J|A|C|S
ARTICLES

Published on Web 09/09/2009

anti-Selective Catalytic Asymmetric Nitroaldol Reaction via a Heterobimetallic Heterogeneous Catalyst

Tatsuya Nitabaru,[†] Akihiro Nojiri,[†] Makoto Kobayashi,[‡] Naoya Kumagai,*[,†] and Masakatsu Shibasaki*[,†]

Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan, and Process Chemistry, R&D, Kissei Pharmaceutical Company, Ltd., 197-5 Kamiyoshi, Kubiki-ku, Joetsu, Niigata 942-0145, Japan

Received July 15, 2009; E-mail: mshibasa@mol.f.u-tokyo.ac.jp; nkumagai@mol.f.u-tokyo.ac.jp

Abstract: Full details of an *anti*-selective catalytic asymmetric nitroaldol reaction promoted by a heterobimetallic catalyst comprised of $Nd_5O(O^iPr)_{13}$, an amide-based ligand, and NaHMDS (sodium hexamethyldisilazide) are described. A systematic synthesis and evaluation of amide-based ligands led to the identification of optimum ligand **1m**, which provided a suitable platform for the Nd/Na heterobimetallic complex. During the catalyst preparation in THF, a heterogeneous mixture developed and centrifugation of the suspension allowed for separation of the precipitate, which contained the active catalyst and which could be stored for at least 1 month without any loss of catalytic performance. The precipitate promoted a nitroaldol (Henry) reaction for a broad range of nitroalkanes and aldehydes under heterogeneous conditions, affording the corresponding 1,2-nitroalkanol in a highly *anti*-selective (up to *anti*/*syn* = >40/1) and enantioselective manner (up to 98% ee). Inductively coupled plasma (ICP) and X-ray fluorescence (XRF) analyses revealed that the precipitate indeed included both neodymium and sodium, which was further supported by high-resolution ESI TOF MS spectrometry.

Introduction

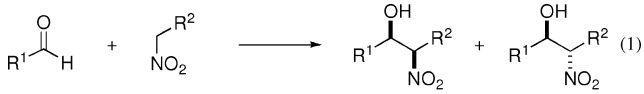
The nitroaldol (Henry) reaction (eq 1) is a valuable methodology for carbon−carbon bond construction, and, despite initially being discovered at the end of the 19th century,[1,2] nearly 100 years passed before the reaction was rendered enantioselective in a catalytic manner. In 1992, $LaLi_3$(binaphthoxide)$_3$ (LLB) was disclosed as an efficient asymmetric catalyst for the nitroaldol reaction of nitromethane.[3] Since then, the catalytic asymmetric nitroaldol reaction has emerged as a powerful protocol for the rapid assembly of enantiomerically enriched 1,2-nitro alkanols. Facile reduction of 1,2-nitro alkanols allows for direct access to 1,2-amino alcohols, a structural motif that occurs ubiquitously in a wide range of natural products, therapeutics, chiral ligands, and their key intermediates.[4] The perfect atom efficiency of the reaction as well as the obvious synthetic utility of the products have substantially advanced this area over the last two decades, uncovering a number of metal catalysts and organocatalysts that promote the nitroaldol reaction in a highly enantioselective manner.[5,6] Despite the intense demand for a diastereo- and enantioselective nitroaldol reaction using nitroalkanes other than nitromethane, progress toward this aim has been limited to a few sporadic reports. Since our report of a *syn*-selective catalytic asymmetric nitroaldol reaction in 1995,[7] several catalytic systems such as chiral guanidine and Cu-diamine catalysts have achieved the transformation.[8] *anti*-Diastereoselectivity in the catalytic asymmetric nitroaldol reac-

[†] The University of Tokyo.
[‡] Kissei Pharmaceutical Co., Ltd.

(1) Henry, L. *C. R. Hebd. Seances Acad. Sci.* **1895**, *120*, 1265.
(2) For recent reviews, see: (a) Shibasaki, M.; Gröger, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; Vol. III, pp 1075−1090. (b) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915. (c) Palomo, C.; Oiarbide, M.; Mielgo, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5442. (d) Shibasaki, M.; Gröger, H.; Kanai, M. In *Comprehensive Asymmetric Catalysis, Supplement 1*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Hidelberg, Germany, 2004; pp 131−133. (e) Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315. (f) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561.
(3) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418.
(4) For reviews on asymmetric synthesis of 1,2-amino alcohols, see:(a) Kolb, H. C.; Sharpless, K. B. In *Transition Metals in Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; p 243. (b) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121. (c) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561.
(5) For selected examples for catalytic asymmetric nitroaldol reaction using aldehydes and nitromethane, see: (a) Christensen, C.; Juhl, K.; Jørgensen, K. A. *Chem. Commun.* **2001**, 2222. (b) Trost, B. M.; Yeh, V. S. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 861. (c) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692. (d) Kogami, Y.; Nakajima, T.; Ashizawa, T.; Kezuka, S.; Ikeno, T.; Yamada, T. *Chem. Lett.* **2004**, *33*, 614. (e) Palomo, C.; Oiarbide, M.; Laso, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3881. (f) Choudary, B. M.; Ranganath, K. V. S.; Pal, U.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 13167. (g) Saá, J. M.; Tur, F.; González, J.; Vega, M. *Tetrahedron: Asymmetry* **2006**, *17*, 99. (h) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 929. (i) Arai, T.; Watanabe, M.; Fujiwara, A.; Yokoyama, N.; Yanagisawa, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5978. (j) Mandal, T.; Samanta, S.; Zhao, C.-G. *Org. Lett.* **2007**, *9*, 943. (k) Xiong, Y.; Wang, F.; Huang, X.; Wen, Y.; Feng, X. *Chem.-Eur. J.* **2007**, *13*, 829. (l) Ma, K.; You, J. *Chem.-Eur. J.* **2007**, *13*, 1863. (m) Bandini, M.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A.; Ventrici, C. *Chem. Commun.* **2007**, 616. (n) Bandini, M.; Benaglia, M.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *Org. Lett.* **2007**, *9*, 2151. (o) Blay, G.; Domingo, L. R.; Hernández-Olmos, V.; Pedro, J. R. *Chem.-Eur. J.* **2008**, *14*, 4725. (p) Ube, H.; Terada, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3895.

 10.1021/ja905885z CCC: $40.75 © **2009 American Chemical Society**

tion, however, has remained a formidable task, likely because a simple chelation model prefers *syn*-diastereoselectivity. A highly *anti*-selective catalytic asymmetric nitroaldol reaction utilizing a chiral *P*-spiro triaminoiminophosphorane as an effective organocatalyst was recently reported by Ooi et al., although low temperature (−78 °C) was required.[9] In our continuing studies on the catalytic asymmetric nitroaldol reaction, we investigated a bimetallic strategy to achieve high *anti*-diastereoselectivity.[10] We reported that a Nd/Na/amide-based ligand heterobimetallic catalytic system promoted an *anti*-selective catalytic asymmetric nitroaldol reaction of nitroethane,[10a] where the presence of the two distinct metal cations was key for *anti*-diastereoselectivity. Herein, we describe a significant advance of the Nd/Na heterobimetallic catalytic system for a scalable and efficient *anti*-selective nitroaldol reaction. Systematic design of the amide-based ligand and careful observation of the catalyst preparation procedure led us to identify a highly diastereo- and enantioselective heterogeneous Nd/Na heterobimetallic catalyst, which was characterized by inductively coupled plasma (ICP), X-ray fluorescence (XRF), and ESI TOF MS analyses. The broad substrate generality and operational simplicity of the present heterogeneous *anti*-selective nitroaldol protocol are particularly valuable for the synthesis of enantioenriched 1,2-amino alcohols, which constitute a versatile substructure in medicinal chemistry.



(1)

Results and Discussion

Catalyst Design. High *anti*-diastereoselectivity was reported in an elegant study of the racemic nitroaldol reaction using silyl nitronates and aldehydes by Seebach et al.[11] An antiparallel orientation of a silyl nitronate and an aldehyde was proposed to explain the observed *anti*-diastereoselectivity (Figure 1a). This strategy for *anti*-diastereoselectivity was valid in a catalytic enantioselective nitroaldol reaction using silyl nitronates as reported by Jørgensen et al.[12] and Maruoka et al.,[13] affording the *anti*-1,2-nitro alkanols in a highly enantioselective manner. The use of silyl nitronates, however, requires an extra process for their preparation and produces unwanted silicon-derived wastes, severely limiting the utility of the nitroaldol reaction as an atom-economical, waste-free, and environmentally benign protocol. We envisioned attaining the antiparallel transition state with an in situ generated metal nitronate, thereby allowing the *anti*-selective catalytic asymmetric nitroaldol reaction to occur for a simple set of substrates (nitroalkanes and aldehydes) under waste-free proton-transfer conditions.[14] In contrast to the reaction with silyl nitronates, a nitroaldol reaction using a metal-based catalyst predominantly affords the *syn* product, likely because a cyclic transition state in which both the nitronate and the aldehyde coordinate to one metal cation M is involved (Figure 1b). We hypothesized that a heterobimetallic complex comprising a ligand with an appropriate spatial arrangement for metal coordination sites would provide a suitable chiral platform for the antiparallel transition state. In this catalyst design, each distinct metal cation, M^1 and M^2, works independently as a Lewis acid to activate an aldehyde and a Brønsted base (metal phenoxide) to form metal nitronates; therefore, the reaction

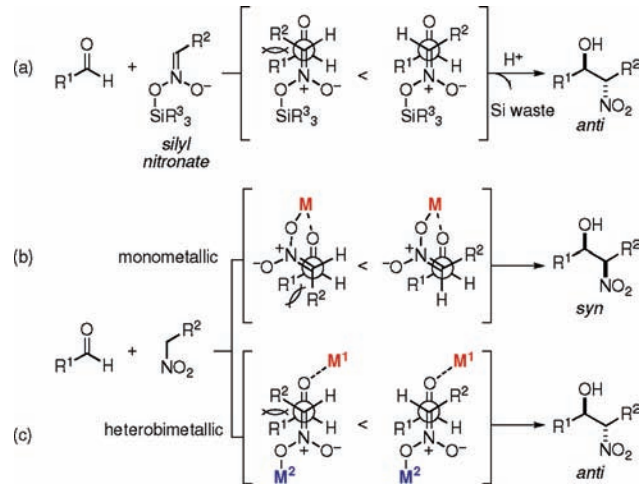


Figure 1. Diastereoselectivity in nitroaldol reactions. (a) Preferential formation of *anti*-diastereomer in the reaction using silyl nitronates. (b) Preferential formation of *syn*-diastereomer in the presence of monometallic catalyst. (c) Preferential formation of *anti*-diastereomer by heterobimetallic catalyst.

