Organic Process Research & Development

Communication

pubs.acs.org/OPRD

Homogeneous Enantioselective Catalysis in a Continuous-Flow Microreactor: Highly Enantioselective Borohydride Reduction of Ketones Catalyzed by Optically Active Cobalt Complexes

Takuo Hayashi,[†] Satoshi Kikuchi,[†] Yukako Asano,[‡] Yoshishige Endo,[§] and Tohru Yamada*,[†]

[†]Department of Chemistry, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

[‡]Hitachi Research Laboratory, Hitachi, Ltd., 832-2 Horiguchi, Hitachinaka, Ibaraki 312-0034, Japan

[§]Hitachi Plant Technologies, Ltd., 603 Kandatsu-machi, Tsuchiura, Ibaraki 300-0013, Japan

Supporting Information

ABSTRACT: Highly enantioselective homogeneous catalysis under continuous-flow conditions was established for the cobalt-catalyzed borohydride reduction of tetralone derivatives. A microreactor allowed higher reaction temperature with the residence time of 12 min than the corresponding batch system to maintain enantioselectivity as well as reactivity. The present system was directly applied to gram-scale synthesis to afford the reduced product with 92% ee.

INTRODUCTION

The enantioselective reaction catalyzed by an optically active metal complex has been employed as one of the most competent methods[1] to provide optically pure compounds for the manufacturing of pharmaceuticals as well as functional materials. A wide variety of enantioselective reactions using metal complex catalysts has been proposed over past decades and also developed using a batch system, while a continuous-flow system has rarely been examined for these catalytic reactions. Since the reaction rate of the metal complex-catalyzed reactions can be regulated by their ligands as well as the reaction conditions, they have a conclusive advantage in volume efficiency compared to biocatalytic or enzymatic reactions. Because the enantioselectivities are often sensitive to the reaction temperature, in order to scale up the reaction, especially for the exothermic reactions with a high reaction rate, the precise control of the reaction temperature would be required to maintain their high enantioselectivities. Our group proposed the enantioselective borohydride reduction of ketones catalyzed by optically active cobalt complexes[2] and applied[3] it to various substrates and reaction conditions (though the largest reaction scale was 350 g[4]) or reported on a 10-g scale for the enantioselective reduction of 1,3-dicarbonyl compounds.[5]

The potential advantage of using a microreactor, rather than a conventional batch reactor, is using high-speed mixing to keep the reaction conditions homogeneous.[6] A direct result of the reactor's extremely high surface-to-volume ratio[7] allows quick removal of the reaction heat to precisely control the temperature of the reactor in order to maintain the high enantioselectivities. In order to scale up the reaction using a microreactor, a simple extension of the operating time can be employed, and the "numbering-up"[8] of the microreactors will be effective. Although the continuous-flow system with a microreactor[9] is one of the most promising methods to shorten the time or effort to scale up the reaction from R&D to the plant stage, few homogeneous asymmetric reactions have been reported to use the continuous-flow system.[10] In addition, their enantioselectivities and catalytic efficiencies were reported to be lower than those of the original batch system. Herein, we describe a continuous-flow microreactor system for the highly enantioselective borohydride reduction catalyzed by optically active cobalt complexes and its application for scale-up synthesis.

