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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.

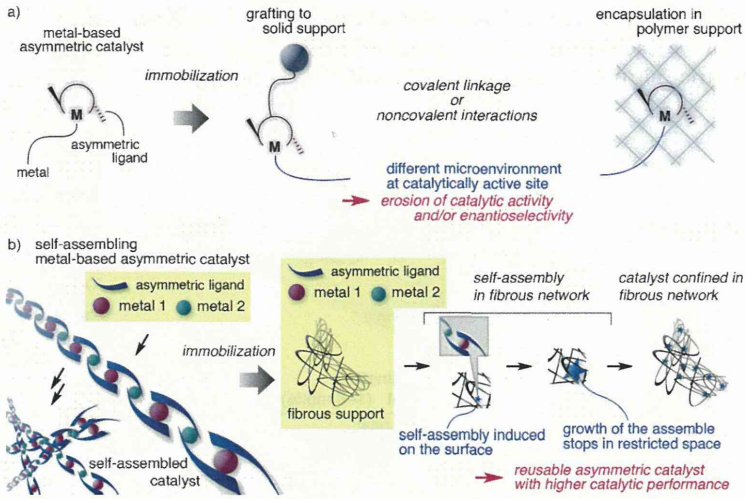

Figure 1. Immobilization of a metal-based asymmetric catalyst. a) Conventional method of immobilization by grafting through a covalent bond or encapsulation in a polymer support. b) Strategic confinement of a self-assembling asymmetric catalyst supported by a solid fibrous network.

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 1 a). 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 1 b). 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*

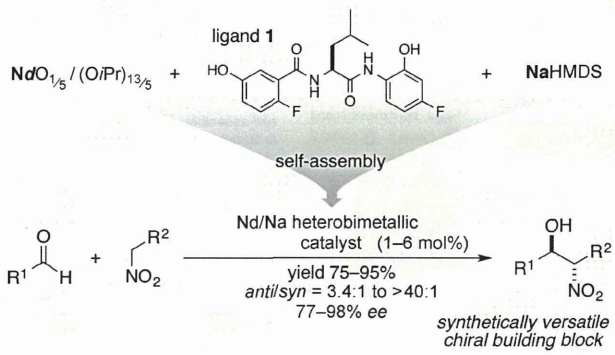


Figure 2. Asymmetric nitroaldol reaction promoted by an *anti*-selective catalytic self-assembling Nd/Na heterobimetallic catalyst.

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

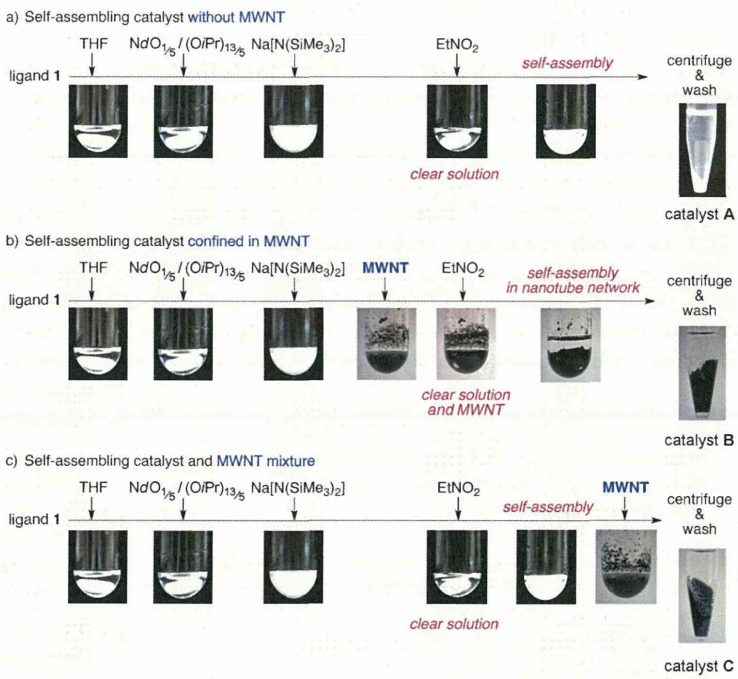


Figure 3. Schematic diagram of the preparation procedure of a self-assembling Nd/Na heterobimetallic catalyst. The white matter in the initial THF solution is a magnetic stirbar. a) Catalyst preparation without MWNT to afford self-assembled powdered catalyst. b) Self-assembled catalyst confined in MWNT.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

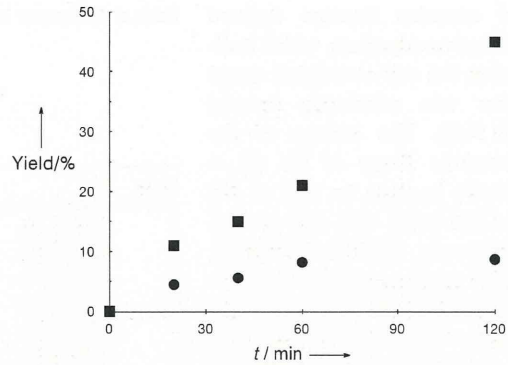
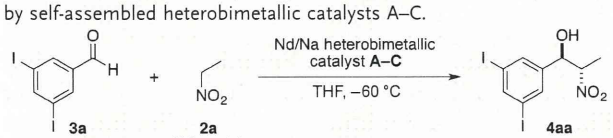


Figure 4. Profile of the initial stage of the reaction with a 1 mol% catalyst loading. Catalyst **A** (●), catalyst **B** (■). Data shown is the average of three runs for catalyst **A**.

