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Catalytic Asymmetric Amination of *meso*-Epoxide Using Soy Polysaccharide (Soyafibe S-DN)

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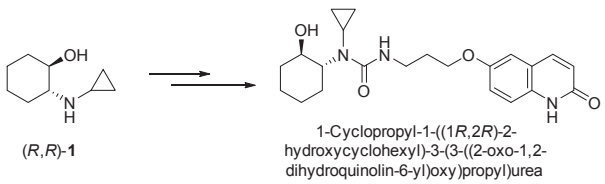
Abstract

The asymmetric amination of epoxides is an effective method to synthesize chiral β-aminoalcohols and their components as pharmaceuticals. We have developed a new catalyst system for the asymmetric amination of 1,2-epoxycyclohexane with cyclopropylamine. We have also found that water-soluble soy polysaccharide (Soyafibe S-DN) functions as a catalyst. This catalytic reaction proceeded under mild conditions in hydrous toluene at 37–40 °C. (1*R*,2*R*)-2-(cyclopropylamino)-cyclohexan-1-ol was obtained at 64% enantiomeric excess (ee) by the asymmetric amination of 1,2-epoxycyclohexane with cyclopropylamine using this catalyst system; it was also made at >99% ee by purification as the fumarate salt. The catalytic activity of this soluble soy polysaccharide remained unchanged, even when treated with a protease, but its activity disappeared when treated with a sugar chain degrading enzyme. These results indicate that the polysaccharide rather than the protein acts as the catalyst for this reaction. Thus, we have discovered for the first time that polysaccharides can act as asymmetric catalysts for the amination of 1,2-epoxycyclohexane.

1. Introduction

Herein, we report a new catalyst for the asymmetric amination of *meso*-epoxide as a method to synthesize (1*R*,2*R*)-2-(cyclopropylamino)cyclohexan-1-ol ((*R*,*R*)-**1**) with moderate enantioselectivity. (*R*,*R*)-**1** is transformed into 1-cyclopropyl-1-((1*R*,2*R*)-2-hydroxycyclohexyl)-3-(3-((2-oxo-1,2-dihydroquinolin-6-yl)oxy)propyl)urea (Scheme 1) as a phosphodiesterase III inhibitor with effects against vascular hypertrophy.[1] Optically active *trans*-2-amino-1-cycloalkanols are produced by amination of 1,2-epoxycycloalkanes with amine compounds by three methods: (**A**) optically resolving racemic mixtures of *trans*-2-amino-1-cycloalkanols,[2] (**B**) introducing asymmetric carbons at other positions and separating the resulting diastereomers,[3] and (**C**) conducting the asymmetric amination of 1,2-epoxycycloalkanes with amines in the presence of chiral catalysts.[4] Among the methods of (**A**), in particular, there are known approaches using optically active acids as resolving agents, methods of separation by column chromatography utilizing optically active packing materials, and syntheses using enzymes derived from animals or microorganisms. With the methods (**A**) and (**B**), the theoretical yield does not exceed 50%, and it is necessary to use a resolving agent in the same amount as the product or to carry out purification with a large-volume column, which is problematic for industrial processes. With the method (**C**), on the other hand, it is possible to produce the desired *trans*-2-amino-1-cycloalkanols by a short process with a 100% maximum theoretical atom efficiency. However, high enantioselectivity has been reported mainly with a combination of an organometallic catalyst and an amine with aromatic substituents, such as aniline or benzylamine, and there are only a few reports using aliphatic amines, such as isopropylamine, *tert*-butylamine, or piperidine. Therefore, the purpose of the present study is to develop a new catalyst for the asymmetric amination of 1,2-epoxycyclohexane using cyclopropylamine.



Scheme 1. Synthesis of a phosphodiesterase III inhibitor.