(6) For selected examples for catalytic asymmetric nitroaldol reaction using ketones and nitromethane, see: (a) Christensen, C.; Juhl, K.; Jørgensen, K. A. *Chem. Commun.* **2001**, 2222. (b) Misumi, Y.; Bulman, R. A.; Matsumoto, K. *Heterocycles* **2002**, *56*, 599. (c) Du, D. M.; Lu, S. F.; Fang, T.; Xu, J. X. *J. Org. Chem.* **2005**, *70*, 3712. (d) Choudary, B. M.; Ranganath, K. V. S.; Pal, U.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 13167. (e) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732. (f) Tosaki, S.-y.; Hara, K.; Gnanadesikan, V.; Morimoto, H.; Harada, S.; Sugita, M.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 11776. (g) Tur, F.; Saá, J. M. *Org. Lett.* **2007**, *9*, 5079. (h) Takada, K.; Takemura, N.; Cho, K.; Sohtome, Y.; Nagasawa, K. *Tetrahedron Lett.* **2008**, *49*, 1623. (i) Blay, G.; Hernández-Olmos, V.; Pedro, J. R. *Org. Biomol. Chem.* **2008**, *6*, 468. (j) Chen, X.; Wang, J.; Zhu, Y.; Shang, D.; Gao, B.; Liu, X.; Feng, X.; Su, Z.; Hu, C. *Chem.-Eur. J.* **2008**, *14*, 10896. (k) Hara, K; Tosaki, S.-y.; Gnanadesikan, V.; Morimoto, H.; Harada, S.; Sugita, M.; Yamagiwa, N.; Matsunaga, S.; Shibaski, M. *Tetrahedron* **2009**, *65*, 5030.

(7) Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388.

(8) (a) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Eur. J. Org. Chem.* **2006**, 2894. (b) Arai, T.; Watanabe, M.; Yanagisawa, A. *Org. Lett.* **2007**, *9*, 3595. (c) Sohtome, Y.; Takemura, N.; Takada, K.; Takagi, R.; Iguchi, T.; Nagasawa, K. *Chem. Asian J.* **2007**, *2*, 1150. (d) Arai, T.; Takashita, R.; Endo, Y.; Watanabe, M.; Yanagisawa, A. *J. Org. Chem.* **2008**, *73*, 4903. For a partially successful example of *syn*-selective catalytic asymmetric nitroaldol reaction, see: (e) Yoshimoto, J.; Sandoval, C. A.; Saito, S. *Chem. Lett.* **2008**, *37*, 1294. See also ref 10c.

(9) Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392. For partially successful *anti*-selective catalytic asymmetric nitroaldol reactions, see refs 5o,p. For *anti*-selective nitroaldol reaction of benzaldehyde catalyzed by hydroxynitrile lyase, see: (a) Purkarthofer, T.; Gruber, K.; Gruber-Khadjawi, M.; Waich, K.; Skranc, W.; Mink, D.; Griengl, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3454. (b) Gruber-Khadjawi, M.; Purkarthofer, T.; Skranc, W.; Griengl, H. *Adv. Synth. Catal.* **2007**, *349*, 1445.

(10) (a) Nitabaru, T.; Kumagai, N.; Shibasaki, M. *Tetrahedron Lett.* **2008**, *49*, 272. (b) Handa, S.; Nagawa, K.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3230. (c) Sohtome, Y.; Kato, Y.; Handa, S.; Aoyama, N.; Nagawa, K.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 2231.

(11) (a) Colvin, E. W.; Seebach, D. *J. Chem. Soc., Chem. Commun.* **1978**, 689. (b) Seebach, D.; Beck, A. K.; Lehr, F.; Weller, T.; Colvin, E. *Angew, Chem., Int. Ed. Engl.* **1981**, *20*, 397. (c) Seebach, D.; Beck, A. K.; Mukhopadhyay, T.; Thomas, E. *Helv. Chim. Acta* **1982**, *65*, 1101.

(12) Risgaard, T.; Gothelf, K. V.; Jørgensen, K. A. *Org. Biomol. Chem.* **2003**, *1*, 153.

(13) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2054.

(14) For a theoretical study on the diastereoselectivity in nitroaldol reaction, see: Lecea, B.; Arrieta, A.; Morao, I.; Cossío, F. P. *Chem.-Eur. J.* **1997**, *3*, 20.

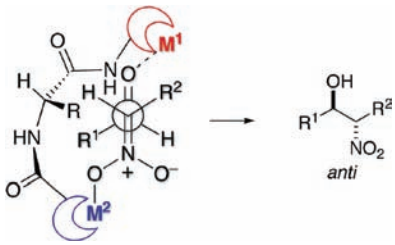
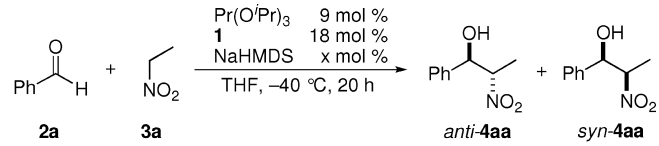


Figure 2. Amide backbone as a platform for bimetallic complex.

proceeds predominantly through an *anti*-periplanar transition state to afford the *anti*-nitroaldol product (Figure 1c). The arrangements of the two metals would be key to overriding the reaction through the undesired cyclic transition state.

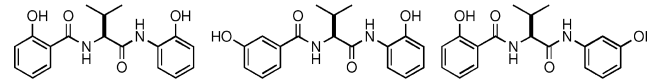
Identification of an Appropriate Amide-Based Ligand for a Heterobimetallic System. To attain the *anti*-periplanar transition state, our primary focus was directed to exploit an amide backbone as a platform for two distinct metal cations.[15] On the basis of transition state analysis, we anticipated that a ligand bearing a binary metal coordination site linked by a stereogenic α-amino acid through two amide bonds would provide a suitable three-dimensional arrangement for the *anti*-periplanar transition state (Figure 2). Taking the acidity of nitroalkanes into account, a phenol is a feasible functional group to incorporate metal cations on the amide-based ligand where facile deprotonation by the action of metal phenoxide is expected. We assumed that the combination of a rare earth (RE) metal (M^1) cation as a Lewis acid and an alkali metal (M^2) phenoxide as a Brønsted base would provide the desired transition state.[16] We then planned to investigate the heterobimetallic catalytic system comprising an amide-based ligand **1**, $RE(O^iPr)_3$, and sodium hexamethyldisilazide (NaHMDS). Initial attempts were made to evaluate three ligands, **1a**−**c**, bearing an L-valine core and differently installed phenol groups in a nitroaldol reaction of benzaldehyde (**2a**) and nitroethane (**3a**). The catalyst was prepared by mixing $Pr(O^iPr)_3$ and ligand **1** in a 1:2 ratio at room temperature in THF, followed by the addition of NaHMDS (equimolar amounts to Pr) at 0 °C. As we expected, the reaction proceeded to afford the product **4aa** with a slight preference for the *anti*-diastereomer in the presence of 9 mol % of the catalyst (based on Pr), although both the yield and the diastereoselectivity were unsatisfactory (Table 1, entries 1−3).

Table 1. Evaluation of Ligands **1a**−**c** for the Construction of Heterobimetallic Catalyst for Nitroaldol Reaction[a]



2a **3a** *anti*-**4aa** *syn*-**4aa**

entry	ligand **1**	NaHMDS (x mol %)	Pr/**1**/Na	yield[b] (%)	*anti*/*syn*[c]	ee (*anti*) (%)
1	**1a**	9	1/2/1	1.5	2/1[d]	ND
2	**1b**	9	1/2/1	2.2	2/1[d]	ND
3	**1c**	9	1/2/1	2.0	2/1[d]	ND
4	**1a**	18	1/2/2	24	2.3/1	10
5	**1b**	18	1/2/2	76	8.4/1	38
6	**1c**	18	1/2/2	16	2.0/1	0



1a **1b** **1c**

[a] **2a**, 0.1 mmol; **3a**, 1.0 mmol. [b] Determined by ^1H NMR with 1,4-dioxane as an internal standard. [c] Determined by ^1H NMR analysis. [d] Approximate value due to low chemical yield.

