Asymmetric Heterogeneous Catalysis

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# Self-Assembling Neodymium/Sodium Heterobimetallic Asymmetric Catalyst Confined in a Carbon Nanotube Network**

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Asymmetric catalysis has established its unwavering position as the most efficient method for producing small molecules with precise control of relative and absolute configurations.[1] Intensive efforts over the last four decades have developed a number of asymmetric catalysts, allowing ready access to enantioenriched small molecules to benefit virtually all research areas using synthetic small molecules. A significant shortcoming is that almost all of the asymmetric catalysts developed to date are homogeneous catalysts, which produce their catalytic function in a uniform solution phase and only a single use is expected. Several options have been developed for recycling asymmetric catalysts,[2] but additional time-, energy-, and material-intensive processes are required for these methods. Immobilization of asymmetric catalysts on a solid support to produce a heterogeneous catalyst would enable expeditious reuse by simple filtration and obviate the above problems. However, the development of such catalysts that exhibit both promotion of the specific reaction and a high level of stereochemical control has been an elusive task. In marked contrast to the widespread usage of achiral heterogeneous catalysts,[3] asymmetric versions of heterogeneous catalysts require the construction of an asymmetric environment on a solid support and producing a reusable and practical asymmetric catalyst is a formidable challenge.[4,5] Herein, we report the development of a self-assembling Nd/Na bimetallic asymmetric catalyst confined in an entangled multiwalled carbon nanotube (MWNT) network.[6] This catalyst achieves higher catalytic efficiency and allows reuse of the catalyst by facile filtration. This exquisite catalytic system culminated in application to a concise enantioselective synthesis of anacetrapib, a promising drug candidate for hypercholesterolemia.

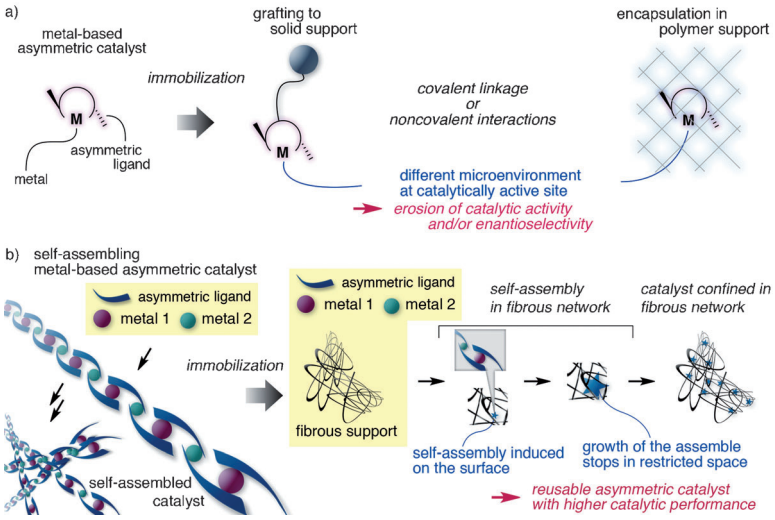


***Figure 1.*** Immobilization of a metal-based asymmetric catalyst. a) Conventional method of immobilization by grafting through a covalent bond or encapsulation in a polymer support. b) Strategic confinement of a self-assembling asymmetric catalyst supported by a solid fibrous network.

Figure 1 shows the construction of a heterogeneous, reusable asymmetric metal-based catalyst. Such catalysts provide function and stereocontrol only when an asymmetric ligand and metal cations are located at the optimum positions. In contrast to commonly used achiral heterogeneous catalysts that hold catalytically active metallic particles and simple achiral organic functional groups, an asymmetric microenvironment adorned with asymmetric organic molecules is essential for asymmetric catalysts. Grafting the asymmetric ligand onto a solid support through covalent linkages or noncovalent interactions occasionally suffers from erosion of catalytic activity, stereoselectivity, or both (Figure 1a). This is presumably because of incomplete metal complex formation and interference of the solid support in the catalysis. To circumvent these undesirable issues, we designed a metal-based heterogeneous catalyst that takes advantage of the interplay between self-assembly of a metal complex and adsorption onto a solid support (Figure 1b). The self-assembly process firmly constructs the requisite asymmetric microenvironment for catalysis with high fidelity to preserve the catalytic performance.[7] We hypothesized that the progression of self-assembly in a catalytically inert and nanoscopic fibrous solid support would render the self-assembled catalyst entangled and caged at a certain degree of assembled cluster size.[8] This approach offers an ingenious method to immobi-

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lize the asymmetric catalyst, because self-assembly guarantees the production of a catalytically active surface to produce the required catalytic functions. Furthermore, restricted growth of the self-assembly in a fibrous network would lead to the formation of smaller, confined catalyst clusters with greater specific surface area, which would exhibit higher catalytic turnover. The catalyst would also be reusable.

