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Practical synthetic process for enantiopure 1-benzyl-3-hydroxypyrrolidine

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ABSTRACT

The synthesis of (*S*)-1-benzyl-3-hydroxypyrrolidine (*S*)-**5** comprised the asymmetric hydroboration of 1-benzyl-3-pyrroline **4**, followed by oxidation and chiral purification via diastereomeric salt formation. The asymmetric borane reagent was generated 'in situ' from $NaBH_4$, BF_3–OEt_2, and (+)-α-pinene **1** (85% ee) and reacted with **4**, prepared from *cis*-1,4-butenediol **3**, to give crude product (*S*)-**5**. The following chiral purification via diastereomeric salt formation proceeded to afford (*S*)-**5** with >99% ee. The optimized process was successfully scaled up to an industrial scale to produce a 252 kg batch of (*S*)-**5**.

1. Introduction

Enantiopure 1-benzyl-3-hydroxypyrrolidine **5** is well known as a useful intermediate for various drugs and clinical drug candidates,[1] such as Darifenacin, Barnidipine, and Panipenem. Thus, a great variety of methods have been reported as follows: the reduction of the imide precursor with an alkaline metal hydride,[2] asymmetric hydroboration of 1-benzyl-3-pyrroline;[3] resolution of racemic 1-benzyl-3-hydroxypyrrolidine (*RS*)-**5** with enantiopure lactic acid,[4] phenylalanine derivative,[5] or isoquinoline carboxylic acid derivative,[6] asymmetric hydrolysis with an esterase enzyme;[7] enzymatic asymmetric reduction of racemic 1-benzyl-3-pyrrolidinone;[8] stereoselective inversion of the mesylate or ester of enantiopure 1-benzyl-3-hydroxypyrrolidine followed by hydolysis;[9] resolution of (*RS*)-**5** via cluster-formation,[10] ring-closure of 4-halo-3-hydroxybutane derivatives[11] or 1-bromo-3-butene-2-one;[12] ring-closure of malic acid followed by hydride reduction;[13] and enzymatic hydroxylation of 1-benzylpyrrolidine.[14]

At an early stage of process development, we established the resolution of (*RS*)-**5** with naturally-denied L-phenylalanine *p*-toluenesulfonamide (Ts-(*S*)-Phe) as a resolving agent, while considering economical points of view and ease of scale-up to an industrial scale.[5] However, the productivity of the resolution process was insufficient because recrystallization of the salt had to be repeated to obtain >99% ee and no effective racemization of the counter enantiomer could be established. Therefore, the maximum yield by direct resolution of (*RS*)-**5** via diastereomeric salt formation is 50% of the racemic form. In order to overcome this low productivity, we sought a practical strategy suited for an industrial-scale production. As a result, we successfully contrived a hybrid process composed of the asymmetric hydroboration of 1-benzyl-3-pyrroline **4** and enantiomeric purity improvement by a resolution process of (S)-enriched **5** with Ts-(*S*)-Phe via diastereomeric salt formation.[15]

2. Results and discussion

The hybrid process is mainly built up over three stages: (a) synthesis of 1-benzyl-3-pyrroline **4**; (b) asymmetric hydroboration to **4** with borane species **2a**, **2b**, and **2c**, followed by alkaline oxidation; and (c) enantiomeric purity improvement of (*S*)-enriched **5** (84% ee) via diastereomeric salt formation, as illustrated in Scheme 1.

2.1. Synthesis of 1-benzyl-3-pyrroline 4

Starting material, *cis*-1,4-butenediol **3** was chlorinated with thionyl chloride to give *cis*-1,4-dichlorobutene followed by cyclization with benzylamine to give **4**.[16] However, residual non-reacted benzylamine deactivated the borane species **2a**, **2b**, and **2c** in the next step, because of an unfavorable side reaction, nitrogen–boron complex formation. Accordingly, the effective removal of excessive benzylamine was crucial and so liquid–liquid extraction was carried out, as shown in Table 1. Considering both the yield of **4** and removal efficiency of benzylamine, liquid–liquid extraction was performed at pH 7.2–7.5. It was found that the recovered benzylamine could be reused in the cyclization reaction of the next batch without any further purification. The isolated **4** was purified by distillation under reduced pressure, minding both its atmosphere and temperature, since intermediate **4** was found to be easily oxidized into 1-benzylpyrrole in the presence of a trace amount of oxygen or by heat.[17]

2.2. Asymmetric hydroboration–oxidation

It is known that enantiopure diisopinocampheylborane **2c**, which was prepared by the reaction between (+)-α-pinene **1** with

