Tetrahedron Letters 57 (2016) 1815–1819

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Preparation of Nd/Na heterogeneous catalyst from bench-stable and inexpensive Nd salt for an *anti*-selective catalytic asymmetric nitroaldol reaction

Akihito Nonoyama, Kazuki Hashimoto, Akira Saito, Naoya Kumagai *, Masakatsu Shibasaki *

Institute of Microbial Chemistry (BIKAKEN), Tokyo, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan

ARTICLE INFO

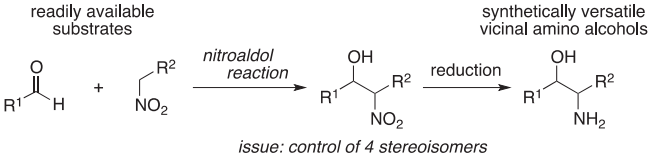
Article history:
Received 13 February 2016
Revised 9 March 2016
Accepted 12 March 2016
Available online 15 March 2016

Keywords:
Nitroaldol
Neodymium
Bimetallic complex
Flow reaction
Enantioselective

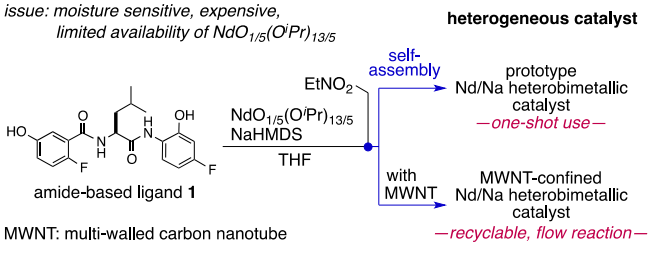
ABSTRACT

A Nd/Na heterobimetallic complex prepared from an amide-based chiral ligand, Nd alkoxide, and NaHMDS is a highly efficient heterogeneous catalyst for an *anti*-selective catalytic asymmetric nitroaldol reaction. Nd alkoxide is sensitive to moisture, expensive, and scarce, making it difficult to use the Nd/Na catalyst in large-scale applications. Herein we describe a new protocol that allows for catalyst preparation from bench-stable and inexpensive $NdCl_3 \cdot 6H_2O$ with comparable catalytic activity.

The nitroaldol (Henry) reaction, a carbon–carbon bond-forming reaction of nitroalkanes and carbonyl compounds (typically aldehydes), offers expeditious access to vicinal amino alcohols after reducing the nitro group.[1,2] Given the ready availability of these substrates and the established synthetic utility of vicinal amino alcohols, particularly for medicinal chemistry,[3] the nitroaldol reaction is one of the most widely used C–C bond-forming reactions in the organic reaction toolbox (Scheme 1). Since our first report rendering this reaction in a catalytic and asymmetric manner with *syn*-diastereoselectivity,[4] major challenges in this field have been simultaneous control of the diastereo- and enantioselectivity, allowing for stereoselective access to one of the four vicinal nitroalkanols.[5] Shortly after Ooi's report on the catalytic *anti*-selective and enantioselective nitroaldol reaction,[6] we disclosed an Nd/Na heterobimetallic complex as an effective heterogeneous catalyst for producing *anti*-nitroaldol products with a broad substrate scope (Scheme 2).[7,8] The Nd/Na catalyst was readily prepared using an amide-based ligand **1**, $NdO_{1/5}(O^iPr)_{13/5}$, and NaHMDS in THF/$EtNO_2$; self-assembly of **1**/Nd/Na proceeded with incorporation of $EtNO_2$ to give the powdered heterogeneous catalyst.[7b,9] Catalyst preparation in the presence of multi-walled carbon nanotubes (MWNT) allowed for self-assembly in the fibrous matrix of the MWNT, thereby affording a MWNT-confined catalyst with smaller catalyst clusters that enabled higher catalytic efficiency, catalyst reuse, and reactions in a continuous-flow platform.[10]



Scheme 1. Overview of nitroaldol (Henry) reaction.