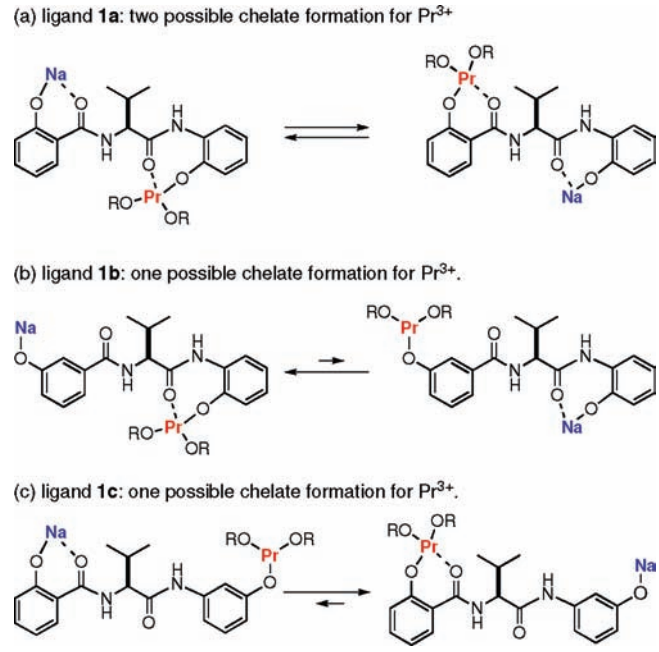


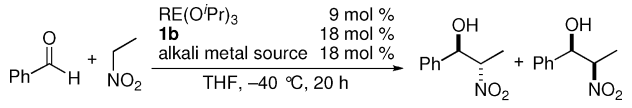
Figure 3. A possible site-selective coordination of Pr^{3+} and Na^+ in ligand **1**.

The catalyst prepared with two molar equivalents of NaHMDS to $Pr(O^iPr)_3$ exhibited higher catalytic activity (entries 4−6), and the highest diastereo- and enantioselectivity were observed with the reaction using the ligand **1b** (entry 5), where *m*-hydroxybenzoyl and *o*-aminophenol groups were furnished as metal coordination sites. It is likely that the Pr^{3+} cation was more prone to be localized at the aminophenol part in a seven-membered chelate with a neighboring amide carbonyl while Na^+ was located at the other side, leading to the appropriate spatial arrangements for the desired *anti*-periplanar transition state (Figure 3b). In contrast, poor stereoselectivity was observed with ligand **1a**, presumably because Pr^{3+} and Na^+ showed no preference for the coordination sites of ligand **1a**; for both metals, chelate formation was possible at either the *o*-hydroxybenzoyl or the *o*-aminophenol moieties (Figure 3a). Whereas the preferential localization of Pr^{3+} and Na^+ was also plausible

(15) Recent selected examples of asymmetric catalysis by peptide-based catalysts: (a) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629. (b) Fierman, M. B.; O'Leary, D. J.; Steinmetz, W. E.; Miller, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 6967. (c) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. C. *Nature* **2006**, *443*, 67. For recent reviews on small peptide-based asymmetric catalysis, see: (d) Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun.* **2004**, 1779. (e) Blank, J. T.; Miller, S. J. *Biopolymers (Pept. Sci.)* **2006**, *84*, 38. (f) Colby Davie, E. A.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759.

(16) For the properties on RE complexes, see: (a) *Lanthanide and Actinide Chemistry*; Cotton, S., Ed.; Wiley: New York, 2006. For reviews, see: (b) Aspinall, H. C. *Chem. Rev.* **2002**, *102*, 1807. (c) Tsukube, H.; Shinoda, S. *Chem. Rev.* **2002**, *102*, 2389. (d) Parker, D. *Chem. Soc. Rev.* **2004**, *33*, 156. (e) Bari, L. D.; Salvadori, P. *Coord. Chem. Rev.* **2005**, *249*, 2854. (f) Bünzli, J.-C. Z. *Acc. Chem. Res.* **2006**, *39*, 53, and references cited therein. For examples of asymmetric catalysis with the combination of amide-based ligand and RE, see: (g) Mashiko, T.; Hara, K.; Tanaka, D.; Fujiwara, Y.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 11342. (h) Nojiri, A.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 5630. (i) Mashiko, T.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 2725. (j) Nojiri, A.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 3779.

Table 2. Screening of Rare Earth Metals and Alkali Metals with Ligand **1b**[a]



2a **3a** *anti*-**4aa** *syn*-**4aa**

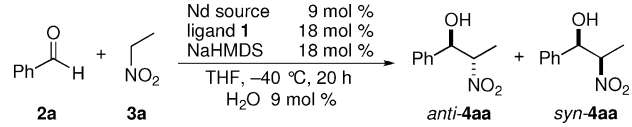
entry	RE	alkali metal source	H_2O (mol %)	yield[b] (%)	*anti*/*syn*[c]	ee (*anti*) (%)
1	La	NaHMDS		73	7.2/1	26
2	Pr	NaHMDS		76	8.4/1	38
3	Nd	NaHMDS		85	8.5/1	40
4	Sm	NaHMDS		78	7.7/1	35
5	Gd	NaHMDS		55	6.5/1	41
6	Dy	NaHMDS		32	2.8/1	18
7	Er	NaHMDS		33	2.6/1	10
8	Yb	NaHMDS		50	2.0/1	−7
9	Nd	LiHMDS		9	2.3/1	4
10	Nd	KHMDS		83	1.8/1	3
11	Nd			1	1.3/1	0
12	Nd	NaHMDS	9	83	10.1/1	43

[a] **2a**, 0.1 mmol; **3a**, 1.0 mmol. [b] Determined by ^{1}H NMR with 1,4-dioxane as an internal standard. [c] Determined by ^{1}H NMR analysis.

with ligand **1c** (Figure 3c), the arrangement of two metals (opposite to the case of ligand **1b**) would not be suitable for the desired *anti*-periplanar transition state. Screening of both RE metals and alkali metals with the prototype ligand **1b** indicated that $Nd(O^iPr)_3$ was the best RE source in combination with NaHMDS, exhibiting the highest diastereo- (*anti*/*syn* = 8.5/1) and enantioselectivity (40% ee (*anti*)) (Table 2, entry 3). The use of LiHMDS or KHMDS as an alkali metal source resulted in worse diastereoselectivity, and no enantioselection was observed (entries 9, 10). Poor catalytic activity and diastereoselectivity in the absence of an alkali metal verified that the heterobimetallic system was crucial for constructing the *anti*-periplanar transitions state (entry 11). Occasional fluctuations in the stereoselectivity prompted us to investigate the addition of water, which proved to be beneficial for both diastereoselectivity and enantioselectivity (entry 12).[17]

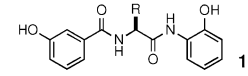
Given the preliminary identification of reaction conditions for the *anti*-selective nitroaldol reaction, we designed ligand analogues bearing different amino acid residues **1d**−**g** based on the structure of **1b**, and we evaluated these ligand analogues in the nitroaldol reaction of **2a** and **3a** (Table 3). Among the ligand analogues prepared from different α-amino acids, ligand **1g** derived from L-Leu was superior in terms of both catalytic activity and stereoselectivity (entries 1−5). Whereas some fluctuation in chemical yield and stereoselectivity was occasionally observed with the catalyst prepared from $Nd(O^iPr)_3$, the use of $Nd_5O(O^iPr)_{13}$ as the Nd source[18] circumvented the reproducibility problem, and a marginally better result was obtained.[19] Further structural manipulation of ligand substructure was conducted by systematically varying conformational flexibility and the electronic nature of the aromatic ring (Chart 1). We anticipated that the conformation of the aminophenol part would be relatively rigid upon complexation with the metal due to the chelate formation with Nd^{3+} (Figure 3b). On the other hand, the meta-orientation of the hydroxyl group of the

Table 3. Evaluation of Ligands **1d**−**g** Derived From Various α-Amino Acids Based on the Structure of **1b**[a]



2a **3a** *anti*-**4aa** *syn*-**4aa**

entry	Nd source	ligand R =		yield[b] (%)	*anti*/*syn*[c]	ee (*anti*) (%)
1	$Nd(O^iPr)_3$	^{i}Pr	**1b**	83	10.1/1	43
2	$Nd(O^iPr)_3$	*c*Hex	**1d**	79	5.7/1	43
3	$Nd(O^iPr)_3$	(*S*)-2-butyl	**1e**	80	2.0/1	24
4	$Nd(O^iPr)_3$	Bn	**1f**	83	5.7/1	32
5	$Nd(O^iPr)_3$	^{i}Bu	**1g**	70	7.9/1	51
6[d]	$Nd_5O(O^iPr)_{13}$	^{i}Bu	**1g**	79	7.9/1	53



1

[a] **2a**, 0.1 mmol; **3a**, 1.0 mmol. [b] Determined by ^{1}H NMR with 1,4-dioxane as an internal standard. [c] Determined by ^{1}H NMR analysis. [d] Average of three runs. 1.8 mol % of $Nd_5O(O^iPr)_{13}$ (9 mol % based on Nd) was used.

m-hydroxybenzoyl part would contribute little to chelate formation as the C−C single bond between the *m*-hydroxy phenyl group and amide carbonyl could freely rotate with two preferable metastable conformers A and B, with dihedral angles of ca. 0° and 180°, respectively (Figure 4). In the proposed transition state model (Figure 1c), the relative location of the two distinct metals is of prime importance, and possible bond rotation may compromise the construction of a suitable heterobimetallic architecture. Thus, we next focused on the restriction of the bond rotation. *o*-Fluorobenzamide forms an intramolecular hydrogen bond between the fluoro substituent and the amide N−H hydrogen, thereby posing a restriction on the bond rotation.[20] The C−F···H−N hydrogen bonding was exploited in a ligand **1h**, where the installed 2-fluoro substituent was anticipated to prefer the conformation of the *m*-hydroxybenzoyl part as conformer A (dihedral angle ca. 0°) (Figure 4).[21] Ligand **1h** outperformed the parent L-Leu ligand **1g** in the standard reaction conditions, affording **4aa** in 97% yield with *anti*/*syn* = 19/1 and 73% ee (*anti*) (Chart 1, entries 1, 2). The installation of a 2-chloro substituent, which hardly formed a hydrogen bond with amide NH,[22] resulted in stereoselectivity inferior to that obtained with **1g** (entry 3). Ligand **1j**, in which conformational

(17) H_2O may dissociate $Nd(O^iPr)_3$ aggregate or serve as an additional ligand to Nd to acquire a more suitable chiral environment for the reaction. See also ref 24.