On the basis of this strategy, we envisaged developing a reusable heterogeneous asymmetric catalyst utilizing the self-assembling Nd/Na heterobimetallic asymmetric catalyst that we had developed for the *anti*-selective catalytic asymmetric nitroaldol reaction (Figure 2).[9,10] Obtaining *anti*

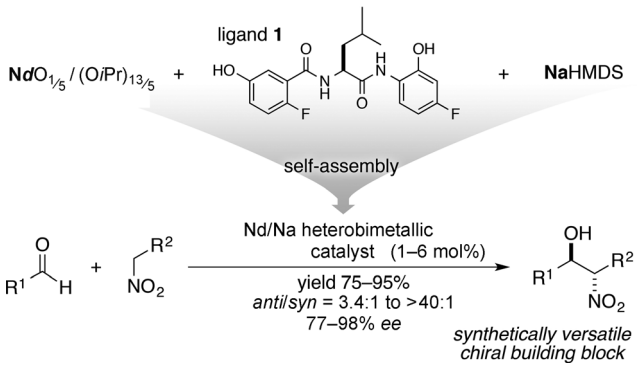



***Figure 2.*** Asymmetric nitroaldol reaction promoted by an *anti*-selective catalytic self-assembling Nd/Na heterobimetallic catalyst.

diastereoselectivity in the nitroaldol reaction has been a longstanding problem,[11] and to date, only a few catalysts have been reported to produce *anti*-1,2-nitroalkanols with high levels of stereoselectivity.[12,13] In 2009, we reported a unique self-assembling Nd/Na heterobimetallic catalyst that exhibited high catalytic efficiency and stereoselectivity, as well as broad substrate generality.[14] The first advantage of the catalyst is its utility in organic synthesis: the nitroaldol product could be readily converted into a synthetically versatile vicinal amino alcohol and exploited in a de novo enantioselective synthesis of the anti-influenza drug zanamivir.[15] Another advantage is its intrinsic self-assembling character. The catalyst is a heterobimetallic assembly composed of asymmetric ligand **1**, $Nd^{3+}$, and $Na^{+}$, which was characterized by high-resolution mass spectrometry (HRMS), inductively coupled plasma atomic emission spectrometry (ICP-MS), and X-ray fluorescence (XRF) to reveal a repetitive pattern of {**1**/Nd/$Na_2$} units.[14b] Although the self-assembled catalyst was used as an insoluble powder and the reaction proceeded in a heterogeneous suspension, recovery of the finely powdered catalyst after the reaction was not a straightforward operation and the catalyst itself did not tolerate the recovery procedure.[16]

By exploiting the unique self-assembly property of the **1**/Nd/Na heterobimetallic catalyst, we further explored confinement of the catalyst clusters through self-assembly based on the strategy outlined in Figure 1b. We focused on the use of carbon nanotubes (CNTs) as a suitable solid support because of their inertness to chemical reactions, their poor solubility in organic solvents, the entangling fibrous network, and the high specific surface area. CNTs have attracted sustained attention as a solid support for achiral catalysts, which are dispersed in the inside channels of the CNTs or adsorbed onto their outer surfaces.[17] However, preparation of CNT-supported catalysts often requires tedious procedures, such as chemical manipulation of the CNTs and formation of covalent linkages, and the development of asymmetric catalysts using the CNTs is still in its infancy.[18] In exploring our confinement strategy, we identified a MWNT called Baytubes C70P, which features a high length-to-diameter ratio (outer mean diameter ca. 13 nm, length $>1$ μm), as the most promising solid support for our purpose (the screening of CNTs is presented in the Supporting Information). Confinement of the catalyst is outlined in Figure 3. In the absence of a solid support, self-assembling asymmetric catalyst was prepared by mixing ligand **1** with $NdO_{1/5}(OiPr)_{13/5}$ and $Na[N(SiMe_3)_2]$ in a molar ratio of 2:1:2 (Figure 3a). The resulting white suspension was turned into a clear solution by adding $EtNO_2$ (**2a**) and the subsequent self-assembly of the heterobimetallic catalyst progressed gradually to afford a white suspension in 2 h. Centrifugation and washing delivered the powdered catalyst