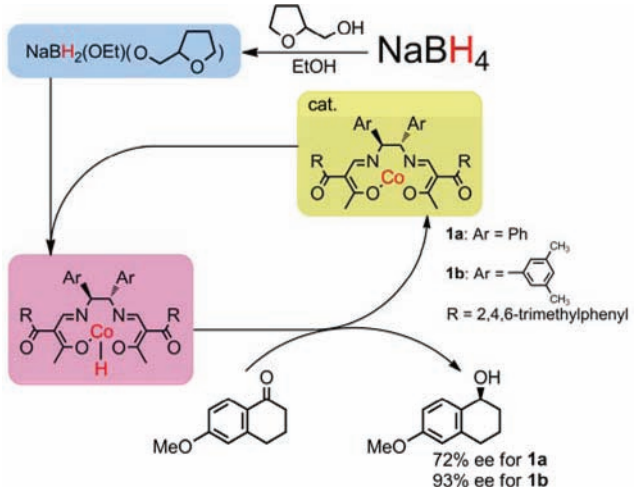
RESULTS AND DISCUSSION

In the original procedure[11] for the enantioselective borohydride reduction catalyzed by optically active cobalt complexes, sodium borohydride was treated with the appropriate amount of ethanol and tetrahydrofurfuryl alcohol to afford the corresponding activated borohydride solution, since sodium borohydride itself is not soluble in ordinary organic solvents. In order to improve the solubility, chloroform[2] was employed as the solvent. It was recently proposed[12] on the basis of analytical and theoretical studies that chloroform not only acts as the solvent but also activates the cobalt complex catalyst to generate the reactive intermediates. The original color of the cobalt complex is yellow-to-orange, whereas the activated cobalt complex treated with the modified borohydride is reddish violet. While this color is maintained, the enantioselective reduction would proceed to afford the corresponding reduced product in high yield with high enantioselectivity. In a batch system, the modified borohydride solution was prepared in the first vessel. To the second vessel containing the substrate and a catalytic amount of the cobalt complex, the modified borohydride solution was slowly injected (Scheme 1). Also, in the continuous-flow system using a Micro Process Server from Hitachi Plant Technology, Ltd., solution **A** containing the substrate and a catalytic amount of the cobalt complex and solution **B** with the modified borohydride were prepared. The microreactor attached to the Micro Process Server is made of SUS316 stainless steel and has a microchannel with a length of 434 mm and a diameter of 0.5 mm. As the shortest reaction

Received: March 9, 2012
Published: May 21, 2012

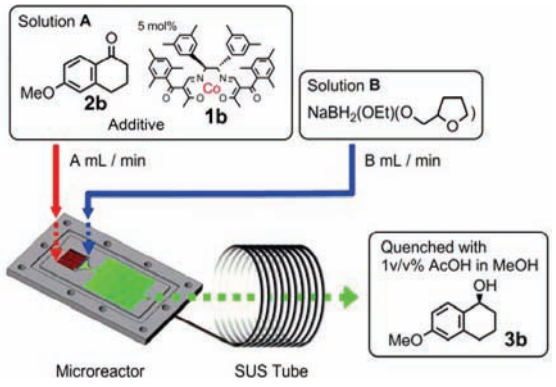
dx.doi.org/10.1021/op300061k | Org. Process Res. Dev. 2012, 16, 1235−1240

Scheme 1. Batch system for cobalt-catalyzed enantioselective borohydride reduction



time in the batch system was reported[13] to be 15 min, the original microreactor connected to a SUS316 tube (2000 mm length and 0.5 mm diameter) was employed as the continuous-flow reactor. From the end of the SUS tube, the reaction mixture was directly poured into a saturated ammonium chloride solution. The reaction temperature was set at 0 °C, and solutions **A** and **B** were both fed at the flow rate[14] of 1.0 mL/min. Under these conditions, the residence time in the reactor was estimated to be 0.2 min. It would not be long enough to complete the catalytic enantioselective reduction. After the usual workup process, the reduced product was obtained in 38% yield with 57% ee (entry 1, Table 1). For extending the residence time, the flow rate and the SUS tube length were evaluated (entries 2 and 3). When solutions **A** and **B** were both fed into the reactor at 0.5 mL/min, the chemical yield was improved to 51%. By using a SUS316 tube of 5000 mm length and 1.0 mm diameter instead of the tube 2000 mm long, the yield was improved to 65%, although the enantioselectivity was still much lower than that of the batch system in Scheme 1. On the basis of these examinations, a reasonable yield or selectivity was not observed, probably due to the background reduction with the excess hydride in the quench vessel. The fact that the excess hydride could not be completely quenched in an ammonium chloride solution to reduce the ketone without any control of the cobalt complex led to the examination of several quencher systems. Eventually, 1.0 v/v % AcOH in THF was found to be a suitable quencher system for the present continuous-flow reaction in order to realize a constant yield and enantioselectivity up to 90% ee (entry 4). When the SUS tube with a 10,000-mm length and 1.0-mm diameter was employed, the chemical yield was improved to 63% (entry 5). In order to improve the chemical yield of the product, the enhancement of the borohydride reactivity was next examined. In a similar 1,4-reduction system catalyzed by cobalt complexes using the modified borohydride, the addition of methanol[15] was reported to effectively enhance the reactivity of the modified borohydride to improve the chemical yield. It is assumed that the electron-donating methanol would release the hydride from the borohydride; consequently, the reactive cobalt hydride would be generated and improve the chemical yield of the product. The addition of methanol to solution **A** was then examined to efficiently accelerate the continuous-flow reaction and to improve the chemical yield as well as the enantioselectivity (entry 6). The optimization of the reaction temperature or the rinsing procedures also effectively improved the chemical yield as