(18) The amount was calculated on the basis of Nd content; cf., the molar relationship of 3 mol % catalyst for 0.3 mmol of aldehyde is the following: $Nd_5O(O^iPr)_{13}$/**1b**/NaHMDS/aldehyde = 1.8 μmol/18 μmol/18 μmol/300 μmol, Nd/**1b**/Na/aldehyde = 9/18/18/300 = 1/2/2/33.3.

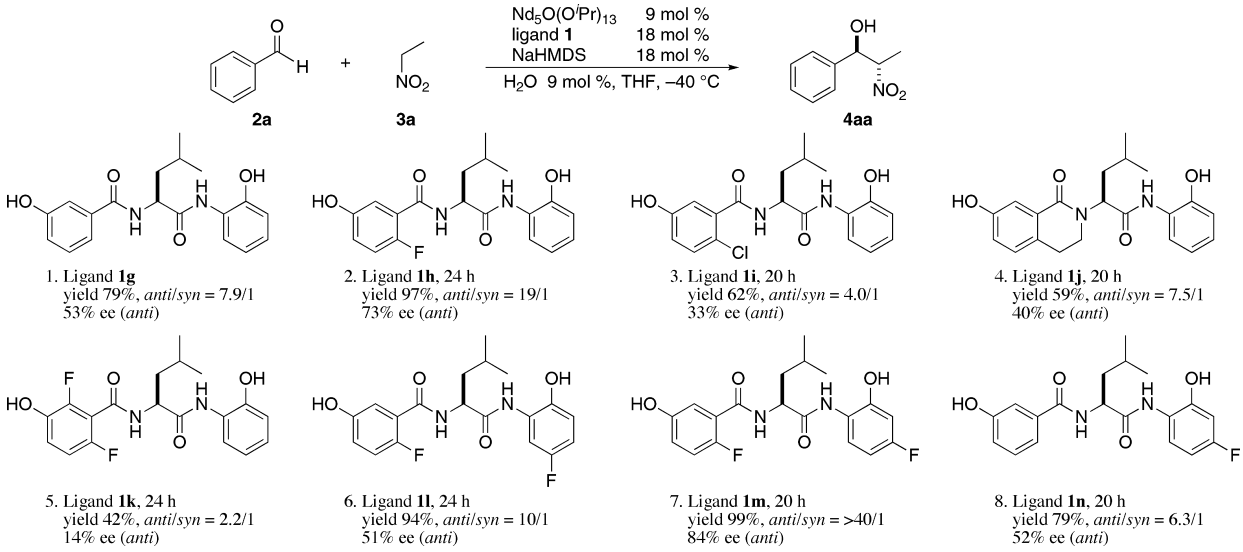
(19) Synthesis and characterization of $Nd_5O(O^iPr)_{13}$, see: Kritikos, M.; Moustiakimov, M.; Wijk, M.; Westin, G. *J. Chem. Soc., Dalton Trans.* **2001**, 1931, and references cited therein. In contrast to the possible incomplete complexation with ligand due to the non-ordered aggregation state of $Nd(O^iPr)_3$, reproducible formation of the desired complex was anticipated with μ-oxo isopropoxide $Nd_5O(O^iPr)_{13}$. $Nd_5O(O^iPr)_{13}$ is available from Kojundo Chemical Co. Ltd. at http://www.kojundo.co.jp/english/index.html; fax, +81-49-284-1351; e-mail,

(20) (a) Zhao, X.; Wang, X.-Z.; Jiang, X.-K.; Chen, Y.-Q.; Li, Z.-T.; Chen, G. J. *J. Am. Chem. Soc.* **2003**, *125*, 15128. (b) Li, C.; Ren, S.-F.; Hou, J.-L.; Yi, H.-P.; Zhu, S.-Z.; Jiang, X. K.; Li, Z.-T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5725. (c) Li, C.; Zhu, Y.-Y.; Yi, H.-P.; Li, C.-Z.; Jiang, X.-K.; Li, Z.-T.; Yu, Y.-H. *Chem.-Eur. J.* **2007**, *13*, 9990. (d) Zhu, Y.-Y.; Wu, J.; Li, C.; Zhu, J.; Hou, J.-L.; Li, C.-Z.; Jiang, X.-K.; Li, Z.-T. *Cryst. Growth Des.* **2007**, *7*, 1490. (e) Tomita, K.; Oishi, S.; Ohno, H.; Fujii, N. *Biopolymers (Pept. Sci.)* **2008**, *90*, 503.

(21) Indeed, a DFT calculation suggested that the rotational conformer A (dihedral angle ca. 0°) was much more stable than that of B (dihedral angle ca. 180°) in ligand **1h**, whereas **1g** displayed a small energy difference between rotational conformers A and B. The energy profile of the C−C bond rotation in a *m*-hydroxybenzoyl ester analogue was similar to that of **1h**, suggesting that the predominance of rotational conformer A (dihedral angle ca. 0°) in **1h** was due to the C−F···H−N hydrogen bond. See the Supporting Information for details.

(22) Zhu, Y.-Y.; Yi, H.-P.; Li, C.; Jiang, X.-K.; Li, Z.-T. *Cryst. Growth Des.* **2008**, *8*, 1294.

Chart 1



restriction was effected by lactam formation, gave the product in low stereoselectivity, likely because the appended ethylene linker would make the preferences of rotational conformers along N−Cα single bond unsuitable for the present reaction (entry 4). Difluoro analogue **1k** was expected to have no preference for conformers A and B and exhibited poor stereoselectivity, although electronic perturbation of the *m*-hydroxybenzoyl group by two fluoro substituents may also be involved (entry 5).[23] Subsequent modification of the electronic nature of the aminophenol part was achieved by introducing a fluoro substituent, revealing that 5-fluoro analogue **1m** further improved the stereoselectivity to nearly perfect *anti*-selectivity with 84% ee (entries 6, 7). The moderate stereoselectivity obtained from the reaction with related ligand **1n** lacking the 2-fluoro substituent on the *m*-hydroxybenzoyl part clearly illustrates the importance of the conformational control of the *m*-hydroxybenzoyl part (entry 8).

Development of Heterogeneous Reaction Conditions. During the catalyst preparation, the addition of $Nd_5O(O^iPr)_{13}$ (0.2 M in THF, based on Nd), NaHMDS (1.0 M in THF), and H_2O (0.2 M In THF) to the clear solution of ligand **1m** in THF produced a white precipitate, and the resulting mixture became a suspension. Occasionally the precipitate partially dissolved upon the addition of the substrates benzaldehyde (**2a**) and nitroethane (**3a**), and the reaction mixture remained heterogeneous until completion of the nitroaldol reaction. The heterogeneous catalyst mixture led us to investigate whether the active catalyst was in the solution phase or in the precipitate. Careful observation of the transition of the mixture during the catalyst preparation process revealed that (1) the addition of $Nd_5O(O^iPr)_{13}$ to the solution of **1m** at room temperature gave a clear mixture; (2) subsequent addition of NaHMDS at 0 °C turned the mixture into a suspension; (3) upon the addition of nitroethane (**3a**) (ca. 70 equiv to Nd) at room temperature, a clear solution developed and the resulting mixture gradually turned into a suspension again within 10 min; and (4) the use of $Nd_5O(O^iPr)_{13}$ as an Nd source instead of $Nd(O^iPr)_3$ allowed us to prepare the catalyst without additional H_2O (Figure 5).[24] The mixture was left to stand at room temperature for 1 h, and the resulting suspension was centrifuged (ca. 10^4 rpm) at room temperature for 30 s. The separated supernatant and the precipitate[25] were individually evaluated in the nitroaldol reaction of **2a** and **3a** (Scheme 1). Based on a comparison of the stereoselectivities obtained in each case (Scheme 1, (a) vs (b)), the active catalyst was in the precipitate, but the reason for the difference in catalytic activity was not conclusive because the mole fraction of distributed catalytically active components to the precipitate and the supernatant was not determined. Of particular note is the substantial enhancement of the enantioselectivity (94%) in the reaction using the precipitate beyond what was obtained in the standard reaction conditions (Scheme 1, (a) vs (c)), where the whole catalyst mixture, including both the precipitate and the supernatant, was used as catalyst. This is likely due to the fact that the reaction partially proceeded through the poor-performing catalyst in the supernatant to reduce the overall stereoselectivity.