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 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

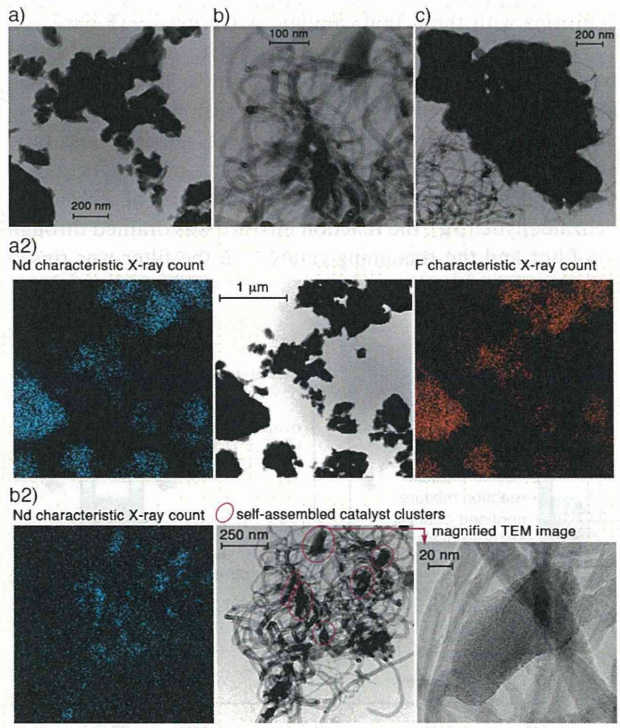
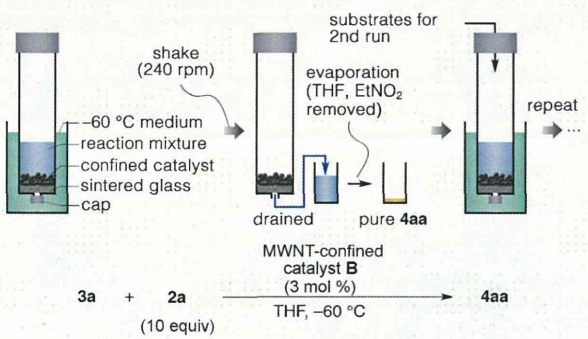


Figure 5. a) STEM image of catalyst **A**. a2) EDS mapping analysis of catalyst **A** for Nd and F detection. b) STEM image of catalyst **B**. b2) EDS mapping analysis of catalyst **B** for Nd detection. The black images in red circles are the catalyst clusters confined in the MWNT network. The magnified 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_α = 0.978 keV) is close to that of Nd (M_α = 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).

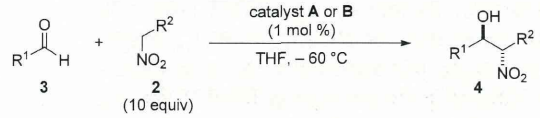
The MWNT-confined catalyst could be readily separated from the reaction mixture through simple filtration, which allowed for repetitive use (Figure 6). With a catalyst loading of 3 mol%, the nitroaldol reaction was run in a test tube equipped with a sintered glass filter at −60 °C with gentle shaking (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).



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.

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

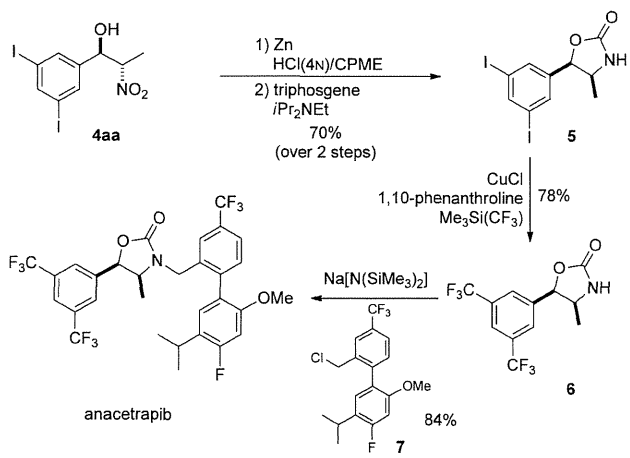


Entry	R^1	3	R^2	2	Cat.	Product	t [h]	Yield [%]	anti/syn[a]	ee [%][a,b]
1	3,5-I_2-C_6H_3	**3a**	Et	**2b**	**A**	**4ab**	20	24	70:30	74
2	3,5-I_2-C_6H_3	**3a**	Et	**2b**	**B**[c]	**4ab**	24	94	86:14	93
3	3,5-I_2-C_6H_3	**3a**	$BnOCH_2$	**2c**	**A**	**4ac**	40	71	81:19	84
4	3,5-I_2-C_6H_3	**3a**	$BnOCH_2$	**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.



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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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.

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A Modified Preparation Procedure for Carbon Nanotube-Confined Nd/Na Heterobimetallic Catalyst for *anti*-Selective Catalytic Asymmetric Nitroaldol Reactions

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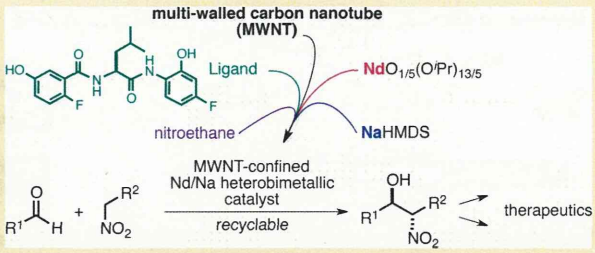
Supporting Information

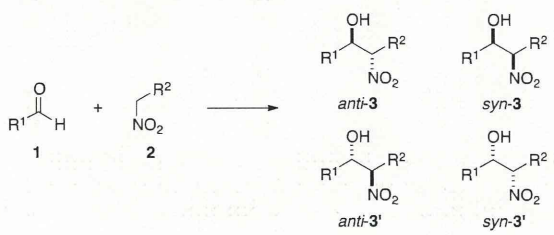
ABSTRACT: A recyclable asymmetric metal-based catalyst is a rare entity among the vast collection of asymmetric catalysts developed so far. Recently we found that the combination of a self-assembling metal-based asymmetric catalyst and multi-walled carbon nanotubes (MWNTs) produced a highly active and recyclable catalyst in which the catalytically active metal complex was dispersed in the MWNT network. Herein we describe an improved preparation procedure and full details of a Nd/Na heterobimetallic complex confined in MWNTs. Facilitated self-assembly of the catalyst with MWNTs avoided the sacrificial use of excess chiral ligand for the formation of the heterobimetallic complex, improving the loading ratio of the catalyst components. Eighty-five percent of the catalyst components were incorporated onto MWNTs to produce the confined catalyst, which was a highly efficient and recyclable catalyst for the *anti*-selective asymmetric nitroaldol reaction. The requisite precautions for the catalyst preparation to elicit reproducible catalytic performance are summarized. Superior catalytic profiles over the prototype catalyst without MWNTs were revealed in the synthesis of optically active 1,2-nitroalkanols, which are key intermediates for the synthesis of therapeutics.



