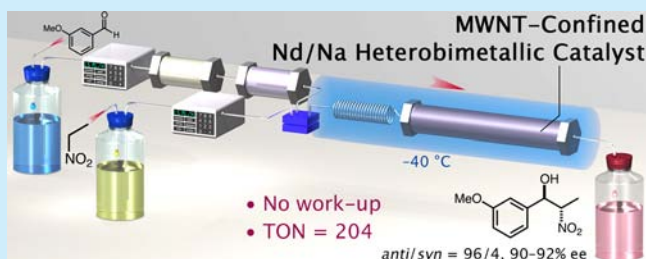


Self-Assembled Asymmetric Catalyst Engaged in a Continuous-Flow Platform: An *Anti*-Selective Catalytic Asymmetric Nitroaldol ReactionKazuki Hashimoto,[†] Naoya Kumagai,^{*,†} and Masakatsu Shibasaki^{*,†,‡}[†]Institute of Microbial Chemistry (BIKAKEN), Tokyo, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan[‡]JST, ACT-C, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan

S Supporting Information

ABSTRACT: An *anti*-selective catalytic asymmetric nitroaldol reaction was manifested in a continuous-flow platform. The requisite Nd/Na heterogeneous catalyst was readily prepared by self-assembly of an amide-based chiral ligand, NdO_{1.5}(OⁱPr)_{13/5}, NaHMDS, and a multiwalled carbon nanotube without covalent linkage. A stainless-steel column filled with the Nd/Na catalyst was incorporated in a flow system to promote the nitroaldol reaction with high stereoselectivity. The flow system with the heterogeneous catalyst obviated the quenching operation, and the cooling system was minimized.

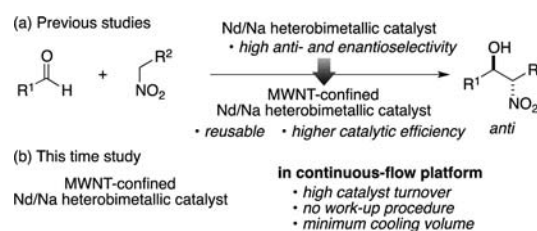


The production of valuable synthetic intermediates using environmentally benign processes has been a growing topic in the chemical community over the past decade. Continuous-flow chemistry is a rapidly emerging technology that allows for continuous production of specialty chemicals in a miniaturized reactor.¹ Systematic optimization of flow-system parameters enables the incorporation of highly reactive and short-lived intermediates as well as hazardous reagents in a safer manner, and sequential reactions can be performed with concatenated substrates and reagents. Enhanced efficiency in mixing, heat control, and photosensitization is also meritorious.¹ The flow system not only confers advantages in a small-scale experimentation, it also attracts increasing attention as a reliable methodology for large-scale production of valuable chemicals because simple scale-up of a reaction in laboratory scale to a large-batch scale often presents unresolvable difficulties.² Integration of heterogeneous catalysts into the flow system allows for catalytic transformations in this valuable continuous production system.³ In particular, the use of heterogeneous asymmetric catalysts offers expeditious access to enantioenriched products. In contrast to the huge collection of homogeneous asymmetric catalysts,⁴ heterogeneous asymmetric catalysts have been less explored and are in high demand along with the rapid progress of continuous-flow chemistry.^{5,6} Although several heterogeneous catalysts have exhibited excellent performance in hydrogenation,⁷ heterogeneous asymmetric catalysts for C–C bond-forming reactions often incur lower catalytic efficiency and stereoselectivity compared with their homogeneous counterparts. Moreover, the tedious preparation procedure through covalent linkage of active catalysts and solid materials compromises the overall synthetic utility. Herein, we document an *anti*-selective asymmetric nitroaldol reaction in a continuous-flow system. The requisite

heterogeneous catalyst was readily prepared via self-assembly, the flow system obviated the quenching operation, and the cooling system was minimized.