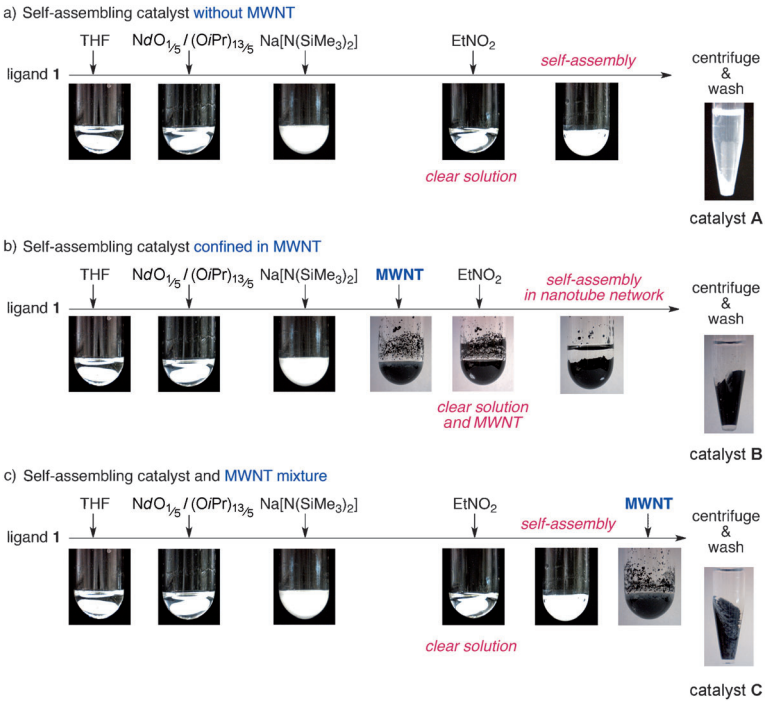
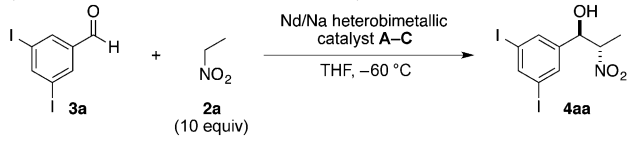



***Figure 3.*** Schematic diagram of the preparation procedure of a self-assembling Nd/Na heterobimetallic catalyst. The white matter in the initial THF solution is a magnetic stirbar. a) Catalyst preparation without MWNT to afford self-assembled powdered catalyst. b) Self-assembled catalyst confined in MWNT. c) A control catalyst prepared by adding MWNT after self-assembly of the Nd/Na heterobimetallic catalyst.

(catalyst **A**). Figure 3b shows the attempted preparation of MWNT-confined catalyst. By introducing MWNT (100 wt% relative to **1**) into the mixture of **1**/ $NdO_{1/5}(OiPr)_{13/5}$/Na[N-$(SiMe_3)_2$] before adding **2a**, self-assembly of the heterobimetallic catalyst was initiated in the presence of MWNT. During 2 h of stirring at room temperature, white precipitates did not appear and a uniform black material that contained the heterobimetallic catalyst was obtained after centrifugation and washing (catalyst **B**). Addition of MWNT (100 wt% relative to **1**) after self-assembly of the Nd/Na heterobimetallic catalyst produced a non-uniform mottled black and white mixture of powdered catalyst and MWNT (catalyst **C**). These three catalysts were evaluated in the *anti*-selective catalytic asymmetric nitroaldol reaction of 3,5-diiodobenzaldehyde (**3a**) and **2a** (Table 1); the reaction product **4aa** can

***Table 1:*** *anti*-Selective catalytic asymmetric nitroaldol reaction promoted by self-assembled heterobimetallic catalysts A–C.




| Entry | Catalyst (mol%) | *t* [h] | Yield[a] [%] | *anti*/*syn*[a] | *ee* [%][a,b] |
|---|---|---|---|---|---|
| 1 | **A** (3) | 1 | 98 | 98:2 | 99 |
| 2 | **A** (1) | 4 | 8 | 97:3 | 98 |
| 3 | **A** (1) | 20 | 24 | 98:2 | 98 |
| 4 | **B** (1) | 20 | 99 | 98:2 | 99 |
| 5 | **C** (1) | 22 | 32 | 94:6 | 92 |
| 6 | **B** (0.5) | 64 | 87 | 96:4 | 95 |
| 7 | **B** (0.5)[c] | 64 | 98 | 96:4 | 95 |

[a] Determined by HPLC analysis on a chiral stationary phase. [b] Enantiomeric excess of the *anti* diastereomer. [c] 200 wt% of MWNT relative to **1** was used for catalyst preparation.

be applied to an enantioselective synthesis of anacetrapib (see below). As shown in entry 1, catalyst **A** completed the reaction within 1 h at −60 °C with a catalyst loading of 3 mol%, affording the corresponding product **4aa** in 98% yield with nearly perfect stereoselectivity. However, lowering the catalyst loading significantly reduced the yield, affording only 24% of **4aa**, even after 20 h, although the high stereoselectivity was maintained (entries 2 and 3). On the other hand, catalyst **B**, in which the self-assembled catalyst was confined in MWNT, exhibited higher catalytic efficiency and the reaction completed even with 1 mol% of catalyst loading (entry 4). The reaction profile in the initial stage of the reaction revealed enhanced catalytic turnover of catalyst **B** versus catalyst **A** (Figure 4). In marked contrast, catalyst **C**, a mixture of self-assembled powdered catalyst and MWNT, showed reactivity comparable with catalyst **A**, indicating that the catalytically active species in catalyst **C** is virtually identical to that of catalyst **A**, and that the MWNT itself had little beneficial effect in promoting the reaction (entry 5). The catalytic performance of the MWNT-confined catalyst **B** was further enhanced with more MWNTs (200 wt% relative to **1**) and this catalyst completed the