INTRODUCTION

The nitroaldol reaction is widely used as a C−C bond-forming reaction and is particularly useful for the construction of carbon frameworks bearing oxygen and nitrogen functionalities in adjacent positions (Scheme 1).[1] Despite its early discovery in the 19th century,[2] the precise control of diastereo- and enantioselectivity in the catalytic nitroaldol reaction has been elusive until recently. We have developed an arsenal of rare earth metal-based asymmetric catalysts,[3] and La/Li,[4] Pd/La,[5] and Nd/Na[6] heterobimetallic catalysts have been developed for *syn*- and *anti*-selective catalytic asymmetric nitroaldol reactions.[7−9] Among them, Nd/Na/amide-based ligand **4** catalysts are particularly important because of their self-assembling property: mixing of the three catalyst components $NdO_{1/5}(O^iPr)_{13/5}$, NaHMDS, and amide-based ligand **4** in THF formed insoluble self-assembled particles together with nitroethane **2a**, and the isolated particles were used as heterogeneous catalysts (Figure 1a).[6b] Recently, we reported that the self-assembly in a fibrous network of multiwalled carbon nanotubes (MWNTs)[10] produced Nd/Na heterobimetallic catalysts dispersed and confined in MWNT (Figure 1b).[11−13] The MWNT-confined catalyst exhibited higher catalytic performance and allowed repetitive use. Although a

Scheme 1. Nitroaldol Reaction



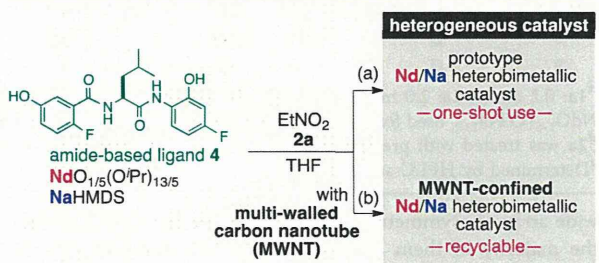


Figure 1. Nd/Na/amide-based ligand **4** heterobimetallic catalyst. (a) Isolated heterogeneous catalyst was used only once. (b) MWNT-confined catalyst allowed repetitive use.

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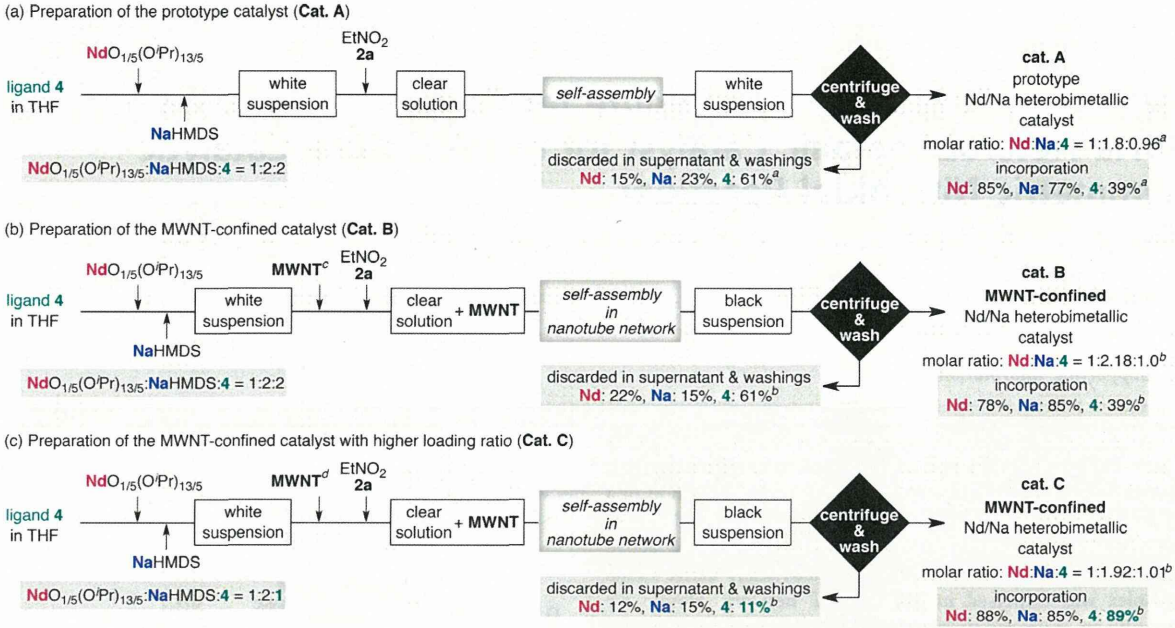
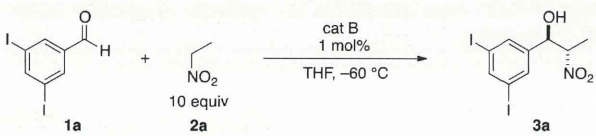
Scheme 2. Schematic Representation of Catalyst Preparation



[a]The molar ratio of Nd:Na:**4** in heterobimetallic catalysts and the loading ratio of catalyst components were determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES) and X-ray fluorescence (XRF).[6b] [b]The molar ratio of Nd:Na:**4** in the heterobimetallic catalysts and the loading ratio of catalyst components were determined by MP-AES and HPLC.[27] [c]200 wt % of MWNT relative to **4** was used. [d]400 wt % of MWNT relative to **4** was used.