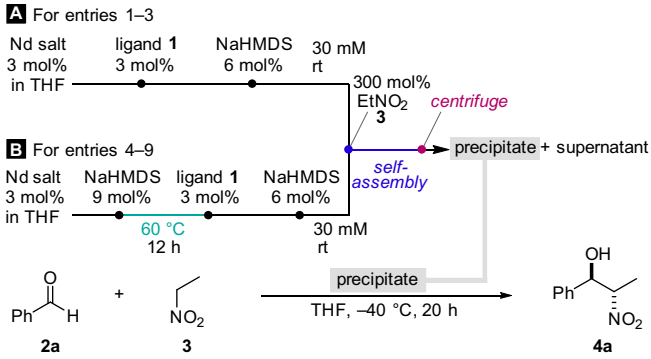
Scheme 2. Overview of the previously developed Nd/Na heterobimetallic heterogeneous catalyst for *anti*-selective nitroaldol reaction.

An inherent problem, however, remained unsolved—the instability and limited availability of $NdO_{1/5}(O^iPr)_{13/5}$. This Nd alkoxide is (1) expensive;[11] (2) unstable to moisture; (3) and requires

* Corresponding authors.
E-mail addresses: nkumagai@bikaken.or.jp (N. Kumagai), mshibasa@bikaken.or.jp (M. Shibasaki).

http://dx.doi.org/10.1016/j.tetlet.2016.03.041
0040-4039/

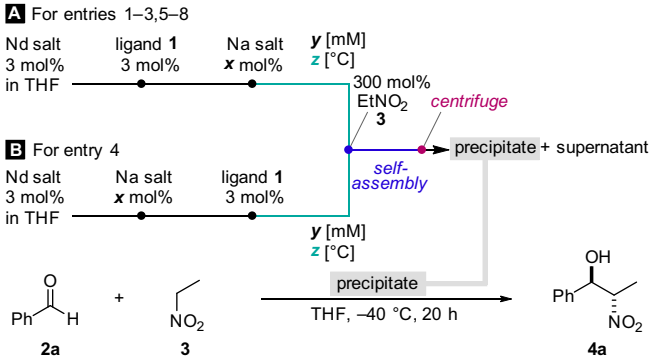
Table 1
Screening of Nd salts[a]



Entry	Nd salt	Ambient conditions	€/g-Nd[b]	Prepn	Yield[c] (%)	*anti*/*syn*[d]	ee[e] (%)
1[f]	$NdO_{1/5}(O^iPr)_{13/5}$	–	239	**A**	99	>20/1	92
2	$Nd(HMDS)_3$	–	240	**A**	>99	>20/1	94
3	$Nd(OH)_3$	+	17	**A**	<5	1.7/1	nd[g]
4	$Nd(NO_3)_3{\cdot}6H_2O$	+	3.3	**B**	<5	2.7/1	nd[g]
5	$Nd(OAc)_3{\cdot}H_2O$	+	1.8	**B**	<5	1.7/1	nd[g]
6	NdF_3	+	0.9	**B**	<5	1.2/1	nd[g]
7	$NdCl_3$	+	11	**B**	99	>20/1	93
8	$NdCl_3{\cdot}6H_2O$	+	1.6	**B**	<5	1.9/1	nd[g]
9	$NdBr_3$	+	40	**B**	42	6.8/1	33

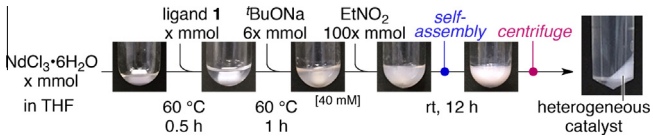
[a] **2a**: 0.4 mmol, **3**: 4.0 mmol.
[b] Cited references are described in ESI.
[c] Determined by ^{1}H NMR analysis of the crude mixture with DMF as an internal standard.
[d] Determined by ^{1}H NMR analysis of the crude mixture.
[e] Ee of *anti* diastereomer. Determined by chiral stationary-phase HPLC analysis.
[f] Data from Ref. 7b. Nd salt in THF was mixed into ligand **1**/THF.
[g] nd: not determined.

Table 2
Screening of Na salts[a]



