyo.ac.jp
mshibasa@mol.f.u-tokyo.ac.jp
Homepage: http://www.f.u-tokyo.ac.jp/~kanai/e_index.html

[**] We thank Z. Chen and H. Mihara at the University of Tokyo for helpful advice on this project, and T. Nitabaru and H. Morimoto for X-ray crystallography. This research was supported by Grants-in-Aid for Scientific Research (S), Scientific Research on Priority Areas (No. 20037010, Chemistry of Concerto Catalysis) (S.M.), and Young Scientists (A) (S.M.) from the JSPS and MEXT.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.200900670>.

Table 1: Optimization of the *anti*-selective direct catalytic asymmetric Mannich-type reaction with α -ketoanilide **2a**.^[a]

Entry	M ¹	M ²	Ligand	PG	t [h]	Yield ^[b] [%]	d.r. ^[b] (<i>anti</i> / <i>syn</i>)	ee (<i>anti</i>) [%]
1 ^[c,d]	Cu	Sm(OAr)	1a	2-thienyl-SO ₂ (3a)	62	93	9.5:1	1
2	Ni	Ni	1b	2-thienyl-SO ₂ (3a)	30	88	> 20:1	82
3	Co(OAc)	Co(OAc)	1b	2-thienyl-SO ₂ (3a)	44	61	1.3:1	16
4	Cu	Cu	1b	2-thienyl-SO ₂ (3a)	38	0	—	—
5	Zn	Zn	1b	2-thienyl-SO ₂ (3a)	38	0	—	—
6	Ni	Ni	1b	Boc (3b)	38	messy	—	—
7	Ni	Ni	1b	Ph ₂ P(O) (3c)	64	trace	—	—
8	Ni	Ni	1b	<i>p</i> -Ts (3d)	41	62	4.5:1	69
9	Ni	Ni	1b	2-pyridyl-SO ₂ (3e)	53	4	9:1	85
10	Ni	Ni	1b	<i>p</i> -Ns (3f)	36	88	> 20:1	79
11	Ni	Ni	1b	<i>o</i> -Ns (3g)	18	93	> 20:1	88
12	Ni	Ni	1c	<i>o</i> -Ns (3g)	21	98	> 20:1	91
13 ^[e]	Ni	Ni	1c	<i>o</i> -Ns (3g)	25	98	> 20:1	93

[a] The reaction was performed at 0 °C in THF under argon unless otherwise noted. [b] The yield and diastereomeric ratio were determined by ¹H NMR spectroscopic analysis. [c] The reaction was carried out at -40 °C. [d] Ar = 4-*t*BuC₆H₄. [e] THF/toluene (1:4) was used as the solvent. Boc = *tert*-butoxycarbonyl, Ts = *p*-toluenesulfonyl.

toluene (1:4), **4ag** (*anti*/*syn* > 20:1) was obtained in 98 % yield with 93 % *ee* (Table 1, entry 13).

The generality and limitations of the reaction were investigated under the optimized reaction conditions (Table 2). The complex Ni₂-**1c** not only catalyzed reactions of the α -ketoanilide **2a**, but also the transformation of **2b** (R² = Et): Product **4bg** was obtained in high yield with high

loading was decreased to 2.5 mol % (Table 2, entry 11).

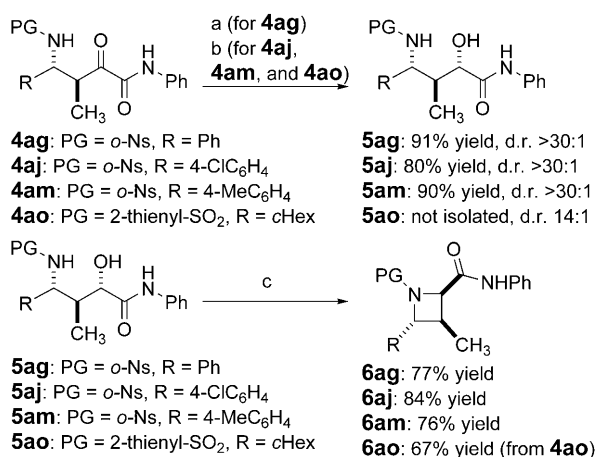
We investigated transformations of the products to demonstrate the synthetic utility of these compounds (Scheme 2). The keto group α to the amide in the Mannich adduct **4ag** was reduced stereoselectively with LiBHET₃ to give the α -hydroxy β -alkyl γ -amino amide **5ag** with three contiguous stereocenters with the relative configuration *anti*-