Table 1. *anti*-Selective Catalytic Asymmetric Nitroaldol Reaction with MWNT-Confined Nd/Na Heterobimetallic Catalyst[a]



				pretreatment					
entry	supplier of **2a**	H_2O content of **2a**[b] (ppm)	dist.[c]	MS 3A[d]	base[e]	time (h)	yield[f] (%)	*anti*/*syn*[g]	ee[g] (%)
1	A	150	–	–	–	4	99	98/2	99
2	B	301	–	–	–	4	96	98/2	99
3	C	1965	–	–	–	8	<1	–	–
4	A	13	–	+	–	4	99	98/2	99
5	B	33	–	+	–	4	99	98/2	99
6	C	3	–	+	–	8	<1	–	–
7	C	311	+	–	–	8	<1	–	–
8	C	1423	–	–	+	4	99	99/1	99
9	C	63	–	+	+	8	95	97/3	98

[a]**1a**: 0.2 mmol, **2a**: 2.0 mmol. The same **2a** was used for catalyst preparation and as substrate. Catalyst loading is noted based on the amount of $NdO_{1/5}(O^iPr)_{13/5}$ used for catalyst preparation. [b]Determined by Karl Fischer titration. [c]Vacuum distillation for **2a** was conducted twice before use. [d]**2a** was treated with predried MS 3 Å pellets before use. [e]**2a** was treated with $NaHCO_3$ solid before use. [f]Determined by ^1H NMR analysis. [g]Determined by HPLC analysis.

wide array of asymmetric catalysts has been developed to date, the majority of them are not designed for repetitive use. In contrast to the recyclable catalysts for nonstereoselective chemical transformations,[14] recyclable asymmetric catalysts have been much less explored despite their huge practical impact.[15−17] Given the versatility of optically active 1,2-amino alcohols in the synthetic point of view,[18] the catalytic asymmetric nitroaldol reaction deserves exploration as a platform for the development of practical stereoselective transformations promoted by recyclable catalysts. In our continuing study directed toward the further sophistication of recyclable MWNT-confined heterobimetallic catalysts,[19] we encountered fluctuating reaction outcomes depending on the purity and moisture content of the reagents for catalyst preparation. Herein we describe the requisite precautions for the preparation of MWNT-confined Nd/Na heterobimetallic catalysts and an improved preparation protocol that gives a higher loading ratio onto MWNTs. The previous preparation protocol required the sacrificial use of ligand **4** to facilitate self-assembly. Our new protocol allowed us to prepare the

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heterobimetallic catalyst with stoichiometry identical to the actual complex, leading to loading ratios >85%.[20]

RESULTS AND DISCUSSION

The preparation procedure of the prototype Nd/Na heterobimetallic catalyst is outlined in Scheme 2a (Cat. **A**). $NdO_{1/5}(O^iPr)_{13/5}$ and then NaHMDS were added to a THF solution of amide-based ligand **4**, affording a white suspension.[6b] A homogeneous solution transiently developed upon the addition of nitroethane **2a** and self-assembly of the heterobimetallic catalyst was initiated within approximately 5 min, affording the catalyst as a white precipitate after centrifugation. This precipitate contained **2a** and the use of **2a** was indispensable for self-assembly of heterogeneous catalyst. By adding MWNTs before the addition of **2a**, self-assembly proceeded in the fibrous network of MWNTs to produce the MWNT-confined catalyst (Scheme 2b, Cat. **B**).[11] For operational simplicity, **2a** was used as received from the commercial suppliers. In a test reaction using 3,5-diiodobenzaldehyde **1a** and nitroethane **2a** with Cat. **B**, significantly different reaction outcomes were produced depending on the supplier of **2a** (Table 1). When **2a** from suppliers A and B was used for the catalyst preparation and as a substrate, high catalytic efficiency and stereoselectivity were observed.[21] However, the reaction with **2a** from supplier C barely proceeded under identical conditions (entries 1–3).[22] The moisture content of **2a** was analyzed for each sample and the poor reaction with **2a** from supplier C seemed to be caused by its excessively high moisture content. Therefore, **2a** from each supplier was desiccated with predried MS 3 Å pellets and these dried samples of **2a** were evaluated in the nitroaldol reaction.[23] Unexpectedly, desiccation of **2a** from each supplier made no difference in reaction outcomes (entries 4–6). HPLC analysis of the desiccated **2a** samples revealed that those from supplier C contained several unidentified impurities, which might interfere with the formation of the Nd/Na heterogeneous catalysts and/or nitroaldol reaction itself.[24] Thus, **2a** from supplier C was double distilled but still the reaction progress was negligible (entry 7). Eventually, we found that when **2a** from supplier C was pretreated with $NaHCO_3$ powder, the efficient reaction progress was observed,[25] suggesting that some acidic impurities contaminated **2a** from supplier C that could not be efficiently removed by distillation (entry 8,9). Reaction reached completion irrelevant of the treatment with MS 3 Å and the reaction with untreated **2a** exhibited a marginally higher reaction rate.

An obvious drawback of Cat. **A** and Cat. **B** was the sacrificial use of excess amounts of amide-based ligand **4**. To prepare the heterobimetallic catalyst, two molar equivalents of **4** relative to $NdO_{1/5}(O^iPr)_{13/5}$ were required, whereas quantitative elemental analysis of Cat. **A** revealed that the molar ratio of Nd:**4** in the catalyst is nearly 1:1, indicating that 61% of **4** remained uncomplexed in the supernatant (Scheme 2a).[6b,26] The 1:1 molarity of Nd and **4** in the complex led us to prepare the catalyst with a 1:1 ratio of $NdO_{1/5}(O^iPr)_{13/5}$:**4**; however, these attempts resulted in poor nucleation of the heterogeneous complex with low reproducibility.[6b] For the MWNT-confined Cat. **B**, for which preparation included the addition of MWNT 200 wt % relative to **4** under otherwise identical conditions, Nd and Na contents were determined using microwave plasma atomic emission spectroscopy (MP-AES) after complete decomposition and elution of the heterobimetallic catalyst confined in MWNT by treatment with 5% HNO_3 aq. under sonication (Scheme 2b).[27] The Nd:Na:**4** ratio of 1:2.18:1.0 and the incorporation profile of Cat. **B** were nearly identical to those of the prototype Cat. **A**. We envisioned that the MWNT surface might facilitate the nucleation of the heterobimetallic catalyst even with a 1:1 ratio of $NdO_{1/5}(O^iPr)_{13/5}$:**4**, thus significantly improving the loading ratio of **4** onto the actual heterogeneous catalyst. The performance of Cat. **C** prepared with the reduced amount of **4** (1 equiv to $NdO_{1/5}(O^iPr)_{13/5}$) under otherwise identical conditions as for Cat. **B** (Scheme 2c) was evaluated in the nitroaldol reaction of **1a** and pretreated **2a** with low catalyst loadings (0.25 mol%). As shown in Figure 2,