The nitroaldol reaction is a reliable C–C bond-forming reaction to access 1,2-nitroalkanol,^{8,9} which are precursors of synthetically versatile 1,2-amino alcohols.¹⁰ Since the first report of catalytic asymmetric nitroaldol reaction,¹¹ a number of catalytic systems for nitromethane have been documented.⁹ However, the simultaneous control of diastereo- and enantioselectivity of nitroalkanes has been a formidable challenge, and only a limited number of asymmetric catalysts have been identified.^{12,13} In 2009, we revealed a Nd/Na heterobimetallic catalyst that promoted an asymmetric nitroaldol reaction in a highly *anti*-selective manner (Scheme 1).¹⁴ Given the particular synthetic utility of 1,2-amino alcohols in medicinal chemistry, we directed this specific research program to practical application, and the Nd/Na heterobimetallic catalyst was further refined into a recoverable heterogeneous catalyst confined in an entangling network of multiwalled carbon nanotubes (MWNT).¹⁵ The unique feature of the

Scheme 1. Evolution of Nd/Na Heterobimetallic Catalyst



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MWNT-confined catalyst is as follows: (1) the active catalyst is supported on a solid material (MWNT) via self-assembly of the chiral ligand and metal salts; (2) the heterogeneous catalyst was prepared by simply mixing each component without covalent bond formation; and (3) the MWNT-confined catalyst exhibited higher catalytic activity because of increased surface area.^{15a} In our continuing program of MWNT-confined heterogeneous catalyst development, we envisioned combining our nitroaldol methodology and continuous-flow chemistry to develop a practical method for the production of enantio-enriched *anti*-1,2-amino alcohols. A continuous-flow system is an ideal platform for the present nitroaldol reaction because the reaction proceeds through proton transfer between substrates and the quenching procedure can be eliminated, thereby affording the desired products by simple evaporation of the solvent and excess nitroalkane substrates.

We set out to investigate the robustness of the MWNT-confined Nd/Na catalyst in the flow stream because strong covalent bonding is not used for entrapment of the Nd/Na heterobimetallic catalyst into the MWNT network. The preparation procedure is outlined in Table 1. To a THF

Table 1. Preparation of MWNT-Confined Nd/Na Heterobimetallic Catalyst and Elution Test

| entry | duration (min) | eluted vol. (mL) | ligand 1 ^b (μmol) | ligand 1 ^b (%) ^d | Nd ³⁺ ^c (μmol) | Nd ³⁺ ^c (%) ^d | Na ⁺ ^c (μmol) | Na ⁺ ^c (%) ^d |
|-------|------------------------|------------------|------------------------------|--|--------------------------------------|--|-------------------------------------|---|
| 0 | initial wash-out (2 h) | 24 | 2.9 | 12 | 1.5 | 6.2 | 5.5 | 11 |
| 1 | 0 – 30 | 6 | 0.047 | 0.19 | 0.017 | 0.071 | 0.031 | 0.064 |
| 2 | 30 – 60 | 6 | 0.027 | 0.11 | 0.017 | 0.071 | 0.031 | 0.064 |
| 3 | 60 – 90 | 6 | 0.024 | 0.10 | 0.017 | 0.071 | 0.027 | 0.056 |
| 4 | 90 – 120 | 6 | 0.024 | 0.10 | 0.018 | 0.075 | 0.029 | 0.060 |
| 5 | 120 – 150 | 6 | 0.024 | 0.10 | 0.020 | 0.083 | 0.034 | 0.071 |
| 6 | 150 – 180 | 6 | 0.025 | 0.10 | 0.020 | 0.083 | 0.039 | 0.081 |

^aDetermined on the basis of the amount of each component in the initial wash-out. ^bDetermined by reversed-phase HPLC. Average of two runs. ^cDetermined by microwave plasma atomic emission spectroscopy (MP-AES). Average of three runs. ^dRelative to the amount used for catalyst preparation. Determined on the basis of the amount of each component in the initial wash-out.