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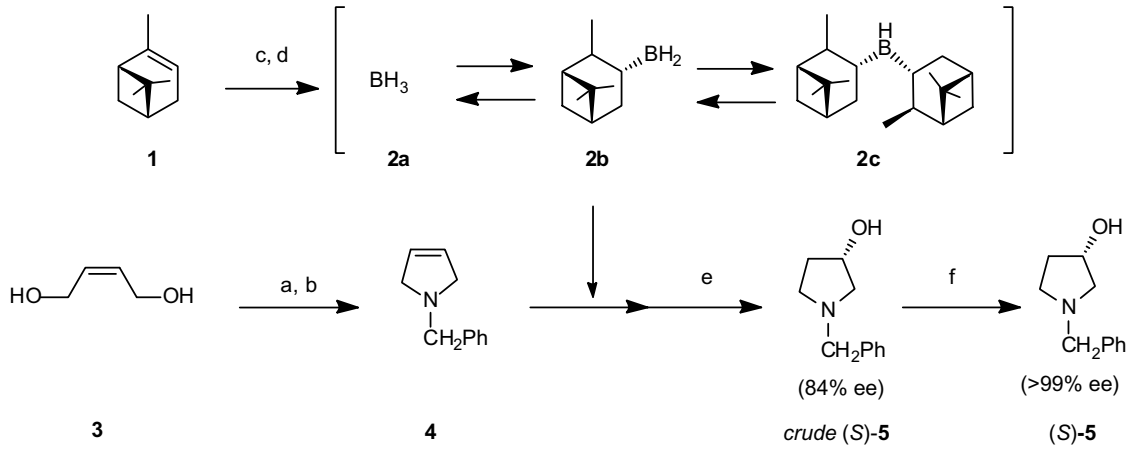

Scheme 1. Reaction conditions: a) $SOCl_2/C_5H_5N$, b) $PhCH_2NH_2$, c) $NaBH_4$/THF, d) BF_3-OEt_2, e) H_2O_2/NaOHaq. f) chiral purification via salt formation, (*S*)-phenylalanine *p*-toluenesulfonamide (Ts-(*S*)-Phe)/denatured EtOH.

Table 1
pH dependency of liquid–liquid extraction

Entry	pH	Recovery of **4**[a] (%)	Removal of benzyl amine[b] (%)
1	6.5	29	>99
2	7.0	58	99
3	7.2	73	99
4	7.5	77	98
5	8.0	85	94

[a] Yield was calculated on the amount of **4** contained in the cyclization solution.
[b] Yield was calculated on the amount of benzylamine contained in the cyclization solution.

Table 2
Effect of activating agent of $NaBH_4$ on reactivity

Entry	Activating agent	Solvent	Yield of limonene[a] (%)	Yield of crude (*S*)-**5** (%)	Enantiomeric purity of crude (*S*)-**5** (% ee)
1	H_2SO_4	Diglyme[b]	Trace	80	81
2	H_2SO_4	Monoglyme[c]	Trace	53	75
3	H_2SO_4	THF	22	—[d]	—[d]
4	H_2SO_4	1,4-Dioxane	15	—[d]	—[d]
5	H_2SO_4	Isopropylether	15	—[d]	—[d]
6	H_2SO_4	Tetrahydropyrane	8	—[d]	—[d]
7	BF_3–OEt_2	THF	nd[e]	92	82

[a] Yield of limonene generated by isomerization of **1** in the synthesis of **2c**.
[b] Diethylene glycol dimethyl ether.
[c] Monoethylene glycol dimethyl ether.
[d] Asymmetric hydroboration with **4** was not carried out when isomers of **1** such as limonene were observed in the synthesis of **2c**.
[e] Not detected.

over 99% ee and 1M BH_3–THF, smoothly underwent asymmetric hydroboration to the intermediate **4** at −25 °C. Subsequent oxidation with H_2O_2 easily affords enantiopure (*S*)-1-benzyl-3-hydroxypyrrolidine (*S*)-**5**, with approximately 100% ee successfully.[3] Regardless of the scientific elegance, however, the reaction conditions are suitable for laboratory experiment, but not for an industrial-scale production without any sufficient improvement. This is because diborane reagents **2a** and **2c** (Scheme 1) are not only very expensive, but also unsafe during transportation and storage due to a lack of stability,[18] although they are commercially available.[19] Moreover, manufacturing at −25 °C is not always available at ordinary multi-purpose facilities.