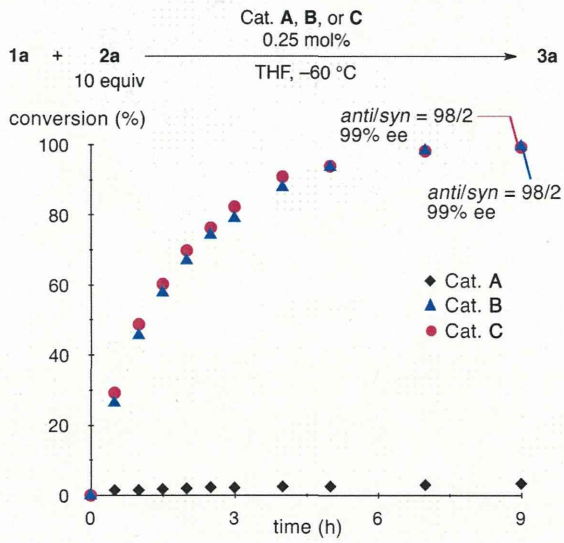

Figure 2. Reaction profile of the reaction promoted by Cat. **A**–**C**. Nitroethane **2a** (supplier A) was pretreated with MS 3 Å pellets. Conversion and diastereo- and enantioselectivity were determined by HPLC analysis. Catalyst loading is noted based on the amount of $NdO_{1/5}(O^iPr)_{13/5}$ used for catalyst preparation.

Cat. **B** and **C** exhibited nearly identical catalytic efficiency with high stereoselectivity, and the reaction rates with these MWNT-confined catalysts were much higher than those with Cat. **A**, as expected from the previous study. The quantitative analysis of Cat. **C** was in line with its catalytic performance; the incorporated amounts of Nd, Na, and **4** were nearly identical for Cat. **B** and **C**, and 89% of **4** was incorporated to constitute the heterobimetallic complex in Cat. **C**. The Nd:Na:**4** ratio for Cat. **A**, **B**, and **C** was consistently ca. 1:2:1 (Scheme 2), suggesting that the microscopic structure of the catalytically active complex was uniform for each catalyst and the higher catalytic performance of Cat. **B** and **C** was ascribed to the increased surface area of the catalyst after dispersion in the MWNT network. By comparing the results in entries 8 and 9 of Table 1, the moisture content of **2a** had some influence on catalytic efficiency. To clarify the optimum range for moisture content, the nitroaldol reaction of **1a** was conducted with nitroethane **2a** containing varied amounts of water (Figure 3). The presence of some water in the reaction mixture was beneficial, whereas excessive moisture content led to a sharp decrease in reaction progress. **2a** with 600–2000 ppm of water and free from any acidic impurities could produce sufficient catalytic efficiency.[28] Cat. **C** could be stored at −25 °C for 1 week without any loss in catalytic efficiency.[29]

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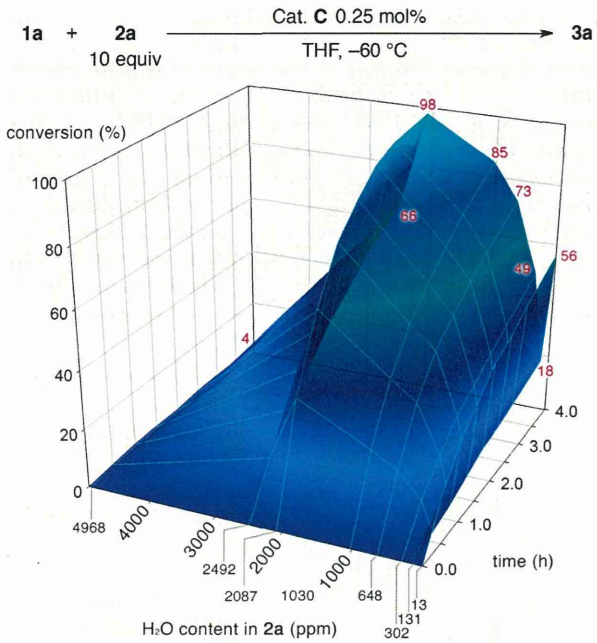

Figure 3. Reaction profile depending on the H_2O content of nitroethane **2a**. **2a** (supplier A) with varied H_2O content was prepared by treatment with MS 3 Å pellets followed by the arbitrary addition of H_2O. Each **2a** was used for catalyst preparation and as substrate. Conversion was determined by HPLC analysis. Diastereo- and enantioselectivity of each reaction were similar, *anti*/*syn* = 97/3 and 98% ee on average. Catalyst loading is noted based on the amount of $NdO_{1/5}(O^iPr)_{13/5}$ used for catalyst preparation.

The synthetic utility of the MWNT-confined catalyst was exemplified by higher catalytic efficiency than the prototype Cat. **A** as well as reusability. The reaction of **1a** and **2a** could be promoted with as little as 0.25 mol% of Cat. **C** to reach completion and to afford *anti*-**3a** almost exclusively in 98% ee, which is a key intermediate to the enantioselective synthesis of anacetrapib, a promising drug candidate for hypercholesterolemia (Scheme 3a).[11,30,31] An *anti*-1,2-amino alcohol motif is embedded in a wide variety of medicinally significant compounds, e.g., β-adrenoceptor agonists (ritodrine, **5**),[32] prophylactic agent **6**,[33] and zanamivir;[34] and the present protocol was utilized for the enantioselective delivery of their intermediates **3b–d** (Scheme 3b–d). In all cases, the MWNT-confined Cat. **B** and **C** outperformed the prototype Cat. **A** in terms of catalytic efficiency. Reuse of the MWNT-confined Cat. **C** for 6 cycles in the reactions of aldehyde **1b** is worthy of notice (Scheme 3b).[35] Stereoselective synthesis of **3d**, a key intermediate for enantioselective synthesis of zanamivir,[36] was performed on 1.0 g scale. Catalyst recycling could be possible using Cat. **C** in this challenging combination of functionalized aldehyde **3d** and 4-nitrobut-1-ene **2b** (Scheme 3d).[35,37]

■ CONCLUSION

We have improved the preparation protocol of MWNT-confined Nd/Na/amide-based ligand **4** heterobimetallic catalysts for the *anti*-selective asymmetric nitroaldol reaction. Precautions for reagents and the effect of moisture content in eliciting optimal catalytic performance were thoroughly investigated. Commercial nitroethane **2a** free from acidic impurities and excess amount of moisture can be used as received. The optimum range of moisture content was identified (600–2000 ppm) for which higher reaction rates were observed than for the reaction under dry conditions. With MWNTs, sacrificial use of **4** was avoided in the formation of the heterobimetallic catalyst. The optimal catalyst was prepared from $NdO_{1/5}(O^iPr)_{13/5}$/NaHMDS/**4** in a ratio 1/2/1, which is identical to the observed ratio of components (Nd/Na/**4**) in the heterobimetallic catalyst. The loading ratio of the catalyst components onto MWNT reached >85%,[20] and high catalytic performance and reusability offer broad synthetic utility. Implementation of a continuous-flow reaction system using the MWNT-confined catalyst for catalytic asymmetric nitroaldol reaction is currently under way.