solution of amide-based ligand **1**, THF solutions of NdO_{1.5}(O'Pr)_{13.5} and NaHMDS were mixed sequentially at room temperature (molar ratio; 1:Nd:Na = 1:1:2), affording a thick white suspension. After addition of the MWNT,¹⁷ nitroethane¹⁸ was added at room temperature. Nitroethane quickly dissociated the white suspension to form a mixture of clear solution and MWNT, and then self-assembly of the Nd/Na heterobimetallic catalyst initiated within the entangling network of MWNT. Thus-obtained MWNT-confined catalyst was suspended in THF and transferred together with dried Celite¹⁸ to a stainless steel column (φ 4.6 mm × 100 mm) equipped with end-capping disk frits (2 μm) on both sides of the column. THF was passed through the column at 200 μL/min, and the amounts of **1**, Nd³⁺, and Na⁺ in the eluent were monitored. The initially collected eluent (Table 1, entry 0)

contained, respectively, 12%, 6.2%, and 11% of ligand **1**, Nd³⁺, and Na⁺ relative to the amount used for catalyst preparation. These eluted solutes were derived from the supernatant at the stage of catalyst preparation, which was composed of the uncomplexed catalyst components. Based on the analysis of the initial wash-out, 88%, 94%, and 89% of ligand **1**, Nd³⁺, and Na⁺, respectively, were incorporated into the MWNT-confined catalyst. This loading ratio (88%) and the proportion of 1:Nd:Na = ca. 1:1:2 are consistent with the data obtained from the previously reported procedure.^{15b} The eluents after the initial wash-out contained only negligible amounts of catalyst components, indicating that the Nd/Na heterobimetallic catalyst was effectively entrapped by the MWNT (entries 1–6).

Next, the performance of the packed catalyst in the nitroaldol reaction in a continuous-flow platform was evaluated. The reaction of *m*-methoxybenzaldehyde **2** and nitroethane was chosen by anticipating the application to the enantioselective synthesis of AZD5423, a candidate drug for the treatment of chronic obstructive pulmonary disease (COPD).¹⁹ Assembly and arrangement of the flow reactor are outlined in Figure 1. Because of the continuous supply of **2** as a THF solution, even a tiny amount of water in THF or acidic impurity in **2** may have a negative effect on the packed catalyst. Therefore, the solution of **2** (0.1 M in THF) was passed through scavenger columns filled with NaHCO₃ and powdered MS 3A¹⁸ at 1.5 mL/h before its entry into the catalyst column. Nitroethane (1.0 M in THF) was concatenated to the stream of **2** via a mixer (mixing volume: 32 μL) before the catalyst column. The mixed stream at room temperature was precooled to –40 °C at the coiled line, and the nitroaldol reaction proceeded in the catalyst column containing 19.5 μmol of the Nd/Na heterobimetallic catalyst (based on Nd). The flow reactor system was operated at 3.0 mL/h, and the reaction progress was monitored every 4 h (Table 2).²⁰ HPLC and NMR analyses of the initial aliquot (12