2. Results and Discussion

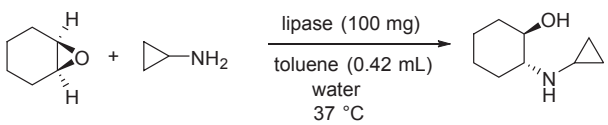
The asymmetric amination of 1,2-epoxycyclohexane **2** by lipases has not been reported, but the same reaction with

styrene oxide as the epoxy component has been reported by other groups.[5] Thus, we screened commercial lipases for catalysis of the reaction of **2** with cyclopropylamine **3**. Generally, enzymatic reactions require the presence of a certain level of water;[6] therefore, the reaction was performed in a hydrous solvent. Toluene is the preferable solvent for screening of enzymes for the catalyzed reaction, since *trans*-2-(cyclopropylamino)-cyclohexan-1-ol ((*rac*)-**1**) was obtained at only 1% conversion in toluene containing 10% water at 40 °C after 21 h. Preliminary investigation revealed that Lipases MY, TL, QLM, and OF were effective for the reaction of **2** with **3** (Table 1, Entries 3–6). Within 18 h at 37 °C, 20–28% conversion rates and 69% ee were obtained. The specific rotation of a solution of (*R*,*R*)-**1** in methanol had been reported previously.[2] The specific rotation of our synthesized (*R*,*R*)-**1** by this reaction, after purification of the fumarate salt, was the same as the reference. The other lipases degraded the reaction mixture, and no enantiomeric excess was observed (Table 1, Entries 1–2). The effect of additional water (10–20 µL) was studied with Lipase OF on a 100 mg scale; (*R*,*R*)-**1** was obtained at a nearly 25% conversion rate at all water levels (Table 1, Entries 9–11). On the other hand, no reaction was observed in the absence of water (Table 1, Entry 7).

In the next study, we investigated the relationship between lipase activity and the conversion rate to the aminoalcohol using Lipases OF, QLM, TL, and MY. Furthermore, the same procedure was carried out for lipases that were autoclaved at 120 °C for 30 min. The lipase activity was determined using Lipase Kit-S, which monitors the absorbance at a wavelength of 412 nm.[7] There is typically a correlation between absorbance and lipase activity; namely, a high absorbance indicates high activity. The absorbance values measured for Lipases OF, QLM, TL, and MY using Lipase Kit-S were nearly the same (∼2), even though differences in the conversion rates of the reaction using these lipases as catalysts (Table 2, Entries 1, 3, 5, and 7) were observed. In the case of Lipase MY, the conversion rate was only 7%, which was lower than with the other lipases. Unexpectedly, there was no correlation between the activity of the lipase and its conversion rate to aminoalcohol. Furthermore, for reactions using autoclaved lipases, the conversion rates were unchanged before and after autoclaving, despite the absence of lipase activity (Table 2, Entries 2, 4, 6, and 8). These results indicated that the lipases were not behaving as catalysts for this reaction. Therefore, we presumed that the true catalyst of this reaction was a thermostable enzyme other than the commercial lipases or, alternatively, a non-enzymatic component in the commercial lipases.

Therefore, we turned our focus to the manufacturing processes and raw materials used in lipase production. Commercially available lipase is produced by culturing microorganisms; materials used for culturing include parched soybean flour, polypeptone, corn-steep-liquor, dipotassium phosphate, soybean oil, and polyoxyethylene cetyl stearyl ether. Specifically, ∼4% of the cultivated raw material components are parched soybean flour.[8] In addition, the method of extraction used to obtain the enzyme from the culture medium is generally carried out by adding ammonium sulfate or acetone. We suspected that the active ingredient in the enzyme was parched soybean flour, which was an insoluble material in the culture broth. Therefore, we investigated this reaction using soybean products, including parched soybean flour, and the results are shown in Table 3. As expected, we confirmed that parched soybean flour acted as a catalyst for the desired reaction. Within 64 h at 37 °C, a 52% conversion rate and 62% ee were obtained (Table 3, Entry 1). However, this ee value was somewhat lower than that obtained using the lipase as a catalyst, and a long reaction time was required. In addition, defatted soybean powder (Soya flour FT-N) had a higher conversion rate in a shorter time than did lipase as catalyst (Table 3, Entry 4). On the other hand, hydrolyzed soy protein (A-1000) did not act as a catalyst,