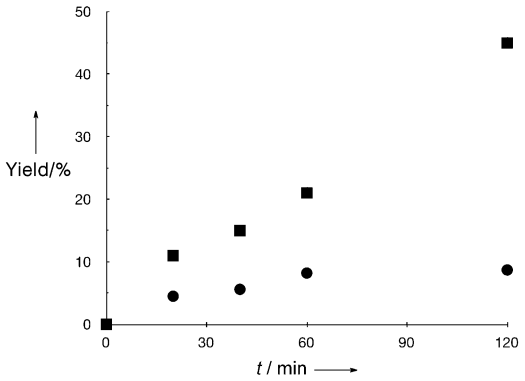



***Figure 4.*** Profile of the initial stage of the reaction with a 1 mol% catalyst loading. Catalyst **A** (●), catalyst **B** (■). Data shown is the average of three runs for catalyst **A**.

reaction with as little as 0.5 mol% of catalyst loading (entries 6, 7).

To probe this enhancement of the catalytic efficiency of MWNT-confined catalyst **B**, we dissected catalysts A–C by scanning transmission electron microscopy (STEM). The size of the clusters of catalyst **A** (without MWNT) ranges from approximately 50 nm to >1 μm (Figure 5a). Energy-dispersive X-ray spectrometry (EDS) analysis confirmed that each

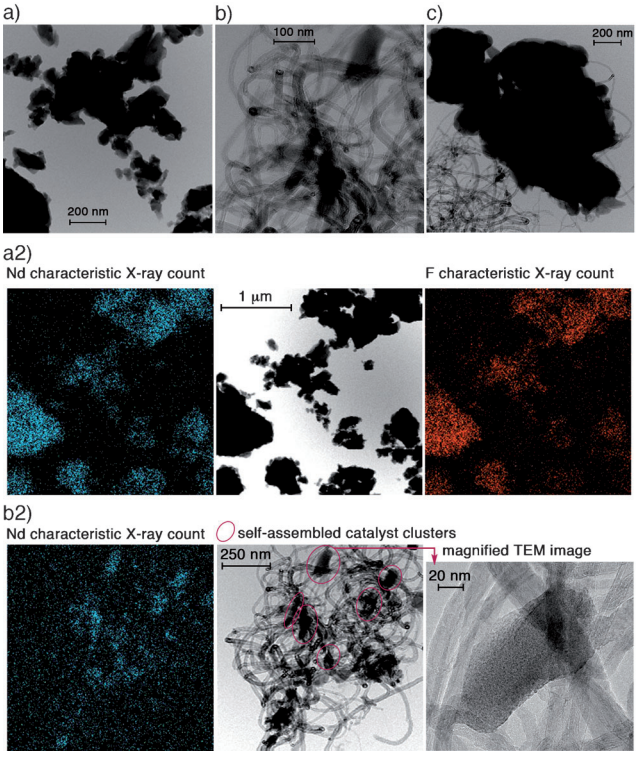
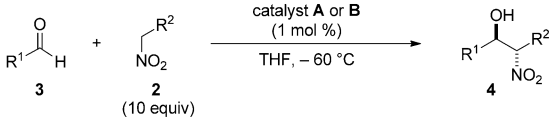



***Figure 5.*** a) STEM image of catalyst **A**. a2) EDS mapping analysis of catalyst **A** for Nd and F detection. b) STEM image of catalyst **B**. b2) EDS mapping analysis of catalyst **B** for Nd detection. The black images in red circles are the catalyst clusters confined in the MWNT network. The magnified image was recorded in TEM mode. c) STEM image of catalyst **C**. The catalyst was not confined in the MWNT network and self-assembly formed large catalyst particles.

cluster contains fluorine derived from **1** and neodymium, which indicates that the self-assembled metal complex was uniformly formed (Figure 5a2). The energy of the characteristic X-ray of Na ($K_\alpha$ = 0.978 keV) is close to that of Nd ($M_\alpha$ = 1.041 keV) and not traceable; however, HRMS, ICP-AES, and XRF analysis proved the presence of Na in these clusters.[14b] On the other hand, the MWNT-confined catalyst **B** contained significantly smaller catalyst clusters, which ranged from 20 to 200 nm in size, confined in the fibrous network of MWNT (Figure 5b). This is presumably because the outer shell of the MWNT-induced self-assembly of the Nd/Na heterobimetallic catalyst and the growth of the assembly were restricted by the tight spaces in the fibrous network. The formation of tiny clusters increased the surface area of catalytically active sites of the catalyst, eliciting higher catalytic efficiency. EDS analysis of catalyst **B** confirmed that each cluster contained Nd (Figure 5b2). Catalyst **C**, prepared by adding MWNT after self-assembly of the Nd/Na heterobimetallic catalyst, was an individual mixture of MWNT and well-grown self-assembled catalyst in the STEM image, which conforms with the actual catalytic performance (Figure 5c).