Table 1. Optimization of catalytic enantioselective borohydride reduction under continuous-flow conditions[a]



entry	residence time/min	flow rate (**A**/**B**)/mL min^{-1}	temperature (MR/tube) /°C	additive	yield /%[e]	ee /%[e]
1[b,f,g]	0.2	1.0/1.0	0/0	none	37.8[m]	57.4
2[b,f,g]	0.4	0.5/0.5	0/0	none	50.7[m]	50.4
3[c,f,h]	4	0.5/0.5	0/0	none	64.7[m]	83.1
4[c,i]	4	0.4/0.6	0/0	none	58.5	89.7
5[d,j]	8	0.4/0.6	0/10	none	63.1	88.8
6[d,k]	12	0.266/0.4	0/10	MeOH[l]	88.2	89.4
7[d,k]	12	0.166/0.5	−20/10	MeOH[l]	90.6	90.2

[a]Reaction conditions: ketone (0.1 M), cobalt catalyst (5 mM), modified borohydride (0.12 M), solvent: $CHCl_3$, quenched with 1.0 v/v % AcOH in MeOH, microreactor: 0.5-mm diameter, 434-mm length. [b]SUS tube: 0.5-mm diameter, 2.0-m length. [c]SUS tube: 1.0-mm diameter, 5.0-m length. [d]SUS tube: 1.0-mm diameter, 10.0-m length. [e]Determined by HPLC analysis. [f]Quenched with sat. aq NH_4Cl. [g]The cobalt catalyst **1a** was employed instead of **1b**. [h]Cobalt catalyst (1 mM). [i]Quenched with 1.0 v/v% AcOH in THF/H_2O = 1:1. [j]Modified borohydride: 0.21 M. [k]Rinsing procedure was improved. [l]0.45 M of methanol was employed as an additive. [m]Isolated yield.

dx.doi.org/10.1021/op300061k | Org. Process Res. Dev. 2012, 16, 1235−1240

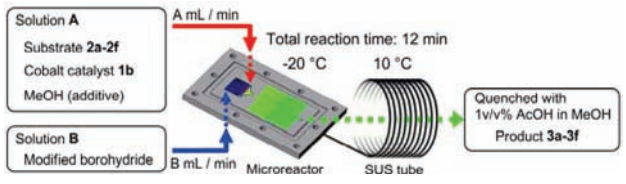
well as the enantioselectivity. For the batch system of the present reaction, a long reaction time was required at −20 °C to achieve high enantioselectivity. The 0 °C reaction temperature was then used to balance the reactivity and selectivity, whereas the examination using the continuous-flow system revealed that cooling at −20 °C during the initial step for mixing of both solutions effectively realized high enantioselectivity and that the following step for the reaction could be performed at 10 °C in order to shorten the reaction time due to the efficient removal of the mixing and/or reaction heat by the microreactor. While the flow ratio of solution **B** vs **A** was increased to 3.0 in order to obtain high yield, a considerably fast reaction rate in a microreactor and the consequent reaction heat could be controlled by its high heat transfer efficiency, allowing both high yield and enantioselectivity. Eventually, the reduced product was obtained in 91% yield with 90% ee in a 12-min residence time (entry 7). It was concluded that the continuous-flow microreactor system could be employed for the enantioselective reaction catalyzed by the optically active metal complexes, since the current chemical yield, enantioselectivity, and reaction time results are the same as those of the batch system.

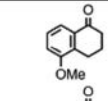
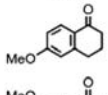
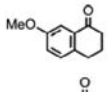
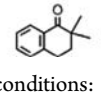
The optimized conditions for the continuous-flow microreactor were successfully applied to enantioselective borohydride reduction of several substrates (Table 2). In a batch reaction of 5-methoxy-1-tetralone, the corresponding reduced product was obtained in 12 min in 80% yield with 87% ee. In the continuous-flow system in 12 min residence time, the reaction smoothly proceeded to afford the desired product in 92% yield with 90% ee (entry 1). For 6-methoxy-1-tetralone, the flow ratio of solution **B** vs **A** was optimized to be 3.0 to afford the reduced product in 91% yield with 90% ee (entry 2). For 7-methoxy-1-tetralone or 1-tetralone, the optimized flow ratio was 2.5, and the reduced products were obtained in 88% or 84% yield with 91% or 90% ee, respectively (entries 3 and 4). In these examinations, it was confirmed that an enantioselective reaction catalyzed by optically active metal complexes could be applied to the continuous-flow microreactor system. Fast reaction was realized, and the chemical yield and the enantioselectivity were rather improved compared with those from the corresponding batch system. For an acyclic ketone or a steric demanding ketone, the enantioselectivities in the batch system[16] were reproduced in the continuous-flow system (entries 5 and 6). Reaction heat generated in the batch system might lead to overreaction due to manual handling of syringes and less efficient heat transfer than that in the flow system. Therefore, in entries 4 and 5, yields in the continuous-flow system were lower than those in the batch system.