These findings prompted us to investigate the quantitative distribution of catalyst components, Nd^{3+}, ligand **1m**, and Na^+ in the precipitate and the supernatant. The catalyst was prepared by following the procedure described in Figure 5 to give the

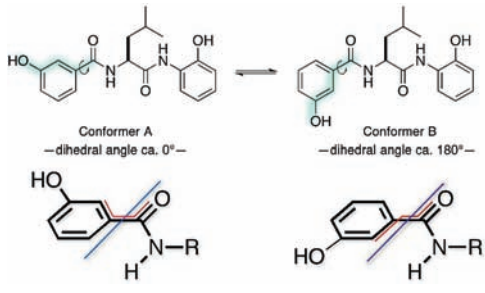


Figure 4. Metastable rotational conformers A and B of ligand **1g**. (A) Dihedral angle between the plane of *m*-hydroxybenzoyl group and the amide plane is ca. 0°. (B) Dihedral angle between *m*-hydroxybenzoyl group and the amide plane is ca. 180°.

(23) Installation of multiple fluorine substitutes may weaken C−F···H−N hydrogen bonding, disfavoring the coplanarity of the aromatic ring and planar amide. See also ref 20e.

(24) The beneficial effect of H_2O was more prominent for the catalyst prepared from $Nd(O^iPr)_3$ than that prepared from $Nd_5O(O^iPr)_{13}$. $Nd(O^iPr)_3$ may form $Nd_5O(O^iPr)_{13}$ in the presence of H_2O.

(25) The precipitate was washed by two cycles of the following procedure: (1) re-suspended with dry THF; (2) mixed by vortex mixer; (3) centrifuged; and (4) decantation of supernatant. See the Supporting Information for details.

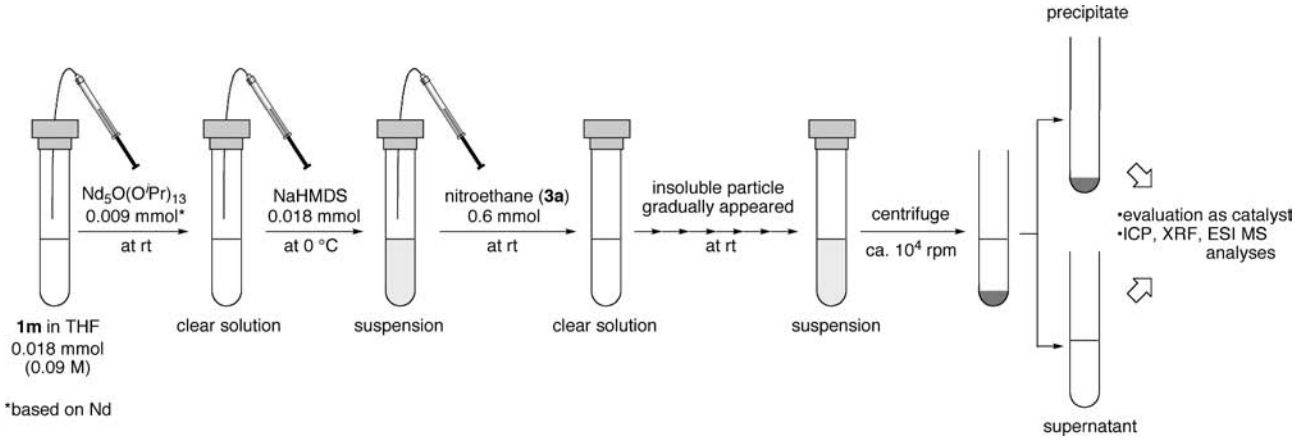
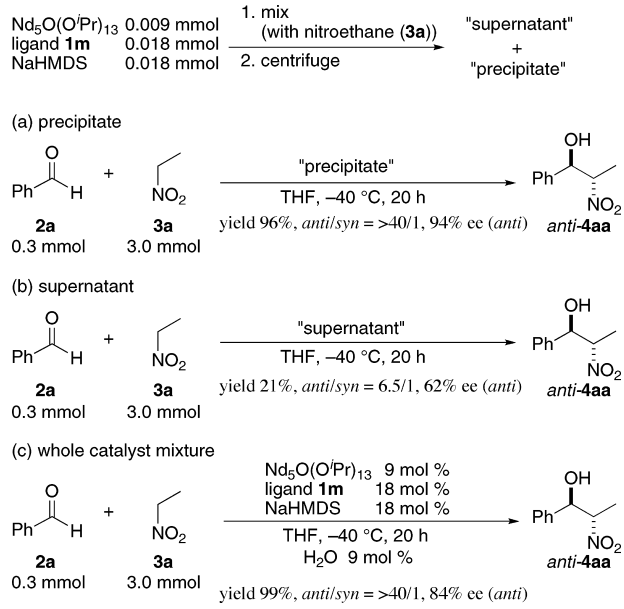


Figure 5. A schematic view of the catalyst preparation procedure.

Scheme 1. Nitroaldol Reaction with the Separated Precipitate and Supernatant



precipitate after washing with dry THF and drying under vacuum, which was then subjected to ICP and XRF analyses (Table 4).[26] Both ICP and XRF analyses proved that ca. 16 mass % of the precipitate came from Nd^{3+}, indicating that ca. 85% of the added Nd^{3+} was incorporated in the precipitate. In contrast, only ca. 39% of ligand **1m** was incorporated based on the fluorine atom content in XRF analysis.[26] Of particular note is that both Nd^{3+} and Na^{+} were incorporated in the precipitates and worked as a highly *anti*-selective and enantioselective heterogeneous heterobimetallic catalyst.[27] Given the approximate molar ratio of Nd/**1m**/Na = 1/0.96/1.8 in XRF analysis, different catalyst preparation procedures with varied ratios of Nd/**1m**/Na were conducted to reduce the amount of the ligand **1m**, ca. 60% of which remained in the supernatant under the standard conditions. These attempts, however, failed to give the active heterogeneous catalyst: either no precipitation or, if any precipitate appeared, lower stereoselectivity in the nitroaldol reaction.[28]

ESI TOF MS Analyses of the Heterobimetallic Complex in the Precipitate. To gain further insight into the structure of the active catalyst, the catalyst preparation procedure was traced

(26) See the Supporting Information for details.

Table 4. Elemental Analysis of the Precipitate and the Supernatant by ICP and XRF Analyses

	ICP precipitates		XRF precipitates	
element	mass %	molar ratio	mass %	molar ratio
Nd	15.8	1	16.2	1
Na	5.81	2.3	4.23	1.8
F	ND	ND	3.91	1.92 (0.96 as **1m**)

by ESI TOF MS analysis.[26] Sample aliquots were withdrawn at each specific stage during the catalyst preparation and subjected to MS analysis in THF solution. Although no prominent peaks appeared in the solution of **1m** and $Nd_5O(O^iPr)_{13}$ (Figure 6a), the subsequent addition of NaHMDS induced a significant change in the MS spectrum, affording a series of peaks derived from $[(\mathbf{1m})_4Nd_2Na_n]^{2-}$ (n = 1,2), $[(\mathbf{1m})_5Nd_2Na_n]^{2-}$ (n = 2−4), and $[(\mathbf{1m})_6Nd_2Na_n]^{2-}$ (n = 4,5) having a matched isotopic pattern with less than 10 mmu accuracy (Figure 6b).[29] The appearance of these related peaks suggested that the **1m**/Nd fragment would, with the aid of Na^{+}, associate to form a white suspension before the addition of nitroethane (**3a**) in Figure 5.[30] The MS spectrum of the precipitate obtained after the addition of nitroethane (**3a**) was

(27) For reviews for chiral catalysts incorporated into metal−organic coordination frameworks, see: (a) Baiker, A. *J. Mol. Catal. A* **1997**, *115*, 473. (b) Yaghi, O. M.; Li, H.; Davis, C.; Richardson, D.; Groy, T. L. *Acc. Chem. Res.* **1998**, *31*, 474. (c) Hagrman, P. J.; Hagrman, D.; Zubieta, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 2639. (d) Blake, A. J.; Champness, N. R.; Hubberstey, P.; Li, W.-S.; Withersby, M. A.; Schroder, M. *Coord. Chem. Rev.* **1999**, *183*, 117. (e) Moulton, B.; Zaworotko, M. J. *Chem. Rev.* **2001**, *101*, 1629. (f) Kesanli, B.; Lin, W. B. *Coord. Chem. Rev.* **2003**, *246*, 305. (g) Studer, M.; Blaser, H. U.; Exner, C. *Adv. Synth. Catal.* **2003**, *345*, 45. (h) Yaghi, O. M.; O'Keeffe, M.; Ockwig, N. W.; Chae, H. K.; Eddaoudy, M.; Kim, J. *Nature* **2003**, *423*, 715. (i) Dai, L. X. *Angew. Chem., Int. Ed.* **2004**, *43*, 5726. (j) Mallat, T.; Orglmeister, E.; Baiker, A. *Chem. Rev.* **2007**, *107*, 4863. For selected leading examples of "self-supported" chiral catalysts comprised of metal−organic coordination networks, see: (k) Sawaki, T.; Aoyama, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4793. (l) Seo, J. S.; Whang, D.; Lee, H.; Jun, S. I.; Oh, J.; Jeon, Y. J.; Kim, K. A. *Nature* **2000**, *404*, 982. (m) Hu, A.; Ngo, H. L.; Lin, W. *J. Am. Chem. Soc.* **2003**, *125*, 11490. (n) Takizawa, S.; Somei, H.; Jayaprakash, D.; Sasai, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5711. (o) Guo, H.; Wang, X.; Ding, K. *Tetrahedron Lett.* **2004**, *45*, 2009. (p) Liang, Y.; Jing, Q.; Li, X.; Shi, L.; Ding, K. *J. Am. Chem. Soc.* **2005**, *127*, 7694.