Entry	Nd salt	Na salt	*x*	€/g-Nd[b]	€/g-Na[b]	Prepn	*y*	*z*	Yield[c] (%)	*anti*/*syn*[d]	ee[e] (%)
1	$NdCl_3$	NaHMDS	18	11	35	**A**	30	rt	93	>20/1	93
2	$NdCl_3{\cdot}6H_2O$	NaHMDS	18	1.6	35	**A**	30	rt	97	>20/1	95
3	$NdCl_3{\cdot}6H_2O$	NaO^{t}Bu	18	1.6	0.6	**A**	40	60	98	>20/1	93
4	$NdCl_3{\cdot}6H_2O$	NaO^{t}Bu	18	1.6	0.6	**B**	40	60	<5	5.2/1	nd[g]
5	$NdCl_3{\cdot}6H_2O$	NaO^{t}Bu	12	1.6	0.6	**A**	40	60	40	>20/1	95
6	$NdCl_3{\cdot}6H_2O$	NaO^{t}Am	18	1.6	2.7	**A**	40	60	98	>20/1	94
7	$NdCl_3{\cdot}6H_2O$	NaOEt	18	1.6	0.3	**A**	40	60	>99	>20/1	93
8[f]	$NdCl_3{\cdot}6H_2O$	NaO^{t}Bu	18	1.6	0.6	**A**	40	60	97	>20/1	93

[a] **2a**: 0.4 mmol, **3**: 4.0 mmol.
[b] Cited references are described in ESI.
[c] Determined by ^{1}H NMR analysis of the crude mixture with DMF as an internal standard.
[d] Determined by ^{1}H NMR analysis of the crude mixture.
[e] Ee of *anti* diastereomer. Determined by chiral stationary-phase HPLC analysis.
[f] 18 mg of MWNT was added before adding $EtNO_2$ (**3a**).
[g] nd: not determined.



Scheme 3. Schematic representation of new preparation protocol of the Nd/Na heterogeneous catalyst. The solid white object is a magnetic stirring bar.

handling in a glove box under an inert atmosphere, which hampers widespread use of this particularly useful catalyst. Herein we report a new catalyst preparation procedure using an alternative bench-stable and inexpensive $NdCl_3{\cdot}6H_2O$ as the Nd salt. The previously required NaHMDS as a Na source was also replaced with more common and less expensive Na alkoxides. The newly formed catalyst was characterized by XRD and STEM, and exhibited catalytic activity comparable to that of $NdO_{1/5}(O^iPr)_{13/5}$.

We selected $NdO_{1/5}(O^iPr)_{13/5}$ as the Nd salt of choice due to its high solubility in the preferred reaction solvent, e.g., THF, and its basic character was also suitable for self-assembly with phenolic ligand **1**. Based on these criteria, $Nd(HMDS)_3$ was an appropriate alternative that produced a similar reaction outcome as $NdO_{1/5}(O^i\text{-}Pr)_{13/5}$ in the nitroaldol reaction of benzaldehyde (**2a**) and $EtNO_2$ (**3**). The cost and instability, however, remained comparable, and thus further modifications were needed (Table 1, procedure **A**, entries 1, 2). We searched for bench-stable and neutral Nd salts to prepare the catalyst with a greater amount of NaHMDS to compensate for the basicity and facilitate self-assembly. Because potentially basic $Nd(OH)_3$ was ineffective for catalyst preparation, likely due to insolubility in THF (entry 3), in situ preparation of $Nd(HMDS)_3$ from various readily available and inexpensive Nd salts was examined with a 3-fold excess of NaHMDS (Table 1, procedure **B**).[12] The highly cost-effective Nd salts, e.g., $Nd(OAc)_3{\cdot}H_2O$, $Nd(NO_3)_3{\cdot}6H_2O$, and NdF_3, barely afforded the catalysts sufficiently active to promote the nitroaldol reaction (entries 4–6). In contrast to NdF_3, the catalyst prepared from $NdCl_3$ produced a nearly similar reaction outcome to that obtained using $NdO_{1/5}(O^iPr)_{13/5}$ (entry 1 vs entry 7). $NdBr_3$ delivered less effective catalyst to afford product **4a** with an inferior yield and stereoselectivity (entry 9). Although the hydrate form of $NdCl_3$ was much less expensive, the use of $NdCl_3{\cdot}6H_2O$ in the identical catalyst preparation procedure afforded only trace amounts of product **4a** (entry 8).