A long operating time for the large-scale synthesis was also examined (Scheme 2). In order to prevent blockage by the precipitated reagents, each flow rate was 2 times faster than the preliminary examination; e.g., 0.333 mL/min for solution **A** and 1.0 mL/min for solution **B**. A 19-m length SUS316 tube was employed as an after-reactor in order to keep the residence time at 12 min. On the basis of the small-scale examination, for the initial step of mixing, both solutions were cooled to −30 °C, and the following reaction step was operated at 10 °C. After some optimization, a long operating time for a gram-scale synthesis was developed; 3.1 g of a ketone was effectively reduced by the modified borohydride in the presence of 5 mol % of the optically active cobalt complex catalyst to afford the corresponding alcohol (3.0 g) in 96% yield with 92% ee. The total operating time of the microreactor system was 9.75 h. For the large-scale synthesis, it was demonstrated that a longer operating time could be used for the enantioselective catalysis. For scale-up, the "numbering-up" with a multireactor in parallel could be employed in principle.

In conclusion, it was determined that a continuous-flow microreactor could be used for the enantioselective borohydride reduction of ketones catalyzed by the optically active cobalt complexes to afford the corresponding reduced product with the same level in chemical yield and enantioselectivity as the batch system even at a higher reaction temperature. Also, a

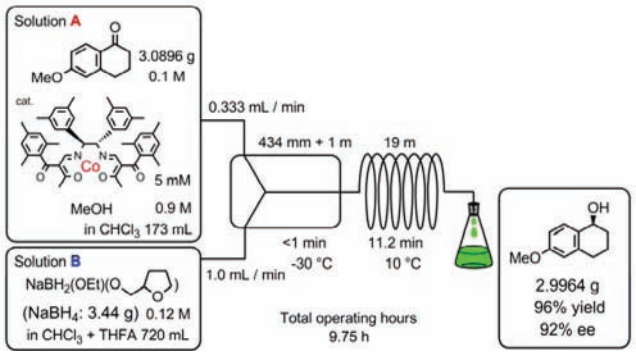
Table 2. Catalytic enantioselective borohydride reduction of various ketones under continuous-flow conditions[a] vs batch reactions



Entry	Substrate		Batch Yield /%[b]	Batch Ee /%[b]	Microreactor Yield /%[b]	Microreactor Ee /%[b]
1[c,d]		2a	80	87	92	90
2[e,f]		2b	95	92	91	90
3[c,g]		2c	87	90	88	91
4[c,g]		2d	96	87	84	90
5[c,f]		2e	96	67	78	68
6[c,f,h]		2f	32	68	37	67

[a]Reaction conditions: ketone (0.1 M), cobalt catalyst (5 mM), modified borohydride (0.12 M), MeOH (0.45 or 0.90 M), solvent: $CHCl_3$, quenched with 1.0 v/v % AcOH in MeOH, microreactor: 0.5-mm diameter, 434-mm length. SUS316 tube: 1.0-mm diameter, 10-m length. For batch reactions, the ratio of volume **B**/**A** corresponded to that of flow rate **B**/**A**. [b]Determined by HPLC analysis. [c]MeOH (0.90 M). [d]Flow ratio **B**/**A** = 1.5. [e]MeOH (0.45 M). [f]Flow ratio **B**/**A** = 3.0. [g]Flow ratio **B**/**A** = 2.5. [h]Catalyst **1a** was employed instead of **1b**.

Scheme 2. Long operating time for large-scale synthesis



dx.doi.org/10.1021/op300061k | Org. Process Res. Dev. 2012, 16, 1235−1240

long operating time for the large-scale synthesis was successfully demonstrated to afford a product on a gram scale with high enantioselectivity.