anti in 91 % yield and with greater than 30:1 diastereoselectivity (Scheme 2). The absolute and relative configuration of **5ag** was determined by X-ray crystallographic analysis (Figure 1).^[16] As Ns amides are known to be suitable nucleophiles for Mitsunobu reactions,^[13a] we anticipated that compound **5ag** would be a good precursor for a fully substituted azetidine-2-amide: a useful nonnatural amino acid derivative.^[17,18] The intramolecular Mitsunobu cyclization proceeded smoothly, and the optically active azetidine-2-amide **6ag** with the *syn*-*anti* configuration was obtained in 77 % yield. The Mannich adducts **4aj** and **4am** were converted successfully into the azetidine-2-amides **6aj** and **6am** by a procedure that differed from that used for **4ag** only in the reagent for reduction. Adduct **4ao** with the 2-thiophenesulfonyl protecting group also underwent stereoselective

Table 2: Direct catalytic *anti*-selective asymmetric Mannich-type reaction of *o*-Ns imines **3g–o** with α -ketoanilides **2**.

Entry	R ¹	R ²	4	Catalyst [mol %]	t [h]	Yield ^[a] [%]	d.r. ^[b] (<i>anti</i> / <i>syn</i>)	ee (<i>anti</i>) ^[c] [%]
1	Ph (3g)	Me (2a)	4ag	10	24	96	28:1	93
2	Ph (3g)	Et (2b)	4bg	10	40	94	45:1	92
3	2-naphthyl (3h)	Me (2a)	4ah	10	48	85	> 50:1	94
4	4-FC ₆ H ₄ (3i)	Me (2a)	4ai	10	24	99	29:1	92
5	4-ClC ₆ H ₄ (3j)	Me (2a)	4aj	10	24	99	48:1	95
6	4-BrC ₆ H ₄ (3k)	Me (2a)	4ak	10	24	99	> 50:1	91
7 ^[d]	4-MeOC ₆ H ₄ (3l)	Me (2a)	4al	10	48	86	> 50:1	93
8	4-MeC ₆ H ₄ (3m)	Me (2a)	4am	10	48	76	> 50:1	91
9	3-thienyl (3n)	Me (2a)	4an	10	24	90	15:1	93
10 ^[e]	cyclohexyl (3o)	Me (2a)	4ao	10	48	87	10:1	91
11	4-ClC ₆ H ₄ (3j)	Me (2a)	4aj	2.5	48	99	50:1	94

[a] Yield of the isolated product after column chromatography. [b] The diastereomeric ratio was determined by ¹H NMR spectroscopic analysis of the crude mixture. [c] The *ee* value was determined by HPLC analysis on a chiral phase. [d] The reaction was performed in THF/toluene (4:1). [e] The 2-thiophenesulfonyl imine was used, as the synthesis of the aliphatic *o*-Ns imine was not successful.



Scheme 2. Transformation of *anti* Mannich adducts into α -hydroxy γ -amino amides and azetidine-2-amides: a) LiBHET₃, THF, -78 °C, 30 min; b) K-selectride, THF, -78 °C, 2 h; c) diisopropyl azodicarboxylate, PPh₃, THF, 0 °C $\rightarrow$ RT, 3 h.

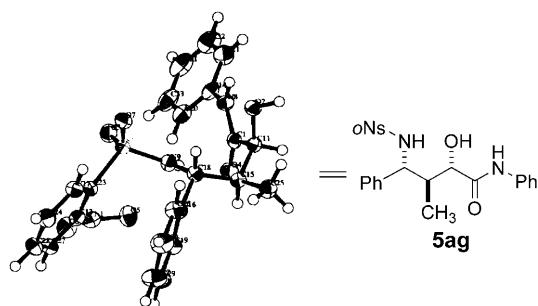


Figure 1. ORTEP plot of the α -hydroxy β -alkyl γ -amino amide **5ag**.

reduction and intramolecular cyclization to give the azetidine-2-amide **6ao** in 67% yield (over the two steps from **4ao**). The present method is synthetically useful; the method reported previously by our research group for *syn-anti* azetidine-2-carboxylic acids gave compounds only in racemic form or in modest optical purity.^[18a]

In summary, we have developed an *anti*-selective direct catalytic asymmetric Mannich-type reaction of α -ketoanilide donors as synthetic equivalents of homoenolates. A homodinuclear Ni complex prepared from the new biphenyldiimine-based dinucleating Schiff base **1c** promoted the reaction of α -ketoanilides **2** with *o*-Ns imines **3** to give the products in up to 99% yield, with an *anti/syn* ratio often greater than 50:1, and with up to 95% *ee*. Stereoselective reduction of the Mannich adduct afforded α -hydroxy β -alkyl γ -amino amides **5** with three contiguous stereocenters with an *anti-anti* relative configuration. An intramolecular Mitsunobu cyclization then gave optically active azetidine-2-amides **6** with a *syn-anti* configuration. Further investigations to clarify the origin of the *anti* selectivity in the Mannich-type reaction are ongoing.^[19]