(28) This is presumably because an excess amount of ligand **1m** was essential for effective nucleation of the precipitate through bridging Nd and Na cations. **1m** on the surface of the heterogeneous catalyst might be washed away. Excess **1m** could be recovered from the supernatant.

(29) Comparison of observed and theoretical isotopic pattern of the prominent peaks was shown in the Supporting Information.

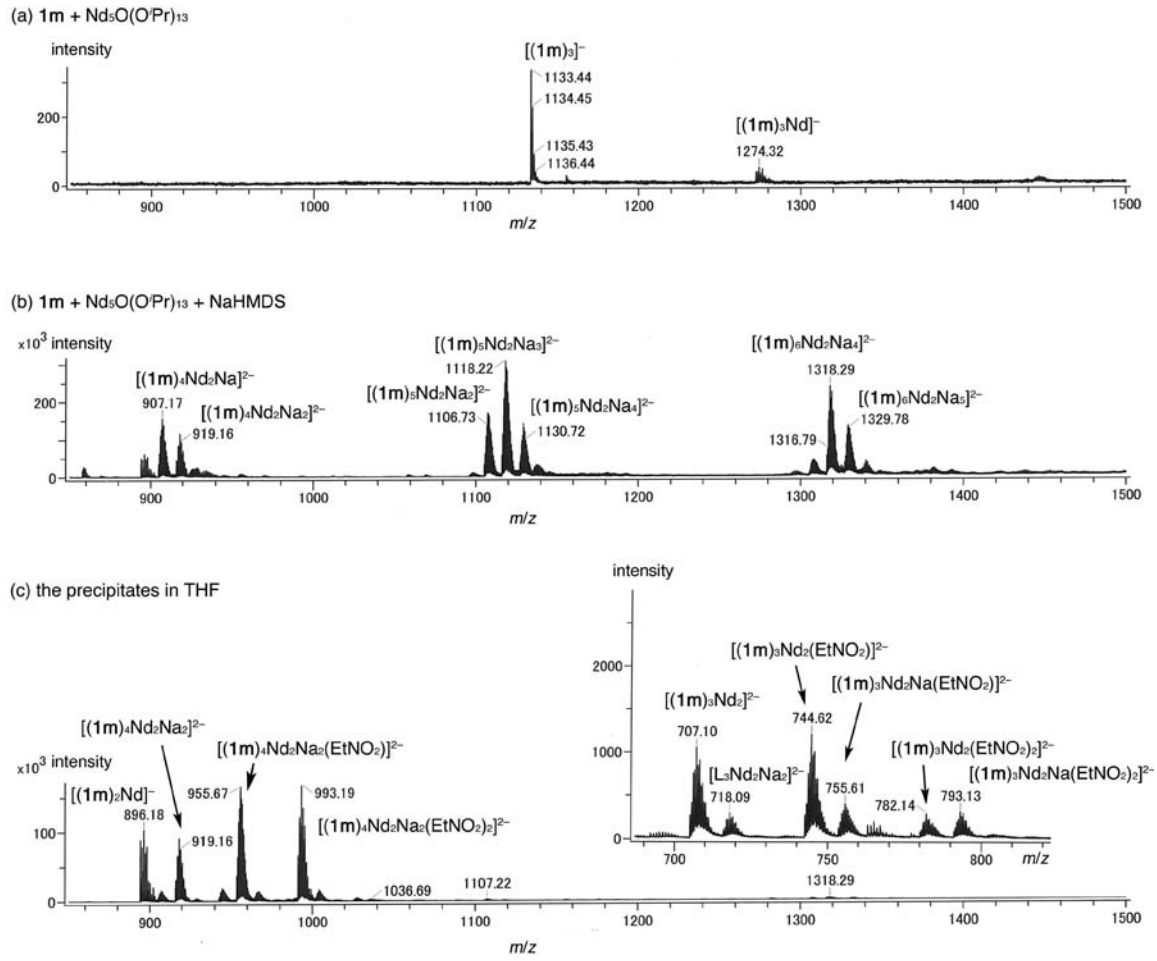
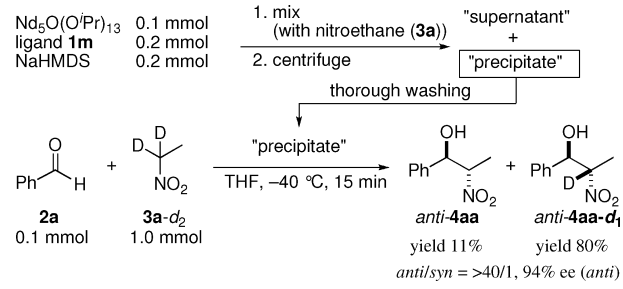


Figure 6. ESI TOF MS spectra (negative ion mode) of the Nd/Na complex at each stage of catalyst preparation. (a) MS spectrum of **1m**/$Nd_5O(O^iPr)_{13}$ = 2/1 (based on Nd) solution in THF; (b) MS spectrum of **1m**/$Nd_5O(O^iPr)_{13}$/NaHMDS = 2/1/2 (based on Nd) diluted solution in THF; and (c) MS spectrum of **1m**/$Nd_5O(O^iPr)_{13}$/NaHMDS/nitroethane (**3a**) = 2/1/2/excess (based on Nd) in THF.

remarkably different. The peaks in Figure 6b mostly disappeared, and peaks derived from a series of **1m**/Nd/Na fragments including nitroethane (**3a**) appeared (Figure 6c).[29,31] Based on observations during the catalyst preparation, upon the addition of NaHMDS, **1m**/Nd/Na heterobimetallic complexes were initially formed, which were then dissolved by the addition of nitroethane (**3a**), and subsequently associated again incorporating nitroethane (**3a**) to afford the heterogeneous Nd/Na heterobimetallic active catalyst. When the nitroaldol reaction using 10 equiv of nitroethane-d_2 (**3a**-d_2) was run with a stoichiometric amount of thoroughly washed precipitate,[32] 11% of the product was derived from nitroethane (**3a**), indicating that nitroethane (**3a**) was tightly bound to the heterobimetallic complex in the precipitate (Scheme 2). According to XRF analysis, which showed that the composition of the precipitate was **1m**/Nd/Na = 0.96/1/1.8, it can be assumed that (**1m**)$_2$$Nd_2$ fragments associated with varying amounts of Na^+ and nitroethane (**3a**) to form an insoluble heterobimetallic entity.[27,30] The predominance of (**1m**)$_4$$Nd_2$ fragments in the MS spectrum was presumably due to the negative ion detection mode.

Scheme 2. Nitroaldol Reaction with Nitroethane-d_2 (**3a**-d_2) Using Stoichiometric Amount of the Precipitate



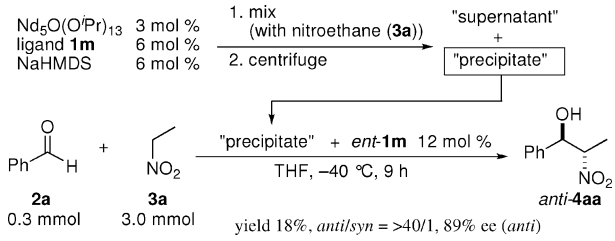
Nonlinear Effect. When the nitroaldol reaction with the preformed precipitates was run in the presence of excess free *ent*-**1m**, an enantiomer of **1m**, the product **4aa** was obtained with stereoselectivity comparable to that obtained in Scheme

(30) For an example of lanthanide coordination polymers from exo-coordination of Na^+, see:(a) Singh-Wilmot, M. A.; Richards-Johnson, R. U.; Dawkins, T. N.; Lough, A. J. *Inorg. Chim. Acta* **2007**, *360*, 3727, and references cited therein. For an example of lanthanide coordination polymer incorporating K^+, see: (b) Bürgstein, M. R.; Roesky, P. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 549. (c) Bürgstein, M. R.; Gamer, M. T.; Roesky, P. W. *J. Am. Chem. Soc.* **2004**, *126*, 5213, and references cited therein.

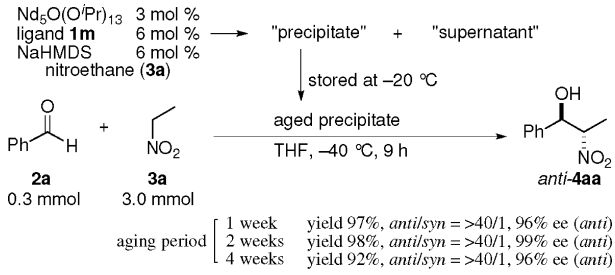
(31) The precipitates were dissolved with THF/DMSO = 100/1 mixture for ESI TOF MS analysis. The nitroaldol reaction of **2a** and **3a** using the precipitates in THF/DMSO = 600/1 afforded the comparable reaction outcome (−40 °C, 20 h, 85% yield (determined by ^{1}H NMR), *anti*/*syn* = 21/1, 86% ee (*anti*)).