EXPERIMENTAL SECTION

MPS-α100 or MPS-α200 from Hitachi Plant Technology, Ltd. was used for experiments under continuous-flow conditions. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL α-400 or AL-400 spectrometer using $CDCl_3$ as a solvent. Melting point was measured with a Stanford Research Systems MPA100 or Shimadzu differential scanning calorimeter DSC-60. Column chromatography was conducted on silica gel (Kanto 60 N). HPLC analyses were performed with a Shimadzu LC-10A$_{VP}$ chromatograph using chiral column (Daicel Chiralpak IA or Chiralpak IB); the peak areas were obtained with a Shimadzu SPD-M10A$_{VP}$ diode array detector and Shimadzu Class-VP. Optical rotation was recorded on JASCO P-2200 digital polarimeters.

Dehydrated $CHCl_3$ was purchased from Kanto Chemical Co., Inc. and used without further purification.

Ee's of alcohols were determined by HPLC analysis. Yields of alcohols were determined by HPLC analysis by using standard curves (see Supporting Information) except for gram-scale synthesis.

Preparation of Cobalt Complex 1b.[17] To a solution of (*S*,*S*)-ligand[17] for **1b** (4.12 g, 5.9 mmol) and Et_3N (1.73 mL, 12.4 mmol) in degassed MeOH (90.0 mL) was added $CoCl_2$ (1.1307 g, 8.7 mmol) in degassed MeOH (23.0 mL) at 58 °C for 30 min under nitrogen atmosphere. After cooled to room temperature, to the solution was added degassed water (12.6 mL) to give precipitate. The resulting mixture was filtered, washed with degassed water (11.7 mL) and degassed MeOH (16.2 mL) and dried in vacuo for 4 h to afford orange-to-green solid (86% yield). Mp 334.68 °C (DSC).

General Procedure for Enantioselective Borohydride Reduction of Ketones (Tables 1 and 2). Solution A: To a solution of cobalt complex **1b** (24.8 mg, 0.033 mmol) and substrate **2b** (107.2 mg, 0.61 mmol) in dehydrated $CHCl_3$ (6.0 mL) was added MeOH (0.109 mL, 2.7 mmol) at room temperature under nitrogen atmosphere. Solution B: A mixture of $NaBH_4$ (118.0 mg, 3.1 mmol), tetrahydrofurfuryl alcohol (4.0 mL, 41.3 mmol), and EtOH (0.176 mL, 3.0 mmol) in dehydrated $CHCl_3$ (20.0 mL) was stirred at 0 °C for 3 h under nitrogen atmosphere.

Continuous-Flow System Using a Microreactor. For reactions in Table 1 and 2, MPS-α100 with two syringes and software to control the syringe pumps were used. Capacity of syringe A was 5 mL and that of syringe B was 25 mL. Syringe A and B were used for solution A and B, respectively. The inlets of a microreactor and two syringes were connected by Teflon tubes and 10-m length stainless tube (SUS316) was equipped to the outlet of the microreactor. The microreactor was kept at −20 °C and the SUS tube was at 10 °C. The end of the SUS tube was dipped in 50 mL of 1 v/v% AcOH in MeOH with stirring at −20 °C. Step 1: The inside of the pathway was washed with MeOH (150 mL) and then with $CHCl_3$ (150 mL). Subsequently, it was washed with 5 mL of dehydrated $CHCl_3$ from vessels under nitrogen atmosphere (5 times from each syringe, 50 mL). Step 2: 2.0 mL of dehydrated $CHCl_3$ from syringe A and 6.0 mL of solution B from syringe B were fed into the pathway at the flow rate of 2.0 mL/min and 6.0 mL/min, respectively. Step 3: 5.0 mL of solution A from syringe A and 15.0 mL of solution B from syringe B were introduced at the flow rate of 0.166 mL/min and 0.5 mL/min, respectively. Step 4: In order to rinse solution A in Teflon tube, syringe A and the pathway, 1.0 mL of dehydrated $CHCl_3$ from syringe A and 3.0 mL of solution B from syringe B were fed at the flow rate of 0.166 mL/min and 0.5 mL/min, respectively. Subsequently, 1.0 and 2.0 mL (0.222 mL/min and 0.444 mL/min) and then 1.0 and 1.0 mL (0.333 mL/min each) were employed to rinse solution A. Step 5: 5.0 mL (0.333 mL/min) of dehydrated $CHCl_3$ were fed from both syringes to give the mixture of product. Water was added to the solution, and the resulting mixture was extracted with $CHCl_3$ three times. The combined organic layers were washed with sat. aq $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated. The HPLC analysis of the crude product showed that the corresponding alcohol **3b** was obtained in 91% yield with 90% ee.