Received: February 4, 2009

Published online: March 30, 2009

Keywords: asymmetric catalysis · azetidines · bifunctional catalysts · Mannich reaction · Schiff bases

- [1] For a recent general review on asymmetric Mannich(-type) reactions, see: G. K. Friestad, A. K. Mathies, *Tetrahedron* **2007**, *63*, 2541.
- [2] For recent reviews on direct catalytic asymmetric Mannich(-type) reactions to give β -amino carbonyl compounds, see: a) M. M. B. Marques, *Angew. Chem.* **2006**, *118*, 356; *Angew. Chem. Int. Ed.* **2006**, *45*, 348; b) M. Shibasaki, S. Matsunaga, *J. Organomet. Chem.* **2006**, *691*, 2089; c) A. Ting, S. E. Schaus, *Eur. J. Org. Chem.* **2007**, 5797; d) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471; e) J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg, F. P. J. T. Rutjes, *Chem. Soc. Rev.* **2008**, *37*, 29.
- [3] a) E. M. Phillips, T. E. Reynolds, K. A. Scheidt, *J. Am. Chem. Soc.* **2008**, *130*, 2416; b) M. Rommel, T. Fukuzumi, J. W. Bode, *J. Am. Chem. Soc.* **2008**, *130*, 17266; for related studies on stereoselective homoenolate additions catalyzed by N-heterocyclic carbenes, see the following review: c) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606.
- [4] K. Juhl, N. Gathergood, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 3083; *Angew. Chem. Int. Ed.* **2001**, *40*, 2995.
- [5] G. Lu, H. Morimoto, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2008**, *120*, 6953; *Angew. Chem. Int. Ed.* **2008**, *47*, 6847.
- [6] For selected examples of other catalytic asymmetric approaches to the synthesis of γ -amino acids, see the following review on the synthesis of glutamic acid derivatives: a) V. A. Soloshonok, *Curr. Org. Chem.* **2002**, *6*, 341; for γ amination, see: b) S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973; see also the following review on the use of glycine Schiff bases as donors in asymmetric synthesis: c) T. Ooi, K. Maruoka, *Angew. Chem.* **2007**, *119*, 4300; *Angew. Chem. Int. Ed.* **2007**, *46*, 4222.
- [7] For the use of related glyoxanilides as electrophiles in catalytic enantioselective reactions, see: a) D. A. Evans, Y. Aye, *J. Am. Chem. Soc.* **2006**, *128*, 11034; b) D. A. Evans, Y. Aye, *J. Am. Chem. Soc.* **2007**, *129*, 9606; for transformations of anilides into carboxylic acids, esters, amides, and alcohols under mild reaction conditions, see: c) D. A. Evans, Y. Aye, J. Wu, *Org. Lett.* **2006**, *8*, 2071; d) S. Saito, S. Kobayashi, *J. Am. Chem. Soc.* **2006**, *128*, 8704; e) Z. Chen, H. Morimoto, S. Matsunaga, M. Shibasaki, *Synlett* **2006**, 3529, and references cited therein.
- [8] For a recent review on bifunctional Lewis acid/Brønsted base asymmetric metal catalysis, see: S. Matsunaga, M. Shibasaki, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 60.
- [9] For a lanthanum/lithium catalyst, see: a) H. Morimoto, G. Lu, N. Aoyama, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2007**, *129*, 9588; for zinc catalysts, see: b) S. Matsunaga, T. Yoshida, H. Morimoto, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 8777; c) T. Yoshida, H. Morimoto, N. Kumagai, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2005**, *117*, 3536; *Angew. Chem. Int. Ed.* **2005**, *44*, 3470; for an indium catalyst, see: d) S. Harada, S. Handa, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2005**, *117*, 4439; *Angew. Chem. Int. Ed.* **2005**, *44*, 4365; for a barium catalyst, see: e) A. Yamaguchi, N. Aoyama, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2007**, *9*, 3387; for an yttrium catalyst, see: f) M. Sugita, A. Yamaguchi, N. Yamagiwa, S. Handa, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2005**, *7*, 5339; for a lanthanum catalyst, see: g) A. Yamaguchi, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2008**, *10*, 2319.
- [10] For bifunctional dinuclear Schiff base catalysts developed by our research group, see: Cu Sm-**1a**: a) S. Handa, V. Gnanadesikan, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2007**, *129*, 4900; Pd La-**1a**: b) S. Handa, K. Nagawa, Y. Sohtome, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2008**, *120*, 3274; *Angew. Chem. Int.*