The MWNT-confined catalyst could be readily separated from the reaction mixture through simple filtration, which allowed for repetitive use (Figure 6). With a catalyst loading of 3 mol%, the nitroaldol reaction was run in a test tube equipped with a sintered glass filter at −60 °C with gentle shaking (ca. 240 rpm). After the consumption of 3,5-diiodobenzaldehyde (**3a**), the reaction mixture was drained through the filter and the remaining catalyst on the filter was rinsed with dry THF to wash out the reaction mixture. The nitroaldol reaction promoted by the catalyst achieved virtually complete conversion, and simple evaporation of the volatiles (solvent THF and excess **2a**) afforded the analytically pure product **4aa** in a highly stereoselective manner. The filtered catalyst could be reused six times.[19] The higher catalytic efficiency of the confined catalyst was observed with other substrate sets, verifying the general utility of the confined catalyst in the *anti*-selective catalytic asymmetric nitroaldol reaction (Table 2).

***Table 2:*** Difference in catalytic efficiencies of catalysts **A** and **B** with other substrates.

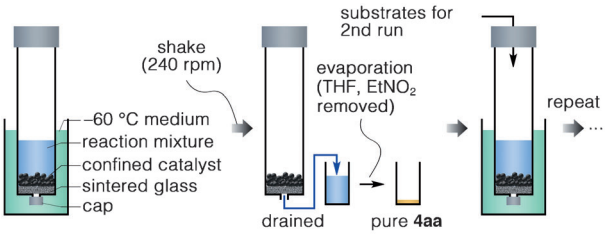



| Entry | $R^1$ | 3 | $R^2$ | 2 | Cat. | Product | *t* [h] | Yield [%] | *anti*/*syn*[a] | *ee* [%][a,b] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 3,5-$I_2$-$C_6H_3$ | **3a** | Et | **2b** | **A** | **4ab** | 20 | 24 | 70:30 | 74 |
| 2 | 3,5-$I_2$-$C_6H_3$ | **3a** | Et | **2b** | **B**[c] | **4ab** | 24 | 94 | 86:14 | 93 |
| 3 | 3,5-$I_2$-$C_6H_3$ | **3a** | $BnOCH_2$ | **2c** | **A** | **4ac** | 40 | 71 | 81:19 | 84 |
| 4 | 3,5-$I_2$-$C_6H_3$ | **3a** | $BnOCH_2$ | **2c** | **B**[c] | **4ac** | 20 | 72 | 83:17 | 89 |
| 5 | $PhCH_2CH_2$ | **3b** | Me | **2a** | **A** | **4ba** | 88 | 5 | 79:21 | 81 |
| 6 | $PhCH_2CH_2$ | **3b** | Me | **2a** | **B**[c] | **4ba** | 40 | 69 | 89:11 | 87 |
| 7 | $CH_3(CH_2)_7$ | **3c** | Me | **2a** | **A** | **4ca** | 88 | 6 | 73:27 | 83 |
| 8 | $CH_3(CH_2)_7$ | **3c** | Me | **2a** | **B**[c] | **4ca** | 40 | 52 | 84:16 | 89 |

[a] Determined by HPLC analysis on a chiral stationary phase. [b] Enantiomeric excess of the *anti* diastereomer. [c] 200 wt% of MWNT relative to **1** was used for catalyst preparation.

The synthetic utility of our reusable asymmetric catalyst is exemplified in a concise enantioselective synthesis of anacetrapib. Atherosclerosis is a major health concern throughout the world and therapeutics that decrease the risk of arteriosclerotic vascular diseases are of sustained interest. Along with drug developments based on decreasing blood low-density lipoprotein (LDL) levels, an increase in high-density lipoprotein (HDL) levels has received growing attention as a new alternative approach. Cholesteryl ester transfer protein (CETP) is a viable target because it helps in recycling HDL into undesirable LDL.[20] Anacetrapib, identified by Merck as a potent CETP inhibitor and under clinical trial for the treatment of hypercholesterolemia (Phase III), displays a good safety profile and the absence of off-target effects, and its *anti*-1,2-amino alcohol unit embedded in an oxazolidinone ring drew our particular attention.[21] Enantiomerically pure **4aa** obtained by the present method was transformed into the requisite oxazolidinone **5** (Scheme 1). A nitro group was reduced with Zn in HCl/cyclopentyl methyl ether and subsequent treatment with triphosgene gave **5**. Two $CF_3$ groups were installed by CuCl/1,10-phenanthroline/$TMSCF_3$ to afford **6** in 78% yield.[22] The biaryl portion, **7**, was synthesized by following the reported procedure and coupled with **6** to furnish anacetrapib.[23]