Table 1. Lipase-mediated amination of 1,2-epoxycyclohexane with cyclopropylamine

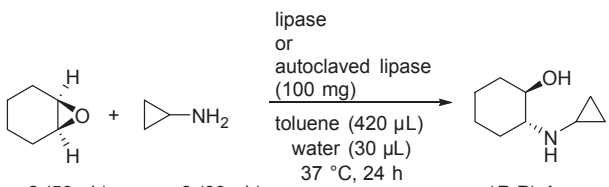


2 (50 µL) **3** (30 µL) (*R*,*R*)-**1**

Entry	Lipase	Water (µL)	Time (h)	Conv. (%)[a]	(*R*,*R*)-**1** (% ee)[a]
1	QLC	15	18	2	0
2	QLG	15	18	2	0
3	MY	15	18	7	65
4	TL	15	18	20	63
5	QLM	15	18	28	65
6	OF	15	18	21	70
7	OF	-	24	0	0
8	OF	5	24	8	65
9	OF	10	24	24	69
10	OF	15	24	25	69
11	OF	20	24	25	69

[a]Conversions and enantiomeric excess (ee) values were determined by GC analysis.

Table 2. Relationship between reactivity and lipase activity[a]



2 (50 µL) **3** (30 µL) (*R*,*R*)-**1**

Entry	Lipase	Auto-clave[a]	Lipase Kit-S Abs. (412 nm)[b]	Conv. (%)[c]	(*R*,*R*)-**1** (% ee)[c]
1	OF	No	2.07	16	71
2	OF	Yes	0	8	67
3	QLM	No	2.03	23	66
4	QLM	Yes	0.13	23	68
5	TL	No	2.03	18	69
6	TL	Yes	0	23	69
7	MY	No	2.15	7	55
8	MY	Yes	0	6	50

[a]The conditions were 121 °C for 30 min. [b]The measurement was carried out at 1 mg/mL of lipase. [c]Conversions and ee values were determined by GC analysis.

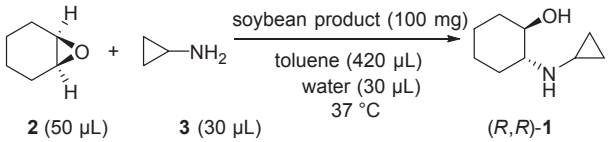
resulting in a conversion rate of only 1% (Table 3, Entry 2). Furthermore, when a soy protein isolate (FUJIPRO F) was used as the catalyst, the conversion rate and ee value were both low (Table 3, Entry 3). It is noteworthy that soluble soy polysaccharide (Soyafibe S-DN) produced excellent catalytic activity, and (*R*,*R*)-**1** was obtained with a high conversion rate and ee value (Table 3, Entry 5). From these results, we determined that the true active ingredient of the catalytic asymmetric amination of **2** with **3** was a substance found in soy components.

Soyafibe S-DN is used as a food additive and is mainly composed of polysaccharides as the dietary fiber, containing only 9.2% crude protein.[9] We speculated that the polysaccharides in soybean were among the active ingredients. To verify this, the amination reaction was carried out using enzymatic digests of Soyafibe S-DN. The digestion method for enzymes such as this has been reported in the literature.[10] When the polysaccharase (hemicellulase and pectinase) digests of Soyafibe S-DN were used as a catalyst, product **1** was not obtained (Table 4, Entries 2 and 3). On the contrary, even if Soyafibe S-DN digested with a proteolytic enzyme was used, the conversion rate was slightly decreased, but the ee value was unchanged (Table 4, Entries 4 and 5). These results indicate that polysaccharide rather than protein acts as a catalyst for this reaction. In other words, we have discovered for the first time that polysaccharides can be asymmetric catalysts for the amination of *meso*-epoxide. Examples using polysaccharides as catalysts have been reported by other groups, including hydrolysis reactions with crystalline cellulose[11] and ring-opening polymerizations of lactones with cyclodextrin.[12] The chemical structure of Soyafibe S-DN has been reported by Nakamura *et al*.[9,10] Soyafibe S-DN is composed of a rhamnogalacturonan backbone with many branched chains of galactan and arabinan, the molecular weight ranged from approximately 5,000 to 550,000 Da. In addition, the three-dimensional molecular structure was observed with scanning probe microscope to be a star shape, in which sugar chains are radially extended. Although the structure of agglomerated Soyafibe S-DN has not been reported, it is expected to have a complicated form of many intertwined star shaped molecular species with many pores on the surface. Therefore, we considered that the asymmetric amination of *meso*-epoxide by Soyafibe S-DN may also transport epoxide **2** or amine **3** into the pore constituted by the sugar chain, much like the case of cyclodextrin.[13]