Table 2. Profile of Nitroaldol Reaction in the Continuous-Flow System

| entry | duration (h) | eluted in total (mL) | passed 2 in total (mmol) | 3 | | | | | amount ^e (mmol) | |
|-------|--------------|----------------------|---------------------------------|-----------------------|----------------------|----------------------------------|---------------------|-------|----------------------------|--|
| | | | | conv ^a (%) | TON ^b (%) | <i>anti/syn</i> ^c (%) | ee ^d (%) | | | |
| 1 | 2 – 6 | 12 | 0.6 | 96 | 29 | 96/4 | 91 | 0.576 | 0.58 | |
| 2 | 6 – 10 | 24 | 1.2 | 97 | 59 | 96/4 | 91 | 0.582 | 1.16 | |
| 3 | 10 – 14 | 36 | 1.8 | 95 | 88 | 96/4 | 90 | 0.570 | 1.73 | |
| 4 | 14 – 18 | 48 | 2.4 | 96 | 118 | 96/4 | 91 | 0.576 | 2.30 | |
| 5 | 18 – 22 | 60 | 3.0 | 96 | 147 | 96/4 | 91 | 0.576 | 2.88 | |
| 6 | 22 – 26 | 72 | 3.6 | 94 | 176 | 96/4 | 92 | 0.564 | 3.44 | |
| 7 | 26 – 30 | 84 | 4.2 | 91 | 204 | 97/3 | 92 | 0.546 | 3.99 | |

^aConversion of each fraction. Determined by reversed-phase HPLC.

^bTON = (total amount of **3** obtained)/(catalyst amount (19.5 μmol)).

^cDetermined by ¹H NMR analysis. ^dDetermined by chiral stationary phase HPLC analysis. ^eCalculation was based on the conversion.

mL) confirmed 96% conversion with an *anti/syn* ratio of 96/4 and 91% ee (*anti*) (entry 1). The subsequent elution contained product **3** with consistently high conversion and stereoselectivity (entries 2–7). For 30 h, the catalyst was operating with high conversion, and TON = 204 was achieved. The continuous-flow reaction without the scavenger columns filled with NaHCO₃ and MS 3A gave inferior results, indicating the beneficial effect of these precolumns for a higher TON. The present continuous-flow system was readily scaled up for the synthesis of more than 10 g of **3** (Scheme 2). With a catalyst column of φ 20 mm × 50 mm containing 0.294 mmol (based

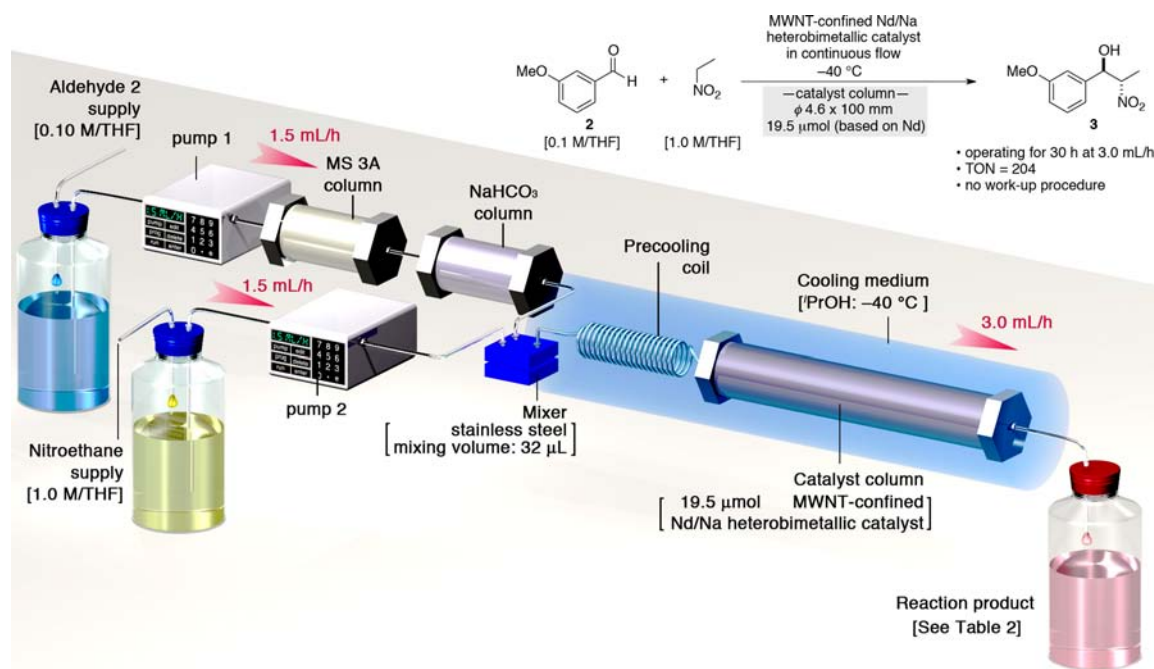
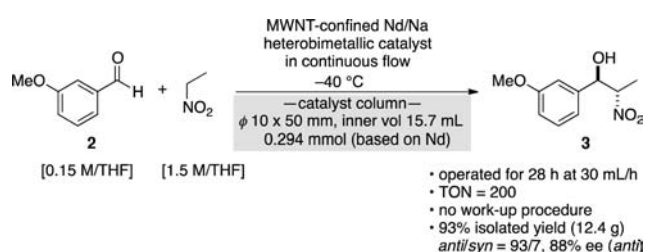