(32) The precipitate was washed by four cycles of the following procedure: (1) re-suspended with dry THF; (2) mixed by vortex mixer; (3) centrifuged; and (4) decantation of supernatant. See the Supporting Information for details.

Scheme 3. Reaction Using the Precipitates in the Presence of *ent*-**1m**

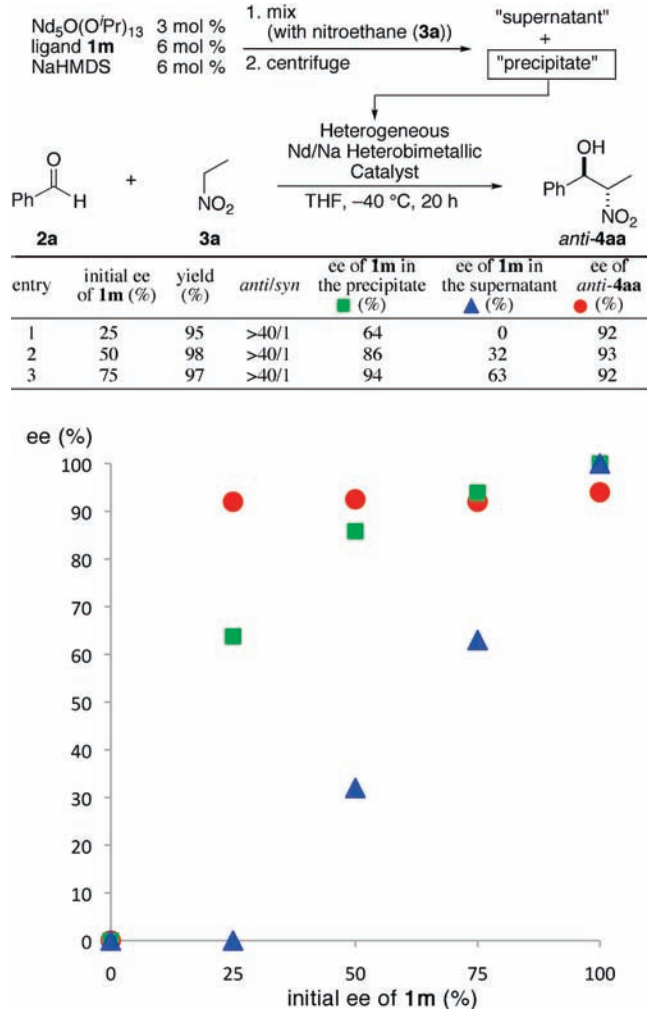


Scheme 4. Storage of the Heterobimetallic Catalyst



1a, suggesting that ligand **1m** in the precipitate was not labile and the architecture of the heterobimetallic complex in the precipitate was rather stable (Scheme 3).[33] Indeed, the precipitate could be stored at −20 °C, and no degradation occurred at least for 1 month in terms of the catalytic activity and stereoselectivity observed in the reaction with the aged precipitate (Scheme 4). Intriguingly, significant enantioenrichment was observed during precipitate formation. When the catalyst was prepared with a partially resolved **1m**, the optical purity of **1m** in the precipitate was positively deviated, whereas that in the supernatant had a negative deviation (Figure 7). The Nd/Na heterobimetallic complex likely grew through the preferential nucleation of the ligand with identical absolute configuration, and the enantiopurity of **1m** in the precipitate reached 86% ee and 64% ee starting with 50% ee and 25% ee of **1m**, respectively. Moreover, prominent enantioamplification was observed in the nitroaldol reaction promoted by the partially heterochiral precipitate, affording **4aa** in *anti*/*syn* = >40/1 and 92% ee with 64% ee precipitate, which was prepared from 25% ee of free **1m**. It can be deduced that the multiple homochiral **1m** was involved in the transition state as the heterobimetallic assembly in the precipitate and the local heterochiral heterobimetallic site had much lower catalytic activity. The double selection process of homochirality (precipitate formation and catalysis) led to a remarkable positive nonlinear effect.[34]

***anti*-Selective Asymmetric Nitroaldol Reaction Promoted by the Heterobimetallic Catalyst.** Having established a preparation procedure for the heterogeneous Nd/Na heterobimetallic catalyst, we examined the substrate scope of the *anti*-selective asymmetric nitroaldol reaction (Table 5).[35,36] The heterogeneous catalyst was prepared by mixing $Nd_5O(O^iPr)_{13}$, **1m**, and NaHMDS in a ratio of 1:2:2 in THF, and the following addition of nitroethane (**3a**) led to the suspension, which was centrifuged



entry	initial ee of **1m** (%)	yield (%)	*anti*/*syn*	ee of **1m** in the precipitate ■ (%)	ee of **1m** in the supernatant ▲ (%)	ee of *anti*-**4aa** ● (%)
1	25	95	>40/1	64	0	92
2	50	98	>40/1	86	32	93
3	75	97	>40/1	94	63	92

Figure 7. Precipitate formation and nitroaldol reaction using partially resolved ligand **1m**. Chemical yield of **4aa** was determined by ^{1}H NMR analysis with 1,4-dioxane as an internal standard. Diastereomeric ratio was determined by ^{1}H NMR.

and washed twice with dry THF. The catalyst amount designates the amount of $Nd_5O(O^iPr)_{13}$ used (based on Nd) for catalyst preparation. In the reaction with benzaldehyde (**2a**), catalyst loading could be reduced to 1 mol % to complete the reaction with marginal loss of stereoselectivity (entry 2).[37] The reaction proceeded smoothly with at least 1.5 equiv of nitroethane (**3a**) (entries 3, 4). Nonpolar functionality on the aromatic ring hardly affected the stereoselectivity (entries 5, 6). Aromatic aldehydes bearing either electron-donating or -withdrawing substituents were suitable substrates, and excellent stereoselectivities were observed (entries 7−11) except for 4-nitrobenzaldehyde **2f**, in which the nitro functionality may competitively coordinate to

(33) Low chemical yield would be due to the competitive protonation by phenol functionality of additional *ent*-**1m**. Low reaction rate was observed when phenolic additives were employed in this catalytic system.

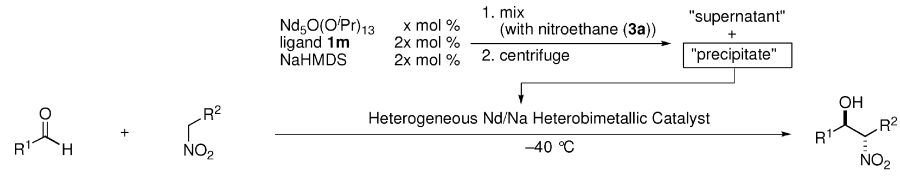
(34) (a) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922. (b) Blackmond, D. G. *Acc. Chem. Res.* **2000**, *33*, 402. (c) Satyanarayana, T.; Abraham, S.; Kagan, H. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 456, and references cited therein.

(35) The heterogeneous catalyst prepared from $Sm_5O(O^iPr)_{13}$ was also effective for nitroaldol reaction of **2a** and **3a**: 3 mol % of catalyst, −40 °C, 20 h, 96% yield, *anti*/*syn* = >40/1, 91% ee. ICP analysis of the heterogeneous catalyst prepared from **1m**/$Sm_5O(O^iPr)_{13}$/NaHMDS revealed that the catalyst was heterobimetallic containing both Sm and Na like the catalyst prepared from $Nd_5O(O^iPr)_{13}$. See the Supporting Information for details.

(36) At higher temperatures (higher than −20 °C), retro-nitroaldol reaction proceeded depending on the substrate used and may decrease the stereoselectivity.

(37) Additional 1 mol % of NaHMDS would scavenge the trace amount of acid included in benzaldehyde (**2a**) without affecting the stereoselectivity.

Table 5. *anti*-Selective Catalytic Asymmetric Nitroaldol Reaction Promoted by the Nd/Na Heterobimetallic Complex[a]



	aldehyde **2**		nitroalkane **3**									
entry	R^1 =		R^2 =		equiv	*x*	solvent	product	time (h)	yield[b] (%)	*anti*/*syn*[c]	ee (*anti*) (%)
1	Ph	**2a**	Me	**3a**	10	3	THF	**4aa**	20	99	>40/1	92
2[d]	Ph	**2a**	Me	**3a**	10	1	THF	**4aa**	20	96	>40/1	91
3	Ph	**2a**	Me	**3a**	3	3	THF	**4aa**	20	95	>40/1	93
4	Ph	**2a**	Me	**3a**	1.5	3	THF	**4aa**	20	91	33/1	89
5	2,4-$Me_2C_6H_3$	**2b**	Me	**3a**	10	3	THF	**4ba**	20	99	>40/1	98
6	4-$BnOC_6H_4$	**2c**	Me	**3a**	10	3	THF	**4ca**	20	89	>40/1	97
7	4-BrC_6H_4	**2d**	Me	**3a**	10	3	THF	**4da**	14	95	37/1	94
8	4-FC_6H_4	**2e**	Me	**3a**	10	3	THF	**4ea**	20	99	>40/1	97
9	4-NO_2	**2f**	Me	**3a**	10	3	THF	**4fa**	20	99	5.7/1	86
10	4-CN	**2g**	Me	**3a**	10	3	THF	**4ga**	20	88	15/1	94
11	4-$MeO_2CC_6H_4$	**2h**	Me	**3a**	10	3	THF	**4ha**	14	96	23/1	89
12	2-furyl	**2i**	Me	**3a**	10	3	THF	**4ia**	20	99	13/1	82
13	*trans*-PhCH=CH	**2j**	Me	**3a**	10	3	THF	**4ja**	20	96	40/1	97
14	$PhCH_2CH_2$	**2k**	Me	**3a**	10	6	DME	**4ka**	20	99	4.91	77
15	^cHex	**2l**	Me	**3a**	10	6	DME	**4la**	22	92	8.3/1	95
16	$^nC_8H_{11}$	**2m**	Me	**3a**	10	6	DME	**4ma**	20	93	3.4/1	87
17	Ph	**2a**	Et	**3b**	10	3	THF	**4ab**	20	99	>40/1	90
18	4-FC_6H_4	**2e**	Et	**3b**	10	3	THF	**4eb**	20	93	19/1	90
19	Ph	**2a**	$TBSOCH_2$	**3c**	5	3	Et_2O	**4ac**	48	85	13/1	90
20	Ph	**2a**	$BnOCH_2$	**3d**	5	3	THF	**4ad**	48	75	19/1	95