Next, optimization of the water content was conducted for the scale-up synthesis of (*R*,*R*)-**1** using Soyafibe S-DN as a catalyst. In this experiment, 1.2 equivalents of amine **3** relative to epoxide **2** were used. Because the boiling point of amine **3** was lower than that of the epoxide, it was easy to remove excess **3** from the product with a rotary evaporator. The results in Table 5 show that this reaction using Soyafibe S-DN requires the addition of water in the same manner as in the case of lipase, and the optimal amount of water is 25 to 40 µL. It was found that Soyafibe S-DN does not act as a catalyst for the reaction unless water is added, even though the water content is 5.4% in the purchased form.[9]

We next performed a multi-gram scale-up synthesis under the identified optimal conditions (Scheme 2). Epoxide **2** (35.0 g, 357 mmol) was reacted with amine **3** (24.4 g, 427 mmol, 1.2 eq.) with Soyafibe S-DN (70.0 g) in water (28.0 mL) and toluene (198 mL). The crude product, (*R*,*R*)-**1**, was obtained with a 95% conversion rate and 64% ee after 26 h, which was approximately the same as the small-scale result. The reaction mixture was filtered under reduced pressure with Kiriyama funnel filter paper, and the filtrate was concentrated under reduced pressure to obtain crude (*R*,*R*)-**1** as an oil. The crude yield of **1** was 87%, indicating that a portion of the product was adsorbed on the

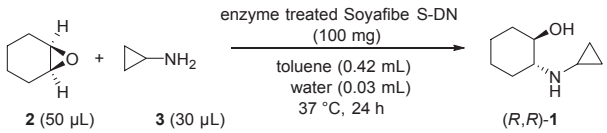
Table 3. Screening of soybean products



Entry	Soybean product	Time (h)	Conv. (%)[a]	(*R*,*R*)-**1** (% ee)[a]
1	Parched soybean flour	64	52	62
2	Hydrolyzed soy protein	64	1	0
3	Soy protein isolate	18	4	19
4	Defatted soybean powder	16	32	63
5	Soluble soy polysaccharide	16	69	67

[a]Conversions and ee values were determined by GC analysis.

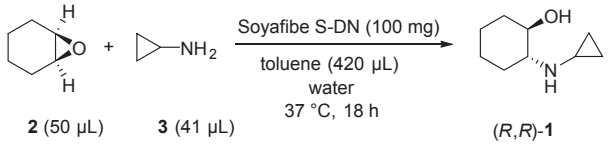
Table 4. Reaction of **2** with **3** using enzymatic digests of soyafibe S-DN



Entry	Enzyme	Enzymatic digestion condition	Conversion (%)[a]	(*R*,*R*)-**1** (% ee)[a]
1	-	-	40	64
2	Hemicellulase 46 mg	50 mmol/L Sodium Acetate Buffer, pH 4.5, 50 °C, 18 h	0	0
3	Pectinase 50 µL	50 mmol/L Sodium Acetate Buffer, pH 5, 40 °C, 20 h	0	0
4	Trypsin 50 mg	20 mmol/L Sodium Acetate Buffer, pH 7, 40 °C, 24 h	35	65
5	Subtilisin A 10.9 mg	50 mmol/L Sodium Phosphate Buffer, pH 7.5, 37 °C, 24 h	34	64