Batch System Using a Round-Bottom Flask. Solutions A and B used in the batch system were the same as those used in the flow system. To solution A (1.0 mL) was added 3.0 mL of solution B with stirring at −20 °C. Soon after that, the temperature was raised to 10 °C, and the mixture stirred for 12 min. The solution of 1 v/v % AcOH in MeOH was added. Then water was added, and the resulting mixture was extracted with $CHCl_3$ three times. The combined organic layers were washed with sat. aq $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated. The HPLC analysis of the crude product showed that the corresponding alcohol **3b** was obtained in 95% yield with 92% ee.

Procedure for Enantioselective Borohydride Reduction of 2b on a Large Scale in Continuous-Flow System Using a Microreactor. Solutions A1 and A2: Solutions were prepared in two vessels and both of them were simultaneously used for two syringes during the operation. To solutions of cobalt complex **1b** (333.3 mg, 0.44 mmol and 330.2 mg, 0.438 mmol) and substrate **2b** (1.5484 g, 8.8 mmol and 1.5412 g, 8.8 mmol) in $CHCl_3$ (86.4 mL for each vessel) were added MeOH (3.14 mL, 77.6 mmol for each vessel) at room temperature under nitrogen atmosphere. Solutions B1 and B2: Solutions were prepared in two vessels. After the first solution was used up, the second one was used. Mixtures of $NaBH_4$ (1.15 g, 30.4 mmol and 2.29 g, 60.5 mmol), tetrahydrofurfuryl alcohol (40 mL, 412.8 mmol and 80 mL, 825.6 mmol) and EtOH (1.75 mL, 30.0 mmol and 3.52 mL, 60.3 mmol) in $CHCl_3$ (200 and 400 mL) were stirred at 0 °C for 3 and 3.5 h under nitrogen atmosphere respectively. MPS-α200 with four syringes and software to control syringe pumps was used. Syringes A1 and A2 were 10 mL and B1 and B2 were 25 mL for solution A and B, respectively. The inlets of a microreactor and two syringes were connected by Teflon tubes and the 20-m length stainless tube (SUS316) was equipped to the outlet of the microreactor. The microreactor and 1-m length of the SUS tube were kept at −30 °C, and the rest of SUS tube was kept at 10 °C. The end of the SUS tube was dipped in 300 mL of 1 v/v % AcOH in MeOH with stirring at 0 °C for every 115 mL of solution B. Step 1: The inside of the pathway was washed with MeOH (150 mL) and $CHCl_3$ (150 mL). Subsequently, it was washed with 5 mL of dehydrated $CHCl_3$ from vessels under nitrogen atmosphere (5 times from each syringe, 100 mL). Step 2: 1.0 mL of dehydrated $CHCl_3$ from syringe A and 3.0 mL of solution B from syringe B were fed into the pathway at the flow rate of 1.0 mL/min and 3.0 mL/min, respectively. Step 3: The program for continuous-flow reactions in the software was used: 2.5 mL of solution A (0.333 mL/min) and 7.5 mL of

solution B (1.0 mL/min) were introduced. Meanwhile, 2.5 mL of solution A (0.375 mL/min) and 8.5 mL of solution B (1.229 mL/min) were charged into syringes, and 1.0 mL of solution B (6.0 mL/min) was pushed away to another vessel in order to exhaust generated hydrogen gas. Step 4: When the amounts of solutions A1 and A2 became less than 2.5 mL, dehydrated $CHCl_3$ was added to prevent introduction of gas to the pathway and to rinse and wash the pathway. The total amount of solution A including dehydrated $CHCl_3$ (195 mL) and solution B (585 mL) were consumed for a total operating time of 9.75 h. After the same workup as mentioned before, cobalt complex was removed by silica gel column chromatography (hexane/ethyl acetate = 10:1 to 4:1). Tetrahydrofurfuryl alcohol was removed under reduced pressure (8.0 mmHg, 75 °C). Purification by silica gel column chromatography (hexane/ethyl acetate = 10:1, 8:1, 7:1 to 6:1) and the second time (hexane/ethyl acetate = 10:1, 6:1 to 4:1) gave the corresponding alcohol **3b** in 2.9964 g (96% yield) with 92% ee.