■ EXPERIMENTAL SECTION

General Procedures. Catalytic asymmetric nitroaldol reaction was performed in a flame-dried 20 mL glass test tube with a Teflon-coated magnetic stirring bar unless otherwise noted. Flasks or test tubes were fitted with a 3-way glass stopcock and reactions were run under Ar atmosphere. Air- and moisture-sensitive liquids were transferred via a gastight syringe and a stainless steel needle. All workup and purification procedures were carried out with reagent-grade solvents under ambient atmosphere. Flash chromatography was performed using silica gel 60 (230–400 mesh). Chemical shifts for protons are reported as δ in units of parts per million downfield from tetramethylsilane and are referenced to residual protons in the NMR solvent ($CDCl_3$: δ 7.26 ppm). For ^{19}F NMR, chemical shifts are reported in the scale relative to trifluoroacetic acid (76.5 ppm) as an external reference. NMR data are reported as follows: chemical shifts, multiplicity (s: singlet, d: doublet, dd: doublet of doublets, t: triplet, q: quartet, sep: septet, m: multiplet, br: broad signal), coupling constant (Hz), and integration. Optical rotation was measured using a 2 mL cell with a 1.0 dm path length. Compounds **3a**, **3b**, **3c**, and **3d** are reported compounds.

General Procedure for *anti*-Selective Catalytic Asymmetric Nitroaldol Reaction (Table 1, Cat. B, entry 1). A flame-dried 20 mL test tube equipped with a magnetic stirring bar and a 3-way glass stopcock was charged with ligand **4** (9.1 mg, 0.024 mmol) and dried under vacuum for ca. 5 min. Ar was backfilled to the test tube, after which dry THF (400 μ L, 2 ppm on average) and 0.2 M THF solution of $NdO_{1/5}(O^iPr)_{13/5}$ (60 μL, 0.012 mmol, 6 mol %, based on Nd) were added via a gastight syringe with a stainless steel needle under an Ar atmosphere at 0 °C. After stirring the mixture at room temperature for 30 min, the slightly cloudy solution was cooled to 0 °C. 1.0 M THF solution of NaHMDS (24 μL, 0.024 mmol) was added via syringe at 0 °C to form a white suspension. After stirring at room temperature for 1 h, carbon nanotubes (Baytubes C 70P, 18 mg) was added. Nitroethane (**2a**) (supplier A, 86 μL, 1.2 mmol, moisture content 150 ppm) was added via syringe at room temperature. After stirring at room temperature for 2 h, the resulting whole black suspension was transferred to Eppendorf safe-lock tube (2 mL volume) with THF washing (ca. 1.2 mL). The tube was centrifuged (ca. 10^4 rpm, 15 s). The supernatant was decanted and dry THF (1.5 mL) was added. The tube was agitated by vortex mixer for 20 s (and occasional finger tapping, if necessary) and centrifuged again (washing process). After the supernatant was decanted, the resulting precipitate was agitated with dry THF (0.7 mL) and the resulting suspension was divided into 6 portions (1 mol % each) and was transferred to a flame-dried 20 mL test tube. Nitroethane (**2a**) (supplier A, 142 μL, 2.0 mmol, 10 equiv, moisture content 150 ppm) were added via a syringe at room temperature. The resulting black suspension was cooled to −60 °C. A solution of 3,5-diiodobenzaldehyde (**1a**) (72 mg, 0.2 mmol) in THF (0.6 mL) was added dropwise via a syringe over 1 min. The resulting suspension was stirred at −60 °C for 4 h under Ar and quenched with 0.2 M THF solution of AcOH (300 μL). After stirring at −60 °C for 1 h, the reaction mixture was warmed to room temperature. Then 1 N HCl aq. (1 mL) was added. The resulting biphasic mixture was filtrated through a syringe filter (0.2 μm) and washed with AcOEt. The

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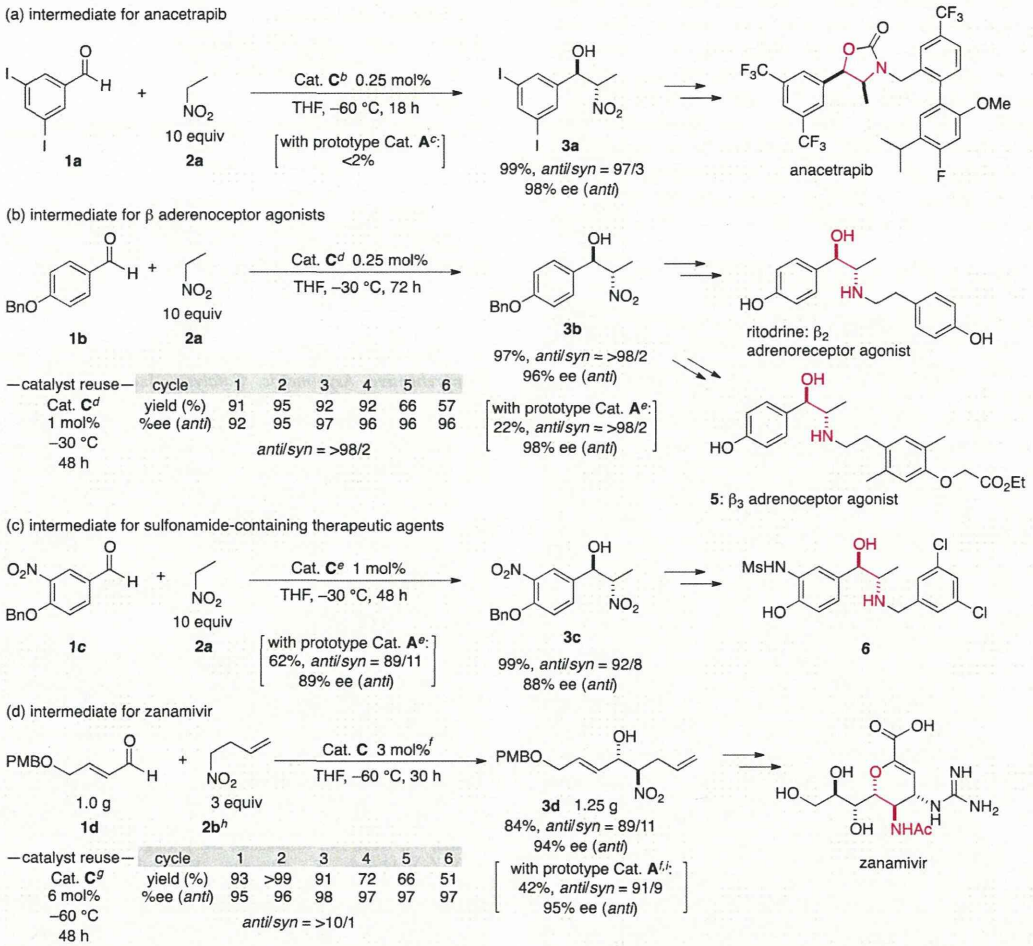
Scheme 3. Enantioselective Synthesis of Key Intermediates for Therapeutics