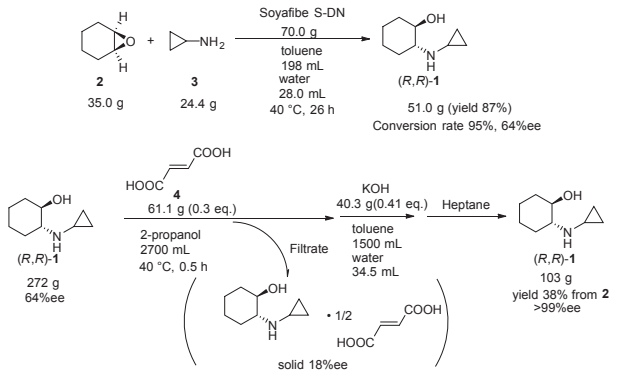
[a]Conversions and ee values were determined by GC analysis.

Table 5. Optimization of water amount



Entry	Water (μL)	Conv. (%)[a]	(*R*,*R*)-**1** (% ee)[a]
1	5	9	59
2	10	36	63
3	15	58	65
4	20	72	66
5	25	75	66
6	30	77	66
7	35	74	66
8	40	74	66
9	45	72	65
10	50	70	65
11	75	50	59
12	100	28	44

[a]Conversions and ee values were determined by GC analysis.

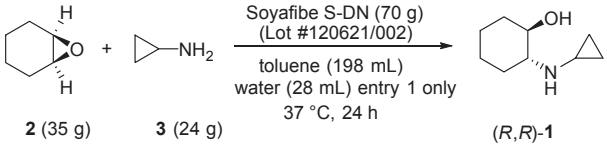


Scheme 2. Scale-up synthesis of (*R*,*R*)-**1**.

Soyafibe S-DN. Next, we examined purification conditions. The (*rac*)-**1** fumarate salt was obtained as a solid in 2-propanol, and the optically active salt was marginally precipitated. The remainder of the crude product (*R*,*R*)-**1** was then subjected to purification. The crude (*R*,*R*)-**1** (content: 272 g, 1.75 mol, 64% ee), fumaric acid (61.1 g, 0.526 mol), and 2-propanol (2700 mL) were stirred at 40 °C, and then the (*rac*)-**1** fumarate salt seed (10 mg) and activated carbon (27.2 g) for decolorization were added. The resulting solid and carbon were filtered, and the filter cake contained (*R*,*R*)-**1** with an 18% ee. The filtrate was concentrated, the residue was basified with KOH (40.3 g, 718 mmol) and water (34.5 mL), then the mixture was extracted with toluene (1500 mL). The organic solvent was evaporated, and the residue was recrystallized from *n*-heptane to obtain (*R*,*R*)-**1** (103 g, colorless crystals, >99% ee). This method could be easily scaled up from the laboratory to the manufacturing scale.

To evaluate the reusability of Soyafibe S-DN as a catalyst, the reaction mixture was filtered through filter paper, and the catalyst was recovered and reused without further treatment. The recycled Soyafibe S-DN was efficient for the conversion of **3** to (*R*,*R*)-**1** even after three uses without a loss of selectivity; the enantiomeric excess was about 64% (Table 6,

Table 6. Reusability of soyafibe S-DN for the amination of 1,2-epoxycyclohexane



Entry	Reuse times	Amount of water[a,b] (w/w)	Conv. (%)[c]	(*R*,*R*)-**1** (%ee)[c]
1	-	0.40	92	64
2	1	0.35	92	65
3	2	0.30	90	64
4[d]	-	0.40	87	64

[a]Determined by Karl Fischer moisture titration. [b]Based on the initial Soyafibe S-DN weight. [c]Conversions and ee values were determined by GC analysis. [d]Soyafibe S-DN of lot #120628/002 was used.