In order to achieve asymmetric hydroboration on an industrial scale, various parameters were examined. We characterized the two key points: (1) to employ in situ generated borane from inexpensive starting materials, and (2) to carry out asymmetric hydroboration at around 0 °C.

First, we employed **1** (85% ee) which is commercially available and economical. A type of activating agent, sodium borohydride ($NaBH_4$) was optimized (Table 2). The results suggested that borontrifluoride–etherate (BF_3–OEt_2) and THF were the best combination to effectively generate borane active species (Table 2, entry 7), where in situ generated diborane immediately hydroborated with **1** to provide **2c** and so forth. Meanwhile, when more cost-effective H_2SO_4 was employed as an activating agent, diglyme gave the best results compared with the other solvents, such as monoglyme, THF, 1,4-dioxane, isopropyl ether, and tetrahydropyran. However, it was not as good as that obtained in the case of BF_3–OEt_2 and THF (Table 2).

Next, the reaction conditions such as reagent molar ratios and reaction time were optimized to maximize both the chemical yield and chiral purity of the resulting crude (*S*)-**5** at around 5 °C. A typical procedure is as follows: BF_3–OEt_2 was added into the reaction mixture composed of **1**, $NaBH_4$, and THF, and stirred for 12 h to give a milky white slurry. To the slurry **4** was added dropwise, and the resulting mixture was stirred for 8 h to complete reaction. The experiments were performed employing the BF_3–OEt_2/**4** molar ratio as a parameter. The most efficient reaction conditions were found in a case using a twofold equivalent of the BF_3–OEt_2 to **4** as observed in the former example (Fig. 1).[20] It is generally known that adducts of borane species with amines exhibit no hydroboration activity.[20b] Therefore, coordination of **4** would lead to a loss in the hydroboration abilities of an equivalent borane species compring **2a**, **2b**, and **2c** to **4**.

The changes in enantiomeric purity of the resulting crude (*S*)-**5** with reaction time at −25, 0, and 25 °C were examined, and are shown in Figure 2.

As seen in Figure 2, it was proven that the enantiomeric purity of crude (*S*)-**5** continued to decrease with reaction time at 0 °C and 25 °C, whereas it remained almost unchanged at −25 °C. The yield of (*S*)-**5** between −22 and 25 °C reached around 92% after 8 h. It was concluded that the optimization of reaction conditions is crucial for establishing the asymmetric hydroboration process with high enantiomeric selectivity.

These test results indicated that the enantiomeric purity of crude (*S*)-**5** decreased with reaction time and could be comprehended by the addition–elimination equilibrium reactions between **4** and three borane species. In general, any **2c** which formed at an initial time could not keep its structure for a long time at around 0 °C due to the steric hindrance of the two pinanyl

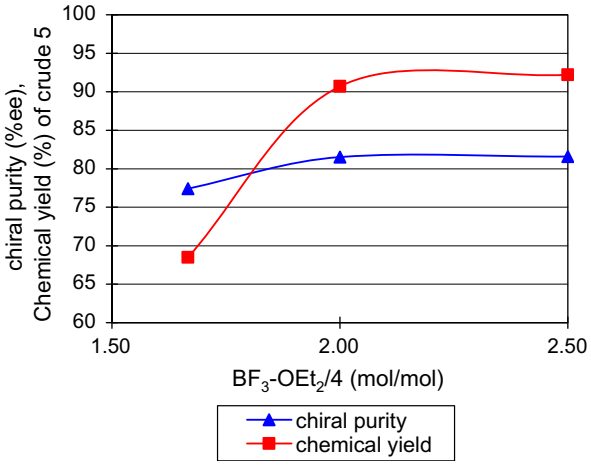

Figure 1. Effect of BF_3–OEt_2/**4** molar ratio.

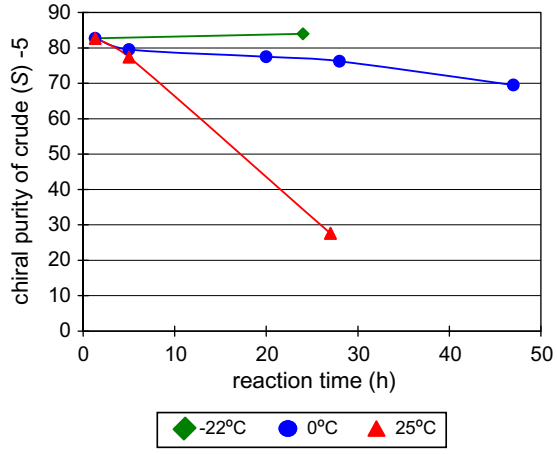

Figure 2. Effect of reaction time and temperature.