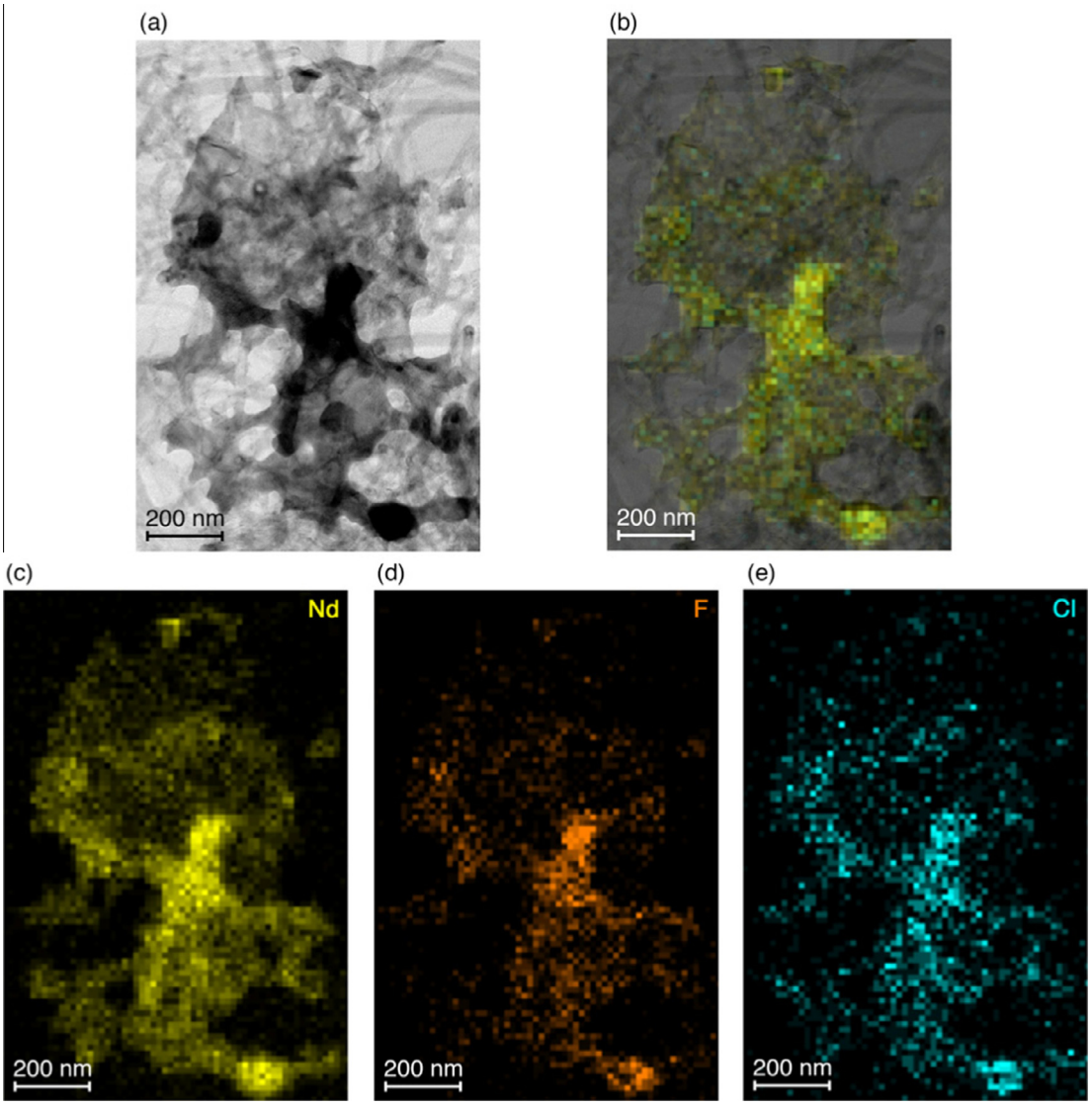
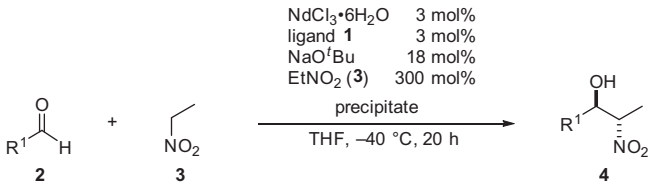


Figure 1. STEM image of MWNT-confined catalyst prepared by new protocol ($NdCl_3{\cdot}6H_2O/NaO^tBu$). (a) STEM image; (b) merged image of STEM and EDS mapping for Nd, F, and Cl; (c) EDS mapping analysis for Nd detection; (d) EDS mapping analysis for F detection; (e) EDS mapping analysis for Cl detection.