[a] **2**, 0.3 mmol; **3**, 3.0 mmol. [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] 1 mol % of NaHMDS was added to the Nd/Na heterobimetallic catalyst.

the coordination site of **3a** to compromise the transition state. A slight decrease in stereoselectivity was observed with heteroaromatic aldehyde **2i** (entry 12). The present protocol was also effective for various aliphatic aldehydes, including linear and branched aldehydes, albeit in lower *anti*-selectivity (entries 13−16). For aliphatic aldehydes, 6 mol % of catalyst loading assured the high stereoselectivity, and the use of DME as the solvent improved the enantioselectivity. To broaden the scope of the present methodology, we next focused on the implementation of nitroalkanes other than **3a** in this catalytic system (entries 17−20). Because the catalyst preparation procedure required **3a** (Figure 5) and **3a** was incorporated in the active heterobimetallic catalyst, catalyst preparation was conducted with nitropropane (**3b**) following the same procedure as described in Figure 5 for the reaction of **2a** and **3c**. Unexpectedly, the precipitate did not appear when **3b** was used for catalyst preparation.[38] Whereas the heterobimetallic catalyst prepared with **3a** included **3a** as its components, the amount of coordinated **3a** in the catalyst was negligible under the conditions of 3 mol % catalyst loading. Thus, the nitroaldol reaction of **2a** and **2e** with **3b** was performed with the catalyst prepared using **3a**, affording *anti*-**4ab** and *anti*-**4eb** in high enantioselectivity without the formation of **4aa** and **4ea** (entries 17, 18).[39] Although functionalized nitroalkanes **3c** and **3d** also failed to form the heterogeneous heterobimetallic catalyst, they served as viable nucleophiles with the catalyst prepared using **3a**, delivering the desired products **4ac** and **4ad** with high stereoselectivity (entries 19, 20).[40] It is intriguing that only nitroethane (**3a**) formed the insoluble Nd/Na heterobimetallic catalyst, allowing for the isolation of the active catalyst exhibiting high stereoselectivity.

A large-scale demonstration of the nitroaldol reaction with the heterogeneous catalyst highlights the utility and operational simplicity of the present protocol. The nitroaldol reaction of 50 g of aldehyde **2c** and nitroethane **3a** (used as received from a commercial source) was run with the heterogeneous heterobimetallic catalyst prepared from 1 mol % $Nd_5O(O^iPr)_{13}$ at −30 °C.[41] 24 h of stirring resulted in 85% conversion (*anti*/*syn* = >40/1, 97% ee), and the following single recrystallization of the crude mixture provided 51.2 g of the nitroaldol product **4ca** in pure form (76% yield) with *anti*/*syn* = >40/1, 98% ee, which is a key intermediate for the potent β_3-adrenoreceptor agonist **5** (Scheme 5).[42,43] The process is now under extensive investigation for an industrial application for the bulk production of **5**.

Conclusion

A new *anti*-selective catalytic asymmetric nitroaldol reaction was achieved with a heterogeneous Nd/Na heterobimetallic

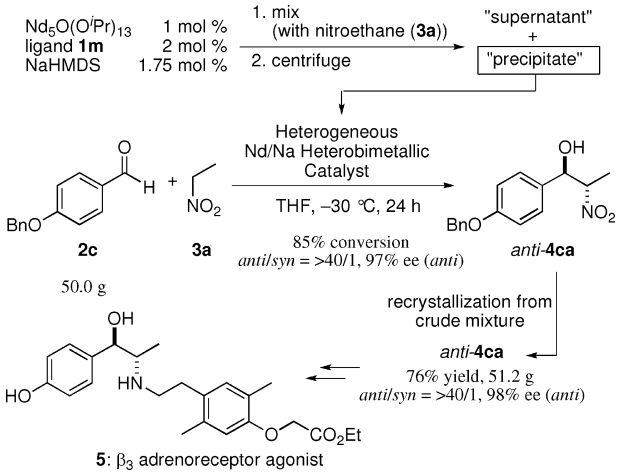
(38) The catalyst prepared from nitropropane (**3b**) did not form the precipitate. When the resulting solution was used as catalyst in the reaction of **2a** and **3b**, the reaction was sluggish (3 mol % of catalyst loading, −40 °C, 21 h), affording <14% (determined by ^1H NMR) of the product **4ab** in *anti*/*syn* = 3.2/1 and 41% ee (*anti*). This is likely due to the fact that the catalytically active Nd/Na heterobimetallic catalyst would not be formed with **3b** even in the solution phase.

(39) In the ^1H NMR spectrum of the crude mixture, the signals derived from **4aa** or **4ea** were not observed. Nitroethane (**3a**) incorporated in the heterogeneous catalyst may be reluctant to be replaced with bulkier nitroalkanes. If initially incorporated nitroethane (**3a**) reacted with an aldehyde, the amount of the nitroaldol product derived from **3a** would be negligible with low catalyst loading.

(40) In the reaction using **3c** in THF, the heterogeneous catalyst dissolved and the reaction mixture became a clear solution, affording the product with slightly lower stereoselectivity.

(41) The reaction conditions were specifically optimized for this substrate, and the heterobimetallic catalyst prepared from $Nd_5O(O^iPr)_{13}$/**1m**/NaHMDS = 1/2/1.75 ratio gave the best performance.

Scheme 5. Large-Scale Demonstration of *anti*-Selective Nitroaldol Reaction Promoted by the Heterogeneous Nd/Na Heterobimetallic Catalyst



complex. The present methodology allowed for easy access to highly versatile enantioenriched *anti*-1,2-amino alcohols, which are of particular importance in the enantioselective synthesis of biologically active natural products and therapeutics. A rational approach toward *anti*-diastereoselectivity through a heterobimetallic strategy led to the identification of the heterogeneous Nd/Na heterobimetallic catalyst organized by amide-based phenolic ligand **1m**, exhibiting an exquisite spatial arrangement of the two distinct metals. ICP, XRF, and ESI MS analyses suggested that the **1m**/Nd complex aggregated with the aid of Na^+ incorporating nitroethane to form a heterogeneous active catalyst. The catalyst was storable and effective for a broad range of aldehydes and nitroalkanes, showcasing the utility of the present protocol.

Acknowledgment. This work was financially supported by a Grant-in-Aid for Scientific Research (S) (M.S.) and a Grant-in-Aid for Scientific Research on Innovative Areas (N.K.) from JSPS and MEXT. T.N. thanks JSPS for a predoctoral fellowship. Mr. S. Ikeda is gratefully acknowledged for XRF analysis of the heterogeneous catalyst. We thank Prof. S. Kobayashi, and Drs. R. Matsubara, H. Miyamura, and R. Akiyama for technical assistance in ICP analysis. Ms. K. Tanaka at JEOL Corp. is gratefully acknowledged for ESI TOF MS analysis of the Nd/Na heterobimetallic catalyst.

Supporting Information Available: Detailed experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA905885Z

(42) (a) Tanaka, N.; Tamai, T.; Mukaiyama, H.; Hirabayashi, H.; Muranaka, M.; Sato, M.; Akahane, M. Patent WO00/02846, 1999. (b) Tanaka, N.; Tamai, T.; Mukaiyama, H.; Hirabayashi, A.; Muranaka, H.; Ishikawa, T.; Kobayashi, J.; Akahane, S.; Akahane, M. *J. Med. Chem.* **2003**, *46*, 105. (c) Tanaka, T.; Tamai, T. JP Patent JP 2002-64840; see also ref 10b.

(43) In this specific case, the diastereomeric ratio of **4ca** was monitored during the progress of the nitroaldol reaction (conditions: precipitate obtained from 2 mol % $Nd_5O(O^iPr)_{13}$, 4 mol % of **1m**, 3 mol % of NaHMDS, 2 mol % H_2O was used as catalyst, −30 °C, THF, 10 equiv of **3a**). The yield and stereoselectivity at the specified period of the reaction time were as follows: 3 h, 55% yield, *anti*/*syn* = >40/1, 97% ee (*anti*); 6 h, 72% yield, *anti*/*syn* = >40/1, 98% ee (*anti*); 12 h, 86% yield, *anti*/*syn* = 34/1, 97% ee (*anti*); 18 h, 89% yield, *anti*/*syn* = 31/1, 96% ee (*anti*); 24 h, 92% yield, *anti*/*syn* = 29/1, 96% ee (*anti*). At temperatures higher than −30 °C and with higher catalyst loading (2 mol %), the retro-nitroaldol reaction competitively occurred to decrease the stereoselectivity slightly.