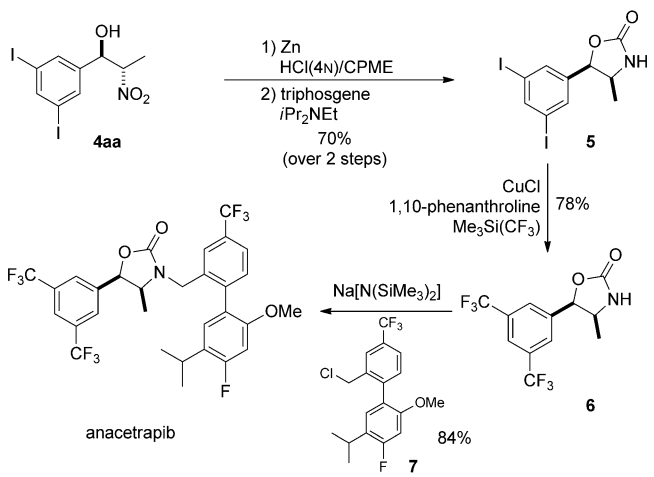
In summary, we have devised the strategic confinement of a self-assembling Nd/Na heterobimetallic catalyst in MWNT networks. Confinement was achieved through self-assembly by a simple operation and the confined catalyst exhibited higher catalytic efficiency than the unconfined catalyst. The potential for repetitive use offers a clear practical advantage.




**3a** + **2a** (10 equiv) → **4aa**: MWNT-confined catalyst **B** (3 mol %), THF, –60 °C

| Run | *t* [h] | Yield [%] | *anti*/*syn* | *ee* [%] |
|---|---|---|---|---|
| 1 | 1 | 90 | 97:3 | 99 |
| 2 | 1 | 95 | 98:2 | 99 |
| 3 | 1 | 92 | 97:3 | 99 |
| 4 | 3 | 87 | 98:2 | 99 |
| 5 | 3 | 85 | 98:2 | 99 |
| 6 | 5 | 83 | 97:3 | 98 |
| 7 | 16 | 58 | 98:2 | 99 |

***Figure 6.*** Reuse of the MWNT-confined catalyst.




***Scheme 1.*** Enantioselective synthesis of anacetrapib. CPME = cyclopentyl methyl ether, DMF = *N*,*N*-dimethylformamide.

The synthetic utility of the catalyst was demonstrated by a concise enantioselective synthesis of anacetrapib.

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[1] a) *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed.: I. Ojima), Wiley-VCH, New York, **2000**; b) *Asymmetric Catalysis on Industrial Scale* (Eds.: H. U. Blaser, E. Schmidt), Wiley-VCH, Weinheim, **2004**; c) P. J. Walsh, M. C. Kozlowski, *Fundamentals of Asymmetric Catalysis*, University Science Books, Sausalito, **2009**; d) E. J. Corey, L. Kürti, *Enantioselective Chemical Synthesis*, Direct Book Publishing, Dallas, **2010**.

[2] For reviews on asymmetric heterogeneous catalysis, see: a) J. M. Thomas, R. Raja, D. W. Lewis, *Angew. Chem.* **2005**, *117*, 6614; *Angew. Chem. Int. Ed.* **2005**, *44*, 6456; b) M. Heitbaum, F. Glorius, I. Escher, *Angew. Chem.* **2006**, *118*, 4850; *Angew. Chem. Int. Ed.* **2006**, *45*, 4732; c) C. Baleizão, H. Garcia, *Chem. Rev.* **2006**, *106*, 3987; d) T. Mallat, E. Orglmeister, A. Baiker, *Chem. Rev.* **2007**, *107*, 4863; e) *Handbook of Asymmetric Heterogeneous Catalysis* (Eds.: K. Ding, Y. Uozumi), Wiley-VCH, Weinheim, **2008**; f) Z. Wang, G. Chen, K. Ding, *Chem. Rev.* **2009**, *109*, 322.

[3] a) *Handbook of Heterogeneous Catalysis, 2nd ed.* (Eds.: G. Ertl, H. Knözinger, F. Schüth, J. Weitkamp), Wiley-VCH, Weinheim, **2008**; b) *Modeling and Simulation of Heterogeneous Catalytic Reactions* (Ed.: O. Deutschmann), Wiley-VCH, Weinheim, **2011**.

[4] For a review on facile non-covalent immobilization of asymmetric catalysts, see: J. M. Fraile, J. I. García, J. A. Mayoral, *Chem. Rev.* **2009**, *109*, 360.