Figure 1. Overhead view of the flow reactor system and a scheme for the nitroaldol reaction of aldehyde 2.

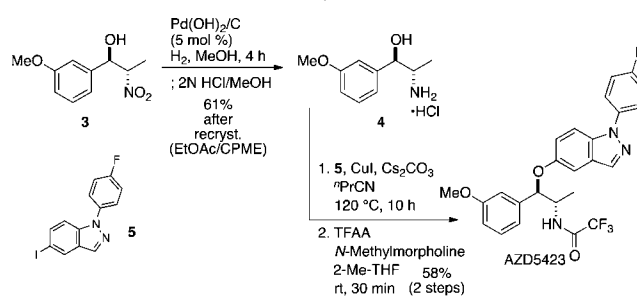
Scheme 2. Scale-up of the Continuous-Flow Nitroaldol Reaction



on Nd) of MWNT-confined Nd/Na heterobimetallic catalyst, the continuous-flow reaction was operated in an identical flow reactor configuration at 15 mL/h for each substrate. After 28 h, 63 mmol of **2** was passed through the catalyst column, and simple evaporation of all the eluents afforded the crude product **3** in 94% yield (based on ¹H NMR analysis) containing a tiny amount of unreacted **2** and leached catalyst components (e.g., ligand **1**: 13.1 mg). After purification by flash chromatography, 12.4 g of **3** (93% yield, TON = 200) was obtained. It is worth noting that the cooling volume was significantly reduced compared with the batch system, circumventing the energy problem of the cryogenic conditions required for the stereocontrolled nitroaldol reaction. The volume of reaction mixture under standard batch-system conditions for the nitroaldol reaction (0.1 M in THF, 63 mmol of **2**) is 630 mL, and a corresponding large cryogenic reactor and associated electric power are required. The size of catalyst column that needs cryogenic control is only 15.7 mL,²¹ allowing for easy implementation in large-scale synthesis.

The nitroaldol product **3** was readily transformed into AZD5423 (Scheme 3). Hydrogenation over Pd(OH)₂/C in MeOH gave amino alcohol **4**, which was isolated as hydrochloride salt in 61% yield after recrystallization. Installation of the requisite indazole unit was carried out by following the reported procedure with slight modification.²² Cu mediated *O*-arylation of **4** with 1-arylated 5-iodoindazole **5** gave

Scheme 3. Enantioselective Synthesis of AZD5423



an aryl ether. Trifluoroacetylation furnished AZD5423 in 58% yield (two steps).

In conclusion, an *anti*-selective catalytic asymmetric nitroaldol reaction was demonstrated in a continuous-flow platform. The heterogeneous catalyst was readily prepared through self-assembly without covalent linkage. More than 200 TON was observed, and the system can be easily scaled up to produce more than 10 g of the product in a minimized cooling volume, which is essential for stereocontrolled nitroaldol reactions. Further refinement of the continuous-flow nitroaldol reaction to pursue an even higher TON is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and detailed data for continuous-flow reaction. 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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