[a]Catalysts were prepared by following the procedures shown in Scheme 2. Catalyst loading is noted based on the amount of $NdO_{1/5}(O^iPr)_{13/5}$ used for catalyst preparation. Diastereoselectivity was determined by ^1H NMR analysis or HPLC analysis. Enantioselectivity was determined by HPLC analysis. [b]**2a** (supplier A, 2087 ppm H_2O) was used for catalyst preparation and as substrate. [c]**2a** (supplier A, 1992 ppm of H_2O) was used for catalyst preparation and as substrate [d]**2a** (supplier A, 356 ppm of H_2O) was used for catalyst preparation and as substrate. [e]**2a** (supplier A, 133 ppm of H_2O) was used for catalyst preparation and as substrate. [f]Catalyst was prepared with *ent*-**4** and **2a** (supplier A, 1992 ppm H_2O). [g]Catalyst was prepared with *ent*-**4** and **2a** (supplier A, 1992 ppm H_2O). [h]H_2O content was 33 ppm. [i]0.4 mmol scale.

filtrate was extracted with AcOEt and the combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ aq., water, and sat. NaCl aq. and then dried over Na_2SO_4. After evaporation of volatiles under reduced pressure, the crude mixture was submitted to ^1H NMR analysis to determine chemical yield (98%) with DMF as an internal standard. The *anti*/*syn* ratio and enantioselectivity were determined to be 98/2 and 99% ee, respectively, by chiral-stationary-phase HPLC analysis [Daicel CHIRALPAK IC, ϕ 0.46 cm × 25 cm, detection at 254 nm, *n*-hexane/^{i}PrOH/TFA = 19/1/0.02, flow rate =1.0 mL/min] t_R = 10.0 min (*anti*/minor), t_R = 11.0 min (*anti*/major).

General Procedure for *anti*-Selective Catalytic Asymmetric Nitroaldol Reaction (Cat. C, Scheme 3d). A flame-dried 30 mL round-bottom flask equipped with a magnetic stirring bar and a 3-way glass stopcock was charged with ligand *ent*-**4** (derived from D-Leu, 55 mg, 0.15 mmol) and dried under vacuum for ca. 5 min. Ar was backfilled to the test tube, after which dry THF (5 mL, 2 ppm on average) and 0.2 M THF solution of $NdO_{1/5}(O^iPr)_{13/5}$ (727 μL, 0.15 mmol, 3 mol %, based on Nd) were added via a gastight syringe with a stainless steel needle under an Ar atmosphere at 0 °C. After stirring the mixture at room temperature for 1 h, the slightly cloudy solution was cooled to 0 °C. 1.0 M THF solution of NaHMDS (291 μL, 0.29 mmol) was added via syringe at 0 °C to form white suspension. After stirring at room temperature for 30 min, carbon nanotubes (Baytubes C 70P, 220 mg) was added. Nitroethane (**2a**) (supplier A, 86 μL, 1.2 mmol, moisture content 1977 ppm) was added via syringe at room temperature. After stirring at room temperature for 2 h, the resulting whole black suspension was transferred to centrifuge tube (2 mL volume) with THF washing (ca. 6.0 mL). The tube was centrifuged (ca. 5000 rpm, 2 min). The supernatant was decanted and dry THF (12 mL) was added. The tube was agitated by vortex mixer for 20 s (and occasional finger tapping, if necessary) and centrifuged again (washing process). The supernatant was decanted. After additional three-cycles of washing procedure, the resulting precipitate was agitated with THF (18 mL) and was transferred to a flame-dried 100 mL test tube under an Ar atmosphere. 4-Nitrobut-1-ene (**2b**) (1.5 mL, 14.55 mmol, 3 equiv, moisture content 33 ppm) were added via a syringe at room temperature. The resulting black suspension was cooled to −60 °C. The solution of (*E*)-4-((4-methoxybenzyl)oxy)but-2-enal (**1d**) (1000 mg, 4.85 mmol) in THF (0.6 mL) was added dropwise via a syringe over 10 min. The resulting suspension was stirred at −60 °C for 30a6 h under Ar and quenched with 0.2 M THF solution of AcOH (5 mL). After stirring at −60 °C for 1 h, the

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reaction mixture was warmed to room temperature. The resulting mixture was filtrated through a pad of Celite and dilute with AcOEt. The resulting mixture was washed sat. NH_4Cl aq., water and dried over Na_2SO_4. After evaporation of volatiles under reduced pressure, the crude mixture was purified by silica gel column chromatography (95:5 to 1:1 *n*-hexane/ethyl acetate) to give the desired product **3d** (1250 mg, 84% yield). The *anti*/*syn* ratio and enantioselectivity were determined to be 89/11 by ^{1}H NMR and 94% ee by chiral-stationary-phase HPLC analysis,[36] respectively [Daicel CHIRALPAK AD-H, ϕ 0.46 cm × 25 cm, detection at 254 nm, *n*-hexane/^{i}PrOH = 9/1, flow rate = 1.0 mL/min] t_R = 13.4 min (*anti*/major), t_R = 15.5 min (*anti*/minor).