[5] For recent examples of non-covalent immobilization of asymmetric catalysts, see: a) T. Yasukawa, H. Miyamura, S. Kobayashi, *J. Am. Chem. Soc.* **2012**, *134*, 16963; b) Y.-X. Tan, Y.-P. He, J. Zhang, *Chem. Mater.* **2012**, *24*, 4711; c) R. Jin, K. Liu, D. Xia, Q. Qian, G. Liu, H. Li, *Adv. Synth. Catal.* **2012**, *354*, 3265; d) Z.-H. Li, Z.-M. Zhou, X.-Y. Hao, J. Zhang, Z. Dong, Y.-Q. Liu, *Chirality* **2012**, *24*, 1092; e) Y. Xu. , T. Cheng, J. Long, K. Liu, Q. Qian, F. Gao, G. Liu, H. Li, *Adv. Synth. Catal.* **2012**, *354*, 3250.

[6] S. Iijima, *Nature* **1991**, *354*, 56.

[7] For reviews, see: a) G. M. Whitesides, J. P. Mathias, C. T. Seto, *Science* **1991**, *254*, 1312; b) J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, Wiley-VCH, Weinheim, **1995**; c) J.-M. Lehn, *Science* **2002**, *295*, 2400; d) G. M. Whitesides, B. Grzybowski, *Science* **2002**, *295*, 2418; e) R. Chakrabarty, P. Mukherjee, P. Stang, *Chem. Rev.* **2011**, *111*, 6810.

[8] a) S. Akabori, S. Sakurai, Y. Izumi, Y. Fujii, *Nature* **1956**, *178*, 323; b) A. Akamatsu, Y. Izumi, S. Akabori, *Bull. Chem. Soc. Jpn.* **1961**, *35*, 1706; T. Ikawa, H. Sajiki, K. Hirota, *Tetrahedron* **2005**, *61*, 2217.

[9] L. Henry, *C. R. Hebd. Seances Acad. Sci.* **1895**, *120*, 1265.

[10] For recent reviews, see: a) M. Shibasaki, H. Gröger in *Comprehensive Asymmetric Catalysis, Vol. III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 1075 – 1090; b) F. A. Luzzio, *Tetrahedron* **2001**, *57*, 915; c) C. Palomo, M. Oiarbide, A. Mielgo, *Angew. Chem.* **2004**, *116*, 5558; *Angew. Chem. Int. Ed.* **2004**, *43*, 5442; d) M. Shibasaki, H. Gröger, M. Kanai in *Comprehensive Asymmetric Catalysis, Supplement 1* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **2004**, pp. 131 – 133; e) J. Boruwa, N. Gogoi, P. P. Saikia, N. C. Barua, *Tetrahedron: Asymmetry* **2006**, *17*, 3315; f) C. Palomo, M. Oiarbide, A. Laso, *Eur. J. Org. Chem.* **2007**, 2561; g) S. E. Milner, T. S. Moody, A. R. Maguire, *Eur. J. Org. Chem.* **2012**, 3059.

[11] For selected examples of *syn*-selective catalytic asymmetric nitroaldol reactions, see: a) H. Sasai, T. Tokunaga, S. Watanabe, T. Suzuki, N. Itoh, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 7388; b) Y. Sohtome, Y. Hashimoto, K. Nagasawa, *Eur. J. Org. Chem.* **2006**, 2894; c) T. Arai, M. Watanabe, A. Yanagisawa, *Org. Lett.* **2007**, *9*, 3595; d) Y. Sohtome, N. Takemura, K. Takada, R. Takagi, T. Iguchi, K. Nagasawa, *Chem. Asian J.* **2007**, *2*, 1150; e) T. Arai, R. Takashita, Y. Endo, M. Watanabe, A. Yanagisawa, *J. Org. Chem.* **2008**, *73*, 4903; for partially successful examples of *syn*-selective catalytic asymmetric nitroaldol reactions, see: f) J. Yoshimoto, C. A. Sandoval, S. Saito, *Chem. Lett.* **2008**, *37*, 1294; g) H. Y. Kim, K. Oh, *Org. Lett.* **2009**, *11*, 5682.

[12] For examples of *anti*-selective catalytic asymmetric Nitroaldol reactions, see: a) D. Uraguchi, S. Sakaki, T. Ooi, *J. Am. Chem. Soc.* **2007**, *129*, 12392; b) S. Handa, K. Nagawa, Y. Sohtome, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2008**, *120*, 3274; *Angew. Chem. Int. Ed.* **2008**, *47*, 3230; c) D. Uraguchi, S. Nakamura, T. Ooi, *Angew. Chem.* **2010**, *122*, 7724; *Angew. Chem. Int. Ed.* **2010**, *49*, 7562; d) K. Lang, J. Park, S. Hong, *Angew. Chem.* **2012**, *124*, 1652; *Angew. Chem. Int. Ed.* **2012**, *51*, 1620; e) K. Xu, G. Lai, Z. Zha, S. Pan, H. Chen, Z. Wang, *Chem. Eur. J.* **2012**, *18*, 12357.