groups. Also, it has been reported that a pinanyl group on a boron atom is apt to release an α-pinene molecule in the presence of amine,[21] that is, longer reaction times led to an increase in the amount of thermodynamically stable **2a** and **2b**, which are unfavorable for asymmetric hydroboration[22] and cause a decrease in the amount of unstable **2c**. Accordingly, it was concluded that stopping the reaction at 8 h (>90% yield) would give the best solution to realize a better result for industrial production employing a common facility without powerful cooling equipment.

2.3. Chiral purification via diastereomeric salt formation

Crude (*S*)-**5** [81% ee, containing 90.5% of (*S*)-form] was purified via salt formation with Ts-(*S*)-Phe[23] from denatured EtOH[24] with MeOH and *n*-PrOH, where the crude (*S*)-**5**/Ts-(*S*)-Phe ratio was 1.0/1.0 (mol/mol).[5] Representative results are indicated in Table 3. Total yield of the resolution followed by recrystallization was 84%, based on the total amount of crude (*S*)-**5** charged. Meanwhile, in the direct resolution, the total yield of the resolution followed by two recrystallizations was 30% based on the total amount of the racemate (*RS*)-**5** (theoretical maximum yield = 50%). It was found that a hybrid process composed of asymmetric hydroboration and chiral purification via salt formation was more cost-effective than a direct resolution process.

Table 3
Chiral purification via diastereomeric salt formation followed by recrystallization

Entry	Operation	Yield (%)	Diastereomeric excess (% de)
1	Salt formation[a]	87[b]	98
2	Recrystallization[c]	97[d]	>99

[a] An equivalent of Ts-(*S*)-Phe to crude (*S*)-**5** with 81% ee was used.
[b] Yield (%) = (amount of **5** in the salt obtained) × 100/(amount of crude (*S*)-**5** charged).
[c] Recrystallization of the salt obtained in the salt formation.
[d] Yield (%) = (amount of the salt obtained) × 100/(amount of the salt charged). De% is based on enantiomeric excess of (*S*)-**5** in the salt.

2.4. Production of (*S*)-5 on an industrial scale

At first, *cis*-1,4-dichlorobutene was produced from *cis*-1,4-butenediol **3** (460 kg) and thionyl chloride under the optimized condition. Subsequently, the resulting intermediate was reacted with benzylamine, followed by extraction and distillation to afford 346 kg (net 331 kg) of 1-benzyl-3-pyrroline **4**, as described in Section 2.1.

Next, we demonstrated the asymmetric hydroboration using a multi-purpose facility, 10 kL reactor, at 0 °C for 8 h. The resulting reaction mixture was treated with aqueous sodium hydroxide followed by oxidation with hydrogen peroxide. The separated organic layer was extracted with diluted sulfuric acid, and crude (*S*)-**5** was isolated from the resulting aqueous layer by reverse-extraction with toluene under alkaline conditions with sodium hydroxide. As a result, crude (*S*)-**5**, 320 kg(net), was obtained in 88% yield (on the basis of **4**) with an enantiomeric purity of 84% ee, without any deterioration in the enantiomeric purity of **1** (85% ee). This result indicates that the industrial-scale hydroboration is advantageous, because the process avoids air contamination.

Isolated crude (*S*)-**5** (84% ee) was treated with Ts-(*S*)-Phe in EtOH to successfully provide enantiopure (*S*)-**5** (>99% ee) via diastereomeric salt formation, **5**/Ts-(*S*)-Phe = 1/1 (mol/mol). Commercially available and inexpensive alcohol denatured solvent[24] with 2-PrOH was used in the production. The resulting diastereomeric salt was recrystallized to give 99.3% de. Subsequently, the removal of the chiral purifying agent Ts-(*S*)-Phe was performed, followed by distillation to afford 252 kg of (*S*)-**5** (99.3% ee). No boron contamination is expected in the final product, judging from the by-products such as $NaBF_4$ and $NaB(OH)_4$ which can be removed by extraction, resolution followed by recrystallization, and distillation.