Entry 3). The conversion rate decreased slightly with the third round because the amount of water in the recovered catalyst was reduced. Therefore, the catalyst can be reused any number of times by supplementing the lost water content. It was not possible to recover the adsorbed (*R*,*R*)-**1** by washing the catalyst with toluene after the reaction. Furthermore, we investigated the difference between lots of Soyafibe S-DN. When Soyafibe S-DN lots #120628/002 and #120621/002 were used, similar ee values were obtained (Table 6, Entries 1 and 4). Although the conversion rates were slightly different between lots, we assumed that this was likely due to the heterogeneous reaction conditions. Therefore, Soyafibe S-DN is a suitable catalyst for the asymmetric amination of *meso*-epoxide that can be used for industrial processes.

3. Conclusion

In summary, we have developed an asymmetric amination reaction of *meso*-epoxide using a water-soluble soy polysaccharide (Soyafibe S-DN) as a catalyst in hydrous toluene. This catalyst system is advantageous for the asymmetric amination of 1,2-epoxycyclohexane with cyclopropylamine, making it possible to efficiently produce (*R*,*R*)-2-(cyclopropylamino)-cyclohexan-1-ol. In addition, sugar chains of polysaccharides are thought to function as the catalysts for this reaction. With further elucidation of the reaction mechanism, we envision that new catalyst fields will be developed.

4. Experimental

General. NMR spectra were recorded on a JEOL AL-300 (^{1}H NMR 300 MHz, ^{13}C NMR 75 MHz) spectrometer. Chemical shifts for the ^{1}H NMR are reported in parts per million (ppm) relative to TMS (tetramethylsilane) at 0 ppm in $CDCl_3$. Chemical shifts for ^{13}C NMR are reported in parts per million (ppm) relative to $CDCl_3$ (77.16 ppm) with complete proton decoupling. Melting points were determined with a micro-melting point apparatus (Yanagimoto) and are uncorrected. Optical rotations were measured on a JASCO P-1020 digital polarimeter. Conversion rate and enantiomeric excess were determined by GC analysis on a SHIMADZU GC-2010

(Supelco β-DEX325 (30 m × 0.25 mm × 0.25 μm)) with comparison to synthesized racemic materials.

Materials. All reagents were obtained commercially and used as received unless otherwise noted. The solvents were purchased from KANTO CHEMICAL CO., INC., and used without further purification. 1,2-Epoxycyclohexane and cyclopropylamine were purchased from Tokyo Chemical Industry Co., Ltd., and used without further purification. Lipase OF, QLM, TL, OF, OLG; Soyafibe S-DN, FUJIPRO F; Soya flour FT-N; and A-1000 were purchased from Meito Sangyo Co., Ltd; Fuji Oil Co., Ltd.; The Nisshin OilliO Group, Ltd.; and AJINOMOTO Co., Inc., respectively. Parched soybean flour was obtained from a general store. Lipase Kit-S was purchased from DS Biomedical Co., Ltd. Hemicellulase AMANO 90G and Papain W-40 were purchased from Amano Enzyme, Inc.; Pectinase, Trypsin, Pepsin, Subtilisin A, and α-Chymotrypsin were purchased from Sigma-Aldrich Co., LLC.

Procedure and Analytical Data. General Procedure for Catalytic Amination of 1,2-Epoxycyclohexane (2) with Cyclopropylamine (3) at the 0.5 mL Scale: A mixture of 1,2-epoxycyclohexane (**2**) (50 μL, 0.49 mmol), cyclopropylamine (**3**) (30 μL, 0.43 mmol), and the catalyst (as lipase or soybean product) (100 mg) in toluene (0.42 mL) with the required volume of water was shaken at 37 °C for the specified time. After removal of the catalyst by filtration, the filtrate was analyzed by GC to obtain the ee value of (1*R*,2*R*)-2-(cyclopropylamino)cyclohexan-1-ol ((*R*,*R*)-**1**). The conversion rate was calculated as follows, using the effective carbon number (ECN) concept:[14]

Product **1**: 9 (number of aliphatic carbon atoms) × 1 (ECN contribution) + 1 (number of secondary alcohol oxygen atoms) × (−0.75) (ECN contribution) + 1 (number of secondary amine nitrogen atoms) × (−0.75) (ECN contribution) = 7.5.