[13] For partially successful examples of *anti*-selective catalytic asymmetric nitroaldol reaction, see: a) G. Blay, L. R. Domingo, V. Hernández-Olmos, J. R. Pedro, *Chem. Eur. J.* **2008**, *14*, 4725; b) H. Ube, M. Terada, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3895; c) A. Noole, K. Lippur, A. Metsala, M. Lopp, T. Kanger, *J. Org. Chem.* **2010**, *75*, 1313; d) G. Blay, V. Hernández-Olmos, J. R. Pedro, *Org. Lett.* **2010**, *12*, 3058; e) L. Yao, Y. Wei, P. Wang, W. He, S. Zhang, *Tetrahedron* **2012**, *68*, 9119; for *anti*-selective nitroaldol reaction of benzaldehyde catalyzed by hydroxynitrile lyase, see: f) T. Purkarthofer, K. Gruber, M. Gruber-Khadjawi, K. Waich, W. Skranc, D. Mink, H. Griengl, *Angew. Chem.* **2006**, *118*, 3532; *Angew. Chem. Int. Ed.* **2006**, *45*, 3454; g) M. Gruber-Khadjawi, T. Purkarthofer, W. Skranc, H. Griengl, *Adv. Synth. Catal.* **2007**, *349*, 1445.

[14] a) T. Nitabaru, N. Kumagai, M. Shibasaki, *Tetrahedron Lett.* **2008**, *49*, 272; b) T. Nitabaru, A. Nojiri, M. Kobayashi, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 13860.

[15] T. Nitabaru, N. Kumagai, M. Shibasaki, *Angew. Chem.* **2012**, *124*, 1676; *Angew. Chem. Int. Ed.* **2012**, *51*, 1644.

[16] The finely powdered catalyst is tiny in particle size and hardly collected by normal sintered-glass filters. Complete separation

  

of the catalyst at low temperature is essential to obtain the product with high stereoselectivity, because raising the temperature in the presence of the catalyst significantly promotes a retro-nitroaldol reaction, diminishing the stereoselectivity.

[17] a) J. M. Planeix et al., *J. Am. Chem. Soc.* **1994**, *116*, 7935; b) G. L. Bezemer, U. Falke, A. J. van Dillen, K. P. de Jong, *Chem. Commun.* **2005**, 731; c) P. Serp, M. Corrias, P. Kalck, *Appl. Catal. A* **2003**, *253*, 337; d) X. Pan, X. Bao, *Chem. Commun.* **2008**, 6271.

[18] Z. Chen, Z. Guan, M. Li, Q. Yang, C. Li, *Angew. Chem.* **2011**, *123*, 5015; *Angew. Chem. Int. Ed.* **2011**, *50*, 4913.

[19] MWNTs were mechanically fractured by shaking the test tube after 3–4 runs, and small amount of the fractured MWNTs passed through the sintered glass filter, which can be ascribed to the gradual extension of reaction time. Implementation of the MWNT-confined catalyst in a continuous flow reaction system to avoid the above problem is currently underway.

[20] a) A. R. Tall, X. Jiang, Y. Luo, D. Silver, *Arterioscler. Thromb. Vasc. Biol.* **2000**, *20*, 1185; b) A. Thompson, E. Di Angelantonio, N. Sarwar, S. Erqou, D. Saleheen, R. P. Dullaart, B. Keavney, Z. Ye, J. Danesh, *JAMA J. Am. Med. Assoc.* **2008**, *299*, 2777.

[21] a) C. J. Smith, A. Ali, M. L. Hammond, H. Li, Z. Lu, J. Napolitano, G. E. Taylor, C. F. Thompson, M. S. Anderson, Y. Chen, S. S. Eveland, Q. Guo, S. A. Hyland, D. P. Milot, C. P. Sparrow, S. D. Wright, A.-M. Cumiskey, M. Latham, L. B. Peterson, R. Rosa, J. V. Pivnichny, X. Tong, S. S. Xu, P. J. Sinclair, *J. Med. Chem.* **2011**, *54*, 4880; b) D. E. Gutstein, R. Krishna, D. Johns, H. K. Surks, H. M. Dansky, S. Shah, Y. B. Mitchel, J. Arena, J. A. Wagner, *Clin. Pharmacol. Ther.* **2012**, *91*, 109.

[22] H. Morimoto, T. Tsubogo, N. D. Litvinas, J. F. Hartwig, *Angew. Chem.* **2011**, *123*, 3877; *Angew. Chem. Int. Ed.* **2011**, *50*, 3793.

[23] S. G. Ouellet, A. Roy, C. Molinaro, R. Angelaud, J.-F. Marcoux, P. D. O'Shea, I. W. Davies, *J. Org. Chem.* **2011**, *76*, 1436.

  