3. Conclusion

For producing (*S*)-1-benzyl-3-hydroxypyrroline **5**, a versatile key intermediate for various chiral drugs, a hybrid process composed of the asymmetric hydroboration of 1-benzyl-3-pyrroline **4** and chiral purification of crude (*S*)-**5** via diastereomeric salt formation was developed. In the key step, the asymmetric hydroboration successfully proceeded to provide crude (*S*)-**5** (84% ee), without a decrease in the enantiomeric excess (% ee) of **1** (85% ee) used as a chiral template, followed by chiral purity improvement via diastereomeric salt formation with Ts-(*S*)-Phe. The proposed hybrid process has been performed in an industrial plant and successfully produced 252 kg of (*S*)-**5** with 99.3% ee.

4. Experimental

4.1. General

Ts-(*S*)-Phe was synthesized from (*S*)-phenylalanine and *p*-toluenensulfonyl chloride according to the literature.[23] The other reagents were purchased from commercial suppliers and used

without further purification. For example, α-pinene **1** and denatured ethanol[24] were manufactured in Bordas (Spain), and Japan Alcohol Co. Ltd, respectively. All reactions were conducted under an air-free atmosphere with nitrogen unless noted otherwise. All of the industrial productions were performed in a glass-lined reactor. Reactions were monitored by GC or HPLC for completion by a small sample from the reaction mixture and analyzed. The diastereomeric excesses (% de) of the diastereomeric salts were determined with the enantiomeric excess (% ee) of (*S*)-**5** isolated from the salt. Enantiomeric excess (% ee) = $|A - B| \times 100/(A + B)$, where *A* and *B* are contents of both enantiomers, respectively. GC analyses were performed according to the following conditions. *cis*-1,4-Dichlorobutene assay: 5% Thermon-3000/Chromosorb W (80–100 mesh), i.d. 3.2 mm × 2 m, FID detector. Chemical assays of **4** and **5**: Unisole 10T + KOH(10 + 3%)/Uniport HP(80–100 mesh), i.d. 3.2 mm × 1 m. Chemical purities of **4** and **5**: NEUTRABOND-1, i.d. 0.25 mm × 60 m. Enantiomeric excess of (*S*)-**5** was determined by HPLC: CAPCELLPAK SG-120 i.d. 4.6 mm × 250 mm, 0.03% aqueous NH_3/MeOH = 50/50 (v/v), UV detector (243 nm). Sample preparation of (*S*)-**5** for chiral purity was individually treated with *O*,*O*′-ditoluoyl (2*S*,3*S*)-tartaric anhydride to give its diastereomeric derivatives prior to analysis. ^{1}H and ^{11}B NMR spectra were recorded on a JEOL JNM-AL400 spectrometer (400 MHz and 128 MHz for a proton and boron, respectively). Melting points were determined with a YAMATO apparatus MODEL MP-21 and are uncorrected. IR spectrum was measured on a PERKIN ELMER SYSTEM 2000 spectrometer. Commercially available anhydrous THF was used as an NMR solvent. (+)-α-Pinene **1** was dried over $LiAlH_4$ prior to NMR measurement and used without any pretreatment. Borane reagent for NMR measurement was prepared from $NaBH_4$ and BF_3–OEt_2 as mentioned above, and transferred into boron-free NMR tube for ^{11}B NMR.

4.2. Optimization of the reaction conditions of the asymmetric hydroboration

To a 300 mL flask were added 74 g of THF, 28.6 g of **1**, and 2.93 g of $NaBH_4$. Subsequently, 14.9 g of BF_3–OEt_2 was added dropwise at 1 °C and stirred overnight. Next, 8.3 g of **4** (0.5 equiv on the basis of BF_3–OEt_2) was added dropwise at the same temperature. A small portion of the resulting slurry was applied to ^{11}B NMR spectrum measurement. The activating agent was optimized by employing BF_3–OEt_2 and H_2SO_4 in an ether solvent, such as THF, diglyme, monoglyme, 1,4-dioxane, isopropyl ether, or tetrahydropyran, where the molar ratios of $NaBH_4$/BF_3–OEt_2 and $NaBH_4$/H_2SO_4 were 3/4 and 2/1, respectively, according to theoretical molar ratios. The molar ratio of BF_3–OEt_2/**4** was optimized in the range of 1.6 and 2.5 with respect to enantiomeric purity and chemical yield of the resulting crude (*S*)-**5**. Also, the dependency of the enantiomeric purity of crude (*S*)-**5** and the reaction time were monitored by HPLC analysis. Furthermore, borane species active in the hydroboration solution were observed on ^{11}B NMR. As a result, four main peaks were observed at 55, 37, 18, and 0 ppm in the reacted solution of $NaBH_4$ with BF_3–OEt_2, which could be attributed to **2c**, monoisopinocampheyl boronic acid, **2b**, and BF_3, respectively. Next, upon addition of **4**, a broad peak at 81 ppm appeared, which was attributed to trialkylborane formed from **2c** and **4**. ^{11}B NMR (128 MHz) δ (ppm) for the reacted solution of $NaBH_4$ with BF_3–OEt_2: 54.8, 48.7, 36.8, 31.8, 17.5, 2.2, 0.0. After addition of **4**: 80.5, 55.9, 2.4, 0.8.