Given the lower cost of $NdCl_3$ (11 euro/1 g-Nd) compared with $NdO_{1/5}(O^iPr)_{13/5}$ (239 euro/1 g-Nd),[11] we directed our attention to establishing a reliable and cost-effective protocol based on its hydrate form, $NdCl_3{\cdot}6H_2O$ (1.6 euro/1 g-Nd) (Table 2).[11] Pre-incubation of $NdCl_3$ and 3-fold excess of NaHMDS could be omitted for operational simplicity; mixing 6-fold excess of NaHMDS with $NdCl_3$/ligand **1** in THF gave a similar result (Table 1, entry 7 vs Table 2, procedure **A**, entry 1). This simplified procedure was valid for $NdCl_3{\cdot}6H_2O$, presumably due to the presence of ligand **1** upon contact with Nd and Na salts, which reduced the negative effect of the hydrates (entry 2). NaHMDS (35 euro/1 g-Na) was also replaced with less expensive and more readily available NaO^tBu (0.6 euro/1 g-Na) under more concentrated conditions (40 mM in ligand **1**) at a higher temperature (60 °C),[11] affording the nitroaldol product **4a** without any detrimental effects on the reaction outcome (entry 3).[13]

Formation of the Nd/Na heterogeneous catalyst under these conditions is delineated in Scheme 3.[14] Unexpectedly, pre-incubation of $NdCl_3{\cdot}6H_2O$ and NaO^tBu in the absence of ligand **1** under otherwise identical conditions gave a solid material with almost no catalytic activity (procedure **B**, entry 4), presumably because $NdCl_3{\cdot}6H_2O$ and NaO^tBu produced an insoluble aggregate and therefore no productive complexation with **1** proceeded. The amount of base was also important; reducing NaO^tBu to 4-fold excess reduced the catalytic efficiency (entry 5).[15] Other Na alkoxides under otherwise identical conditions produced similar reaction outcomes (entries 6, 7). Under the optimized conditions for catalyst preparation, mixing the MWNT before adding $EtNO_2$ produced MWNT-confined catalyst for potential use in a flow reaction (vide infra). The MWNT-confined catalyst had increased durability, was easily filtered for recovery, and produced similar reaction outcome in a batch system (entry 8). Replacing the Nd and Na salts from $NdO_{1/5}(O^iPr)_{13/5}$/NaHMDS to $NdCl_3{\cdot}6H_2O/NaO^tBu$ resulted in a ca. 120-fold cost reduction.

Table 3
Substrate generality of the nitroaldol reaction promoted by the Nd/Na heterobimetallic catalyst via new protocol ($NdCl_3{\cdot}6H_2O/NaO^tBu$)[a]



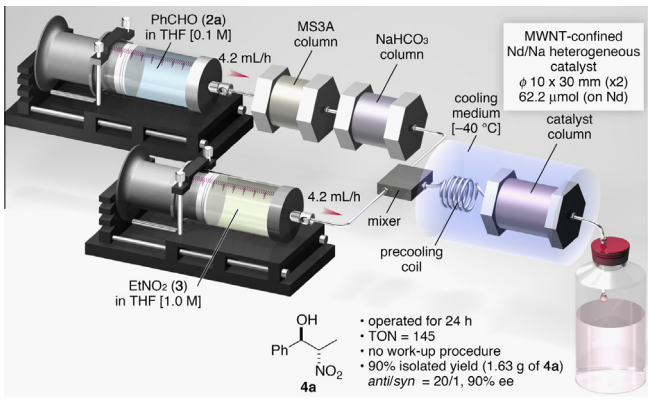
Entry	Aldehyde **2**		**4**	Yield[b,c] (%)	*anti*/*syn*[b,d]	ee[b,e] (%)
	R^1=					
1	Ph	**2a**	**4a**	96 (99)	>20/1 (>20/1)	93 (92)
2	2,4-$Me_2C_6H_3$	**2b**	**4b**	95 (99)	>20/1 (>20/1)	99 (98)
3	4-$BnOC_6H_4$	**2c**	**4c**	87 (89)	>20/1 (>20/1)	99 (97)
4	4-NCC_6H_4	**2d**	**4d**	91 (88)	19/1 (15/1)	97 (94)
5[f]	4-$MeO_2CC_6H_4$	**2e**	**4e**	92 (99)	>20/1 (>20/1)	96 (96)
6	4-$NO_2C_6H_4$	**2f**	**4f**	92 (99)	6.5/1 (5.7/1)	88 (86)
7	(*E*)-PhCH=CH	**2g**	**4g**	95 (96)	>20/1 (>20/1)	98 (97)
8[g,h]	[c]Hex	**2h**	**4h**	90 (92)	6.8/1 (8.3/1)	94 (95)
9[g]	$PhCH_2CH_2$	**2i**	**4i**	94 (99)	4.4/1 (4.9/1)	82 (77)
10[g]	$^nC_8H_{17}$	**2j**	**4j**	90 (93)	3.3/1 (3.4/1)	85 (87)