General Procedure for *anti*-Selective Catalytic Asymmetric Nitroaldol Reaction (repetitive use of Cat. C, Scheme 3d). A flame-dried 20 mL test tube equipped with a magnetic stirring bar and a 3-way glass stopcock was charged with ligand *ent*-**4** (derived from D-Leu, 9.1 mg, 0.024 mmol) and dried under vacuum for ca. 5 min. Ar was backfilled to the test tube, after which dry THF (400 μL, 2 ppm on average) and 0.2 M THF solution of $NdO_{1/5}(O^iPr)_{13/5}$ (120 μL, 0.024 mmol, 6 mol %, based on Nd) were added *via* a gastight syringe with a stainless steel needle under an Ar atmosphere at room temperature. After stirring the mixture at room temperature for 30 min, the slightly cloudy solution was cooled to 0 °C. 1.0 M THF solution of NaHMDS (48 μL, 0.048 mmol) was added *via* syringe at 0 °C. After stirring for 30 min at room temperature, carbon nanotubes (Baytubes C 70P, 18 mg) was added. Nitroethane (supplier A, 80 μL, moisture content 133 ppm) was added *via* syringe at room temperature. After stirring at room temperature for 2 h, the resulting whole black suspension was transferred to Eppendorf safe-lock tube (2.0 mL volume) with THF washing (ca. 1 mL). The tube was centrifuged (ca. 10^4 rpm, 15 s). The supernatant was decanted and dry THF (1 mL) was added. The tube was agitated by vortex mixer for 30 s and centrifuged (washing process). The supernatant was decanted. After additional two-cycles of washing procedure, the resulting precipitate was agitated with dry THF (1.0 mL) and the resulting suspension was transferred to a flame-dried 20 mL test tube under an Ar atmosphere. THF (1.5 mL) and 4-nitrobut-1-ene (**2b**) (124 μL, 1.2 mmol, 3 equiv, moisture content 33 ppm) were added *via* a syringe at room temperature. The resulting black suspension was cooled to −60 °C. The solution of (*E*)-4-((4-methoxybenzyl)oxy)but-2-enal (**1d**) (82.4 mg, 0.4 mmol) in THF (0.5 mL) was added dropwise *via* a syringe over 1 min. The resulting suspension was stirred at −60 °C for 48 h under Ar. The test tube was cool down to −78 °C (dry ice/acetone bath) and the tube was quickly centrifuged (ca. 10^4 rpm, 5 s). The separated supernatant was immediately decanted and quenched by transferring into another test tube containing 0.2 M THF solution of AcOH (300 μL) at −78 °C. The test tube containing the catalyst was placed to the cooling bath at −60 °C again and the catalyst was used for next cycle by repeating same procedure mentioned above. The quenched reaction mixture was warmed to room temperature and sat. NH_4Cl aq. (1 mL) was added. The resulting biphasic mixture was filtrated with Celite pad under reduced pressure and washed with AcOEt. The filtrate was extracted with AcOEt and then dried over Na_2SO_4. After evaporation of volatiles under reduced pressure, the crude residue was obtained which was directly subjected to NMR analysis. Yields of **3d** were calculated based on ^{1}H NMR using DMF as an internal standard. The *anti*/*syn* ratio and enantioselectivity were determined by ^{1}H NMR and 94% ee by chiral-stationary-phase HPLC analysis,[36] respectively [Daicel CHIRALPAK AD-H, ϕ 0.46 cm × 25 cm, detection at 254 nm, *n*-hexane/^{i}PrOH = 9/1, flow rate =1.0 mL/min] t_R = 13.5 min (*anti*/major), t_R = 15.6 min (*anti*/minor).

■ ASSOCIATED CONTENT

Supporting Information

Additional notes and HPLC charts for nitroethane **2a** and nitroaldol products **3a-d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(20) Incorporation ratio: Nd = 88%, Na = 85%, ligand **4** = 89%.

(21) Nitroethane **2a** purchased from TCI Co. Ltd. (supplier A) and Wako Pure Chemical Co. Ltd. (supplier B) could be used as received in this reaction under 1 mol% catalyst conditions.

(22) When nitroethane **2a** purchased from Sigma-Aldrich (supplier C, without treatment with $NaHCO_3$) was used for catalyst preparation or as substrate, no reaction proceeded in our hands. Trace amount of acidic impurity might interfere the self-assembly of the catalyst and decompose the catalyst (prepared from **2a** from suppliers A or B) during the reaction.

(23) Long-term contact with dried MS 3Å and **2a** led to the accumulation of unidentified impurities in HPLC analysis, probably because of gradual decomposition. Separation of **2a** from MS 3Å is recommended after 1 h.

(24) Several unidentified peaks appeared in a reverse-phase HPLC trace of nitroethane **2a** from supplier C. See Supporting Information.

(25) Commercial powdered $NaHCO_3$ was suspended with **2a** for 1 h at room temperature, then filtered. See Supporting Information.

(26) The use of supernatant as a catalyst resulted in poor stereoselectivity (see ref 6b), presumably because some defective complexes promoted the reaction in much less stereoselective fashion.

(27) See Supporting Information for details.

(28) Under the reaction conditions for Figure 2, ca. 2000 ppm of H_2O corresponds to an equimolar amount of H_2O to $NdO_{1/5}(O^iPr)_{13/5}$.

(29) In the reaction of **1a** and **2a** under 1 mol% conditions (−60 °C, 5 h), **3a** was obtained in 99% yield (*anti*/*syn* = 98/2, 99% ee).

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(35) Decrease in catalytic activity was observed, which would be ascribed to mechanical damage of the nanotube catalyst and leaching of the catalyst during the reaction. This problem would be addressed by implementation of the MWNT-confined catalyst to a continuous-flow system.

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(37) Use of nitroethane **2a** was essential for the preparation of self-assembling of heterobimetallic catalyst. Contamination of the nitroaldol product derived from **2a** was negligible due to the presence of large excess amount of **2b** in the reaction mixture.