- Ed.* **2008**, *47*, 3230; Ni₂-**1b**: c) Z. Chen, H. Morimoto, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 2170; Co₂-**1b**: d) Z. Chen, M. Furutachi, Y. Kato, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2009**, *121*, 2252–2254; *Angew. Chem. Int. Ed.* **2009**, *48*, 2218–2220.
- [11] For selected examples of related bifunctional bimetallic Schiff base complexes in asymmetric catalysis, see: a) V. Annamalai, E. F. DiMauro, P. J. Carroll, M. C. Kozlowski, *J. Org. Chem.* **2003**, *68*, 1973, and references cited therein; b) G. M. Sammis, H. Danjo, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 9928; c) M. Yang, C. Zhu, F. Yuan, Y. Huang, Y. Pan, *Org. Lett.* **2005**, *7*, 1927; d) W. Li, S. S. Thakur, S.-W. Chen, C.-K. Shin, R. B. Kawthekar, G.-J. Kim, *Tetrahedron Lett.* **2006**, *47*, 3453; e) W. Hirahata, R. M. Thomas, E. B. Lobkovsky, G. W. Coates, *J. Am. Chem. Soc.* **2008**, *130*, 17658; for related early studies with dinuclear Ni₂-Schiff base complexes as epoxidation catalysts, see also: f) T. Oda, R. Irie, T. Katsuki, H. Okawa, *Synlett* **1992**, 641.
- [12] For selected recent examples of the use of sulfonyl imines to improve stereoselectivity in asymmetric Mannich-type reactions, see: a) J. Hernández-Toribio, R. Gómez Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2008**, *130*, 16150, and references cited therein; b) S. Nakamura, H. Nakashima, H. Sugimoto, H. Sano, M. Hattori, N. Shibata, T. Toru, *Chem. Eur. J.* **2008**, *14*, 2145, and references cited therein.
- [13] For a review on the use of the Ns group in organic synthesis, see: a) T. Kan, T. Fukuyama, *Chem. Commun.* **2004**, 353; Ns-substituted imines **3** were synthesized by a literature procedure: b) I. T. Raheem, E. N. Jacobsen, *Adv. Synth. Catal.* **2005**, *347*, 1701.
- [14] K. M. Gillespie, C. J. Sanders, P. O'shaughnessy, I. Westmoreland, C. P. Thickitt, P. Scott, *J. Org. Chem.* **2002**, *67*, 3450. Biphenyldiamine for the synthesis of ligand **1c-H₄** was purchased from Aldrich and used as received.
- [15] A preliminary investigation with a linear aliphatic imine protected with a 2-thiophenesulfonyl group resulted in poor diastereoselectivity. Further attempts to extend the reaction to aliphatic imine substrates, including the synthesis of aliphatic *o*-Ns-protected imines, are ongoing.
- [16] CCDC 716642 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [17] For the stereoselective synthesis of azetidine-2-carboxylic acids (L-aze analogues) and their incorporation into peptides, see the following review: a) F. Couty, G. Evano, D. Prim, *Mini-Rev. Org. Chem.* **2004**, *1*, 133, and references cited therein; for selected examples, see: b) D. Enders, J. Gries, *Synthesis* **2005**, 3508, and references cited therein; c) F. Couty, G. Evano, N. Rabasso, *Tetrahedron: Asymmetry* **2003**, *14*, 2407; d) S. Hanessian, N. Bernstein, R.-Y. Yang, R. Maguire, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1437; e) A. P. Kozikowski, Y. Liao, W. Tückmantel, S. Wang, S. Pshenichkin, A. Surin, C. Thomsen, J. T. Wroblewski, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2559; for related studies, see also: f) A. Münch, B. Wendt, M. Christmann, *Synlett* **2004**, 2751, and references cited therein.
- [18] a) H. Morimoto, T. Yoshino, T. Yukawa, G. Lu, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2008**, *120*, 9265; *Angew. Chem. Int. Ed.* **2008**, *47*, 9125; for related studies on the synthesis of azetidines with the *syn-syn* and the *anti-syn* configuration, see also: b) H. Morimoto, S. H. Wiedemann, A. Yamaguchi, S. Harada, Z. Chen, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2006**, *118*, 3218; *Angew. Chem. Int. Ed.* **2006**, *45*, 3146.
- [19] At the moment, the reason for the high *anti* selectivity is not clear. We speculate that the cooperative function of two Ni centers may be important, as observed in our previous studies on different reactions with bimetallic Schiff base complexes.^[10] Mechanistic studies to clarify the role in the present reaction of the two nickel atoms in the catalyst are ongoing.