[a] **2a**: 0.4 mmol, **3a**: 4.0 mmol.
[b] Data in parentheses are obtained from the catalyst prepared from the original protocol ($NdO_{1/5}(O^iPr)_{13/5}$/NaHMDS).[7b]
[c] Isolated yield of diastereomixture.
[d] Determined by ^1H NMR analysis of the crude mixture.
[e] Ee of *anti* diastereomer. Determined by chiral stationary-phase HPLC analysis.
[f] Run for 14 h.
[g] DME was used as solvent with 6 mol% of catalyst.
[h] Run for 22 h.

The Nd/Na heterobimetallic heterogeneous catalysts prepared by the original ($NdO_{1/5}(O^iPr)_{13/5}$/NaHMDS)[7b] and new ($NdCl_3{\cdot}6H_2O/NaO^tBu$) protocol were analyzed by powder XRD analysis.[16] As expected based on the comparable reaction outcomes in the nitroaldol reaction, we observed nearly identical diffraction patterns. Several unique peaks observed for the new catalyst were assigned as peaks derived from NaCl. STEM and EDS mapping images of the MWNT-confined catalyst confirmed that the catalyst clusters were trapped in the fibrous network of the MWNT (Fig. 1); characteristic X-ray areas of fluorine (derived from ligand **1**), chlorine, and Nd were superimposed with the catalyst image. Chloride anions derived from $NdCl_3{\cdot}6H_2O$, which is absent in the original method, located uniformly in the catalyst and had no negative effect on the catalyst activity.

The Nd/Na catalyst prepared via the new protocol was evaluated using various substrates in comparison with the catalyst prepared via the original protocol (Table 3). The results of the original catalyst using the same catalyst loading (based on Nd) are shown in parentheses,[7b] and almost identical reaction outcomes were obtained for a series of aldehydes (entries 1–10). *ortho*-Substituent, electron-donating and -withdrawing substituents at para position were tolerated to afford the nitroaldol products in high yields, *anti*-selectivity, and enantioselectivity (entries 2–5), albeit with a little erosion in stereoselectivity for 4-nitrobenzaldehyde (**2f**) (entry 6). Although the reaction with cinnamaldehyde (**2g**) as an archetypal α,β-unsaturated aldehyde afforded reasonable yields and stereoselectivity without forming a 1,4-adduct (entry 7), lower diastereoselectivity was generally observed for aliphatic aldehydes (entries 8–10). A branched aldehyde, e.g., cyclohexanecarboxaldehyde (**2h**) exhibited better stereoselectivity (entry 8) and self-condensation of aliphatic aldehydes was barely detected (entries 8–10).

The MWNT-confined Nd/Na heterobimetallic catalyst prepared via the new protocol was applied to a continuous-flow reaction (Scheme 4).[17] The MWNT-confined catalyst was suspended in THF with dried Celite and packed in a stainless steel column with end-capping disk frits (2 μm) (62.2 μmol based on Nd). Benzaldehyde (**2a**) (0.1 M/THF) and $EtNO_2$ (**3**) (1.0 M/THF) were introduced in separate streams at 4.2 mL/h using syringe pumps and **2a** was passed through an MS3A column and a $NaHCO_3$ column to remove trace amounts of water and acidic impurities. The two streams merged in a mixer and the resulting substrate mixture was precooled to −40 °C before entering the catalyst column. The flow system was operated for 24 h with high conversion and stereoselectivity to afford 1.63 g of product **4a** (90% yield, *anti*/*syn* = 20/1, 90% ee, TON = 145). The flow system is advantageous because (1) the heterogeneous catalyst was prepared by simple



Scheme 4. Nitroaldol reaction in a continuous-flow platform with MWNT-confined Nd/Na heterogeneous catalyst prepared via new protocol.

mixing without any covalent linkage;[18] (2) no work-up procedure was required and evaporation of the eluent gave the crude product; (3) the cooling volume was significantly reduced to decrease the electric power required for cryogenic conditions. The nitro product of **4a** can be readily reduced to give (−)-norephedrine.[8e]

In conclusion, we established a new preparation protocol for an Nd/Na heterobimetallic heterogeneous catalyst. Replacing of $NdO_{1/5}(O^iPr)_{13/5}$/NaHMDS with $NdCl_3{\cdot}6H_2O$/NaO^{t}Bu allowed us to prepare the catalyst under ambient conditions with a ca. 120-fold reduction in the cost. The catalyst prepared via the new protocol was characterized by XRD and STEM, which indicated the catalyst was essentially identical to that prepared with the original protocol, a finding supported by the similar reaction outcomes in nitroaldol reactions. The new protocol was compatible with MWNT confinement and the MWNT-confined catalyst was operative in a continuous-flow platform.