1,2,3,4-Tetrahydro-5-methoxy-1-naphthalenol[11,18] (3a): white solid; mp 76.3−77.3 °C; ^{1}H NMR ($CDCl_3$) δ 1.72−2.00 (m, 4H), 2.56 (m, 1H), 2.74 (m, 1H), 3.83 (s, 3H), 4.78 (m, 1H), 6.76 (d, 1H, J = 8.0 Hz), 7.06 (d, 1H, J = 8.0 Hz), 7.20 (dd, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 18.0, 22.9, 31.7, 55.3, 68.1, 108.6, 120.5, 126.0, 126.5, 140.0, 157.0; HPLC Daicel chiralpak IA (2.5% EtOH in hexane; flow = 1.0 mL/min), 8.0 min (ketone), 12.8 min (minor), 14.5 min (major).

1,2,3,4-Tetrahydro-6-methoxy-1-naphthalenol[11,19] (3b): yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 2H), 1.92 (m, 3H), 2.64−2.83 (m, 2H), 3.78 (s, 3H), 4.73 (t, 1H, J = 4.4 Hz), 6.62 (d, 1H, J = 2.8 Hz), 6.76 (dd, 1H, J = 3.0, 8.0 Hz), 7.32 (d, 1H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 18.5, 29.6, 32.3, 55.2, 67.6, 112.4, 113.3, 130.1, 131.2, 138.6, 158.8; HPLC Daicel chiralpak IA (2.0% EtOH in hexane; flow = 1.0 mL/min), 16.9 min (ketone), 19.7 min (major), 26.1 min (minor).; $[\alpha]^{D}_{23}$ +22.8 (c 1.08, $CHCl_3$) (ref 5.: $[\alpha]^{D}_{20}$ +23.4 (c 1.01, $CHCl_3$), 98% ee (S)).

1,2,3,4-Tetrahydro-7-methoxy-1-naphthalenol[11,20] (3c): yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.70−2.02 (m, 4H), 2.61−2.80 (m, 2H), 3.80 (s, 3H), 4.75 (t, 1H, J = 4.8 Hz), 6.78 (dd, 1H, J = 3.0, 8.0 Hz), 6.97−7.04 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 19.1, 28.3, 32.3, 55.2, 68.4, 112.6, 114.2, 129.0, 129.8, 139.8, 157.9; HPLC Daicel chiralpak IA (2.5% EtOH in hexane; flow = 1.0 mL/min), 8.5 min (ketone), 17.2 min (minor), 18.5 min (major).

1,2,3,4-Tetrahydro-1-naphthalenol[11,19] (3d): orange oil; ^{1}H NMR ($CDCl_3$) δ 1.66 (br s, 1H), 1.78 (m, 1H), 1.86−2.05 (m, 3H), 2.68−2.78 (m, 1H), 2.79−2.90 (m, 1H), 4.79 (t, 1H, J = 4.8 Hz), 7.11 (m, 1H), 7.18−7.25 (m, 2H), 7.44 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 18.7, 29.2, 32.2, 68.1, 126.1, 127.5, 128.6, 128.9, 137.0, 138.7; HPLC Daicel chiralpak IB (0.8% EtOH in hexane; flow = 1.0 mL/min), 7.2 min (ketone), 15.9 min (major), 17.7 min (minor).

1-Phenyl-1-butanol[11,21] (3e): colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H, J = 7.4 Hz), 1.23−1.50 (m, 2H), 1.62−1.87 (m, 3H), 4.69 (m, 1H), 7.22−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.0, 19.0, 41.2, 74.4, 125.9, 127.5, 128.4, 144.9; HPLC Daicel chiralpak IB (0.8% EtOH in hexane; flow = 1.0 mL/min), 4.9 min (ketone), 11.3 min (minor), 12.8 min (major).