Substrate **2**: 6 (number of aliphatic carbon atoms) × 1 (ECN contribution) + 1 (number of ether oxygen atoms) × (−1) (ECN contribution) = 5.

$$\text{Conversion (\%)} = 100 \times (A_p/7.5)/((A_p/7.5) + (A_s/5))$$

A_p = peak area for total of (*R*,*R*)-**1** and (*S*,*S*)-**1** from filtrate

A_S = peak area for **2** from filtrate

Procedure for Preparation of Autoclaved Lipase: Lipase (100 mg) was autoclaved at 121 °C for 30 min. The autoclaved lipase was dried under vacuum and used without further purification.

General Procedure for Preparation of Digested Soyafibe S-DN: Hemicellulase (46 mg) was added to 50 mL of a 1% (w/w) Soyafibe S-DN solution in 50 mM sodium acetate buffer, pH 4.5, and incubated at 50 °C for 18 h. The reaction mixture was heated at 90 °C for 20 min to inactivate the enzyme and then freeze-dried. The obtained enzyme digests were used without further purification.

Large Scale Preparation of (1*R*,2*R*)-2-(Cyclopropylamino)cyclohexan-1-ol ((*R*,*R*)-1): Under a nitrogen atmosphere, **2** (35.0 g, 357 mmol), **3** (24.4 g, 427 mmol, 1.2 eq.), Soyafibe S-DN (70.0 g), water (28.0 mL), and toluene (198 mL) were stirred at 40 °C for 26 h. The reaction mixture was filtered. The filtrate was evaporated to give (*R*,*R*)-**1** (58.4 g, 64% ee) as a crude product.

Purification of (1*R*,2*R*)-2-(Cyclopropylamino)cyclohexan-1-ol ((*R*,*R*)-1): The crude (*R*,*R*)-**1** (272 g, 1.75 mol, 64% ee), fumaric acid (61.1 g, 0.526 mol), and 2-propanol (2700 mL) were stirred at 40 °C, and then racemic *trans*-2-(cyclopropylamino)-cyclohexan-1-ol fumarate salt crystals (10 mg) and activated carbon (27.2 g) were added and stirred for 30 min. The mixture was cooled to room temperature and stirred for 60 min and then filtered through Celite, which was then washed with 2-propanol (272 mL). The filtrate was concentrated. The residue was basified with KOH (40.3 g, 0.718 mol) and water (34.5 mL), then the mixture was extracted with toluene (1500 mL). The organic layer was washed with water (68 mL × 3) and concentrated. The residue was recrystallized from *n*-heptane to obtain (*R*,*R*)-**1** (103 g, colorless crystals, >99% ee). Yield: 38% from **2**, mp 46 °C, $[\alpha]^{22}_D$ −60.1° (c = 1.0, methanol). The ee value was determined by GC (β-DEX 325, 30 m × 0.25 mm × 0.25 μm; carrier gas, He (pressure 94 kPa); column temperature, 120 °C); t_R of (*S*,*S*)-**1**, 26.3 min; t_R of (*R*,*R*)-**1**, 27.1 min. ^{1}H NMR (300.40 MHz, $CDCl_3$): δ 0.19–0.55 (4H, m), 0.94–1.07 (1H, m), 1.18–1.30 (3H, m), 1.71–1.76 (2H, m), 2.00–2.06 (1H, m), 2.19–2.36 (3H, m), 3.06–3.14 (1H, m). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 5.69 (CH_2), 7.22 (CH_2), 24.19 (CH_2), 24.85 (CH_2), 27.50 (CH), 30.71 (CH_2), 33.26 (CH_2), 63.54 (CH), 72.94 (CH).

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