Acknowledgments

This work was financially supported by ACT-C, JST, and KAKENHI (20229001) from JSPS. N.K. thanks the Japan Agency for Medical Research and Development (AMED) for financial support. SCAS (Sumika Chemical Analysis Service) is gratefully thanked for XRD and STEM analyses.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.03.041.

References and notes

1. Henry, L. C. R. *Hebd. Seances Acad. Sci.* **1895**, *120*, 1265.
2. For recent reviews, see: (a) Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315; (b) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561; (c) Blay, G.; Hernández-Olmos, V.; Pedro, J. R. *Synlett* **2011**, 1195.
3. (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835; (b) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159; (c) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561; d Anaya de Parrodi, C.; Juaristi, E. *Synlett* **2006**, 2699.
4. (a) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418; (b) Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388.
5. For selected examples of highly syn-selective catalytic asymmetric nitroaldol reactions, see: (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; (e) Yoshimoto, J.; Sandoval, C. A.; Saito, S. *Chem. Lett.* **2008**, *37*, 1294; (f) Kim, H. Y.; Oh, K. *Org. Lett.* **2009**, *11*, 5682; (g) Jin, W.; Li, X.; Wan, B. *J. Org. Chem.* **2011**, *76*, 484; (h) White, J. D.; Shaw, S. *Org. Lett.* **2012**, *14*, 6270; (i) Qin, D.-D.; Yu, W.; Zhou, J.-D.; Zhang, Y.-C.; Ruan, Y.-P.; Zhou, Z.-H.; Chen, H.-B. *Chem. Eur. J.* **2013**, *19*, 16541.
6. Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392.
7. (a) Nitabaru, T.; Kumagai, N.; Shibasaki, M. *Tetrahedron Lett.* **2008**, *49*, 272; (b) Nitabaru, T.; Nojiri, A.; Kobayashi, M.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 13860.
8. For *anti*-selective catalytic asymmetric nitroaldol reactions, see: (a) Handa, S.; Nagawa, K.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3230; (b) Sohtome, Y.; Kato, Y.; Handa, S.; Aoyama, N.; Nagawa, K.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 2231; (c) Uraguchi, D.; Nakamura, S.; Ooi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 7562; (d) Lang, K.; Park, J.; Hong, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 1620; (e) Xu, K.; Lai, G.; Zha, Z.; Pan, S.; Chen, H.; Wang, Z. *Chem. Eur. J.* **2012**, *18*, 12357; For partially successful (moderate stereoselectivity) examples, see: (f) Blay, G.; Domingo, L. R.; Hernández-Olmos, V.; Pedro, J. R. *Chem. Eur. J.* **2008**, *14*, 4725; (g) Ube, H.; Terada, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3895; (h) Noole, A.; Lippur, K.; Metsala, A.; Lopp, M.; Kanger, T. *J. Org. Chem.* **2010**, *75*, 1313; (i) Blay, G.; Hernández-Olmos, V.; Pedro, J. R. *Org. Lett.* **2010**, *12*, 3058; (j) Ji, Y. Q.; Qi, G.; Judeh, Z. M. A. *Eur. J. Org. Chem.* **2011**, 4892; (k) Yao, L.; Wei, Y.; Wang, P.; He, W.; Zhang, S. *Tetrahedron* **2012**, *68*, 9119; (l) Boobalan, R.; Lee, G.-H.; Chen, C. *Adv. Synth. Catal.* **2012**, *354*, 2511; (m) Arai, T.; Joko, A.; Sato, K. *Synlett* **2015**, 209.
9. For reviews for the utility of amide-based ligand **1** in combination with rare-earth metals, see: (a) Kumagai, N. *Chem. Pharm. Bull.* **2011**, *59*, 1; (b) Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 223.
10. (a) Ogawa, T.; Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 6196; (b) Sureshkumar, D.; Hashimoto, K.; Kumagai, N.; Shibasaki, M. *J. Org. Chem.* **2014**, *79*, 3272; (c) Hashimoto, K.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2014**, *16*, 3496.