1,2,3,4-Tetrahydro-2,2-dimethyl-1-naphthalenol[16,22] (3f). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 3H), 0.99 (s, 3H), 1.53 (m, 1H), 1.68 (br s, 1H), 1.81 (m, 1H), 2.79 (m, 2H), 4.25 (s, 1H), 7.10 (m, 1H), 7.16−7.21 (m, 2H), 7.43 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.5, 25.6, 25.9, 31.9, 33.8, 76.6, 126.1, 127.3, 128.7, 128.8, 135.8, 138.4; HPLC Daicel chiralpak IA (1.0% EtOH in hexane; flow = 1.0 mL/min), 5.2 min (ketone), 13.3 min (minor), 15.9 min (major).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Analytical data including ^{1}H, ^{13}C NMR, and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*yamada@chem.keio.ac.jp.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Mikami, K.; Lautens, M., Eds. *New Frontiers in Asymmetric Catalysis*; John Wiley & Sons, Inc.: New York, 2007; Ojima, I., Ed. *Catalytic Asymmetric Synthesis*, 3rd ed.; John Wiley & Sons, Inc.: New York, 2010.

(2) Nagata, T.; Yorozu, K.; Yamada, T.; Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2145−2147.

(3) Yamada, T.; Nagata, T.; Sugi, K. D.; Yorozu, K.; Ikeno, T.; Ohtsuka, Y.; Miyazaki, D.; Mukaiyama, T. *Chem.—Eur. J.* **2003**, *9*, 4485−4509.

(4) Nagata, T. Unpublished results.

(5) Ohtsuka, Y.; Kubota, T.; Ikeno, T.; Nagata, T.; Yamada, T. *Synlett* **2000**, 535−537.

(6) Benson, R. S.; Ponton, J. W. *Trans. Inst. Chem. Eng.* **1993**, *A71*, 160−168.

(7) Schubert, K.; Bier, W.; Keller, W.; Linder, G.; Seidel, D. *Chem. Eng. Process* **1993**, *32*, 33−43.

(8) Asano, Y.; Togashi, S.; Tsudome, H.; Murakami, E. *Pharm. Eng.* **2010**, *30* (Jan/Feb), 1−8.

(9) (a) Yoshida, J.-i.; Saito, K.; Nokami, T.; Nagaki, A. *Synlett* **2011**, 1189−1194. (b) Jähnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 406−446. (c) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300−2318. (d) Baumann, M.; Baxendale, I. R.; Ley, S. V. *Mol. Diversity* **2011**, *15*, 613−630. (e) Ahmed-Omer, B.; Brandt, J. C.; Wirth, T. *Org. Biomol. Chem.* **2007**, *5*, 733−740.

(10) (a) Jönsson, C.; Lundgren, S.; Haswell, S. J.; Moberg, C. *Tetrahedron* **2004**, *60*, 10515−10520. (b) Odedra, A.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 2699−2702. (c) Hamberg, A.; Lundgren, S.; Wingstrand, E.; Moberg, C.; Hult, K. *Chem.—Eur. J.* **2007**, *13*, 4334−4341.

(11) Sugi, K. D.; Nagata, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1996**, 737−738.

(12) Iwakura, I.; Hatanaka, M.; Kokura, A.; Teraoka, H.; Ikeno, T.; Nagata, T.; Yamada, T. *Chem.—Asian J.* **2006**, *1*, 656−663.

(13) Sugi, K. D.; Nagata, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1996**, 1081−1082.

(14) In a flow rate lower than 1.0 mL/min, efficient mixing cannot be expected.

(15) Yamada, T.; Ohtsuka, Y.; Ikeno, T. *Chem. Lett.* **1998**, 1129−1130.

(16) Nagata, T.; Sugi, K. D.; Yamada, T.; Mukaiyama, T. *Synlett* **1996**, 1076−1078.

(17) Nagata, T.; Imagawa, K.; Yamada, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 2139−2150.

(18) Penick, M. A.; Mahindaratne, M. P. D.; Gutierrez, R. D.; Smith, T. D.; Tiekink, E. R. T.; Negrete, G. R. *J. Org. Chem.* **2008**, *73*, 6378−6381.

(19) Matsumura, K.; Arai, N.; Hori, K.; Saito, T.; Sayo, N.; Ohkuma, T. *J. Am. Chem. Soc.* **2011**, *133*, 10696−10699.
(20) Inagaki, T.; Ito, A.; Ito, J.; Nishiyama, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9384−9387.
(21) Ooka, H.; Arai, N.; Azuma, K.; Kurono, N.; Ohkuma, T. *J. Org. Chem.* **2008**, *73*, 9084−9093.
(22) Ohkuma, T.; Sandoval, C. A.; Srinivasan, R.; Lin, Q.; Wei, Y.; Muñiz, K.; Noyori, R. *J. Am. Chem. Soc.* **2005**, *127*, 8288−8289.