11. Retail prices of Nd and Na salts are summarized in Supplementary material.
12. (a) Schuetz, S. A.; Way, V. W.; Sommer, R. D.; Rheingold, A. L.; Belot, J. A. *Inorg. Chem.* **2001**, *40*, 5292; (b) Dash, A. K.; Razavi, A.; Mortreux, A.; Lehmann, C. W.; Carpentier, J.-F. *Organometallics* **2002**, *21*, 3238.
13. Grinded $NdCl_3{\cdot}6H_2O$ was used to reduce the fluctuation depending on the production lot.
14. *Representative experimental procedure:* A flame dried test tube (20 mL) equipped with a magnetic stirring bar and a 3-way glass stopcock was charged with $NdCl_3{\cdot}6H_2O$ (4.3 mg, 0.012 mmol), and dried under vacuum at room temperature. Ar was backfilled (evacuation/backfill was repeated for several times) to the test tube, and THF (100 μL) and ligand **1** (200 μL, 0.012 mmol, 0.6 M/THF) were added successively by well-dried syringes and needles at room temperature. After stirring the resulting slightly cloudy solution at 60 °C for 30 min, NaO^{t}Bu (36 μL, 0.072 mmol, 2.0 M/THF) was added dropwise at the same temperature. After stirring the resulting mixture at 60 °C for 1 h (white precipitate appeared), the mixture was cooled to room temperature and nitroethane (**3**) (86 μL, 1.2 mmol) was added (the precipitate was partly dissolved). Self-assembly of Nd/Na catalyst initiated in a few minutes and the resulting mixture was stirred at room temperature for 12 h to give a thick white suspension. The whole suspension was transferred to an Eppendorf tube and the tube was centrifuged at ca. 10^4 rpm for 30 s. The supernatant was decanted and dry THF (1.2 mL) was added to the precipitate. The tube was agitated using a vortex mixer for 30 s and the resulting tube was centrifuged again, then the supernatant was decanted (washing process). The resulting precipitate was agitated with dry THF (1.6 mL) and the resulting suspension was transferred to a flame-dried test tube (20 mL) for the nitroaldol reaction.
15. Although the use of 5-fold excess of NaO^{t}Bu is sufficient for complexation (3-fold for trivalent Nd and 2-fold for two phenolic protons of **1**), 6-fold excess of NaO^{t}Bu is recommended for higher reproducibility.
16. See Supplementary material for details.
17. For selected recent reviews on flow chemistry, see: (a) Wiles, C.; Watts, P. *Green Chem.* **2012**, *14*, 38; (b) Wegner, J.; Ceylan, S.; Kirschning, A. *Adv. Synth. Catal.* **2012**, *354*, 17; (c) Elvira, K. S.; i Solvas, X. C.; Wootton, R. C. R.; deMello, A. J. *Nat. Chem.* **2013**, *5*, 905; (d) Pastre, J. C.; Browne, D. L.; Ley, S. L. *Chem. Soc. Rev.* **2013**, *42*, 8849; (e) McQuade, D. T.; Seeberger, P. H. *J. Org. Chem.* **2013**, *78*, 6384; (f) Yoshida, J.; Takahashi, Y.; Nagaki, A. *Chem. Commun.* **2013**, 9896. and references cited therein.
18. Recent selected examples of noncovalent immobilization of asymmetric catalysts: (a) Yasukawa, T.; Miyamura, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2012**, *134*, 16963; (b) Tan, Y.-X.; He, Y.-P.; Zhang, J. *Chem. Mater.* **2012**, *24*, 4711; (c) Jin, R.; Liu, K.; Xia, D.; Qian, Q.; Liu, G.; Li, H. *Adv. Synth. Catal.* **2012**, *354*, 3265; (d) Li, Z.-H.; Zhou, Z.-M.; Hao, X.-Y.; Zhang, J.; Dong, Z.; Liu, Y.-Q. *Chirality* **2012**, *24*, 1092; (e) Xu, Y.; Cheng, T.; Long, J.; Liu, K.; Qian, Q.; Gao, F.; Liu, G.; Li, H. *Adv. Synth. Catal.* **2012**, *354*, 3250; (f) Miyamura, H.; Kobayashi, S. *Acc. Chem. Res.* **2014**, *47*, 1054; (g) Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 4439.