4.3. Industrial production of (*S*)-5

4.3.1. 1-Benzyl-3-pyrroline 4

To a 10 kL reactor were added 1380 kg of toluene, 460 kg of *cis*-1,4-butenediol **3**, (5.22 kmol) and 165 kg of pyridine (0.40 equiv) and cooled to 0–5 °C under stirring. To the cooled mixture was carefully added 1329 kg of thionyl chloride (2.1 equiv to **3**) dropwise and the reaction mixture was warmed up to 50 °C. The resulting solution was concentrated under reduced pressure and the residual oil layer was extracted with toluene (806 kg) to afford a solution containing 442 kg of *cis*-1,4-dichlorobutene (1820 kg). To the separated organic layer was added the mixture of toluene, 1343 kg of benzylamine, and 215 kg of water, with the pH of the solution maintained from 9 to 12 by adding 48% aq NaOH (total 933 kg). After the confirmation of disappearance of *cis*-1,4-dichlorobutene by GC analysis, 2847 kg of water and 780 kg of 35% HCl were added to adjust the pH to 7.2. The organic layer was distilled at 75 °C under reduced pressure (133 Pa) to afford 346 kg of **4** (95.5% a/a (GC), yield 40% on the basis of **3**).

IR (neat) (cm^{-1}) 3065, 3026, 2938, 2873, 2781, 1604, 1586, 1493, 1472, 1453, 1376, 1350, 1337, 1294, 1244, 1209, 1156, 1127, 1073, 1028, 1010, 977, 929, 906, 851, 743, 699, 654, 467. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.41–7.29 (m, 5H), 5.83 (s, 2H), 3.86 (s, 2H), 3.53 (s, 4H).

4.3.2. 1-Benzyl-(3*S*)-hydroxypyrrolidine crude (*S*)-5

2915 kg of THF, 1114 kg of **1** (85.8% ee, 4.0 equiv to **4**), and 116 kg of $NaBH_4$ (1.5 equiv to **4**) were fed into 10 kL reactor. To the reaction mixture were added dropwise 285 kg of THF and 580 kg of BF_3–OEt_2 (2.0 equiv to **4**), while keeping the temperature between −2 and 6 °C for 12 h. Next, 341 kg of **4** was added at below 5 °C and the resulting solution was kept stirring. After the yield of crude (*S*)-**5** was confirmed to be over 90% by GC analysis after 8 h, 508 kg of water and 818 kg of 48% aq NaOH were added carefully, followed by oxidation with 924 kg of 35% aq H_2O_2. After the addition of 1250 kg of 20% aq Na_2SO_3, the oil layer was acidified with 539 kg of 30% aq H_2SO_4 and mixed with 1312 kg of toluene and 984 kg of H_2O. To the resulting aqueous layer were added 240 kg of 48% aqueous NaOH and 3280 kg of toluene to extract crude (*S*)-**5**. The concentration of the oil layer gave 352 kg of crude (*S*)-**5** [91.1% a/a (GC), 84.1% ee, yield 87.6% on the basis of **4**]. Otherwise, $NaBF_4$ generated in the oxidation was treated with $CaCl_2$ to be transformed to harmless CaF_2.

4.3.3. 1-Benzyl-(3*S*)-hydroxypyrrolidine enantiopure (*S*)-5

To a 3 kL reactor were added 909 kg of denatured ethanol,[24] 74 kg of water, and 620 kg of Ts-(*S*)-Phe [chemical purity 95.3% by HPLC, 1.0 equiv to crude (*S*)-**5**] as a chiral purifying agent. After the addition of crude (*S*)-**5**, the resulting slurry was completely dissolved at 70 °C, followed by gradual cooling to 5 °C. The precipitated crude salt crystals were centrifuged to afford 941 kg of wet cake (95.8% de). The crude cake was recrystallized from water to produce 911 kg of wet cake (99.4% de), which was added to 1496 kg of H_2O and 170 kg of H_2SO_4, followed by addition of 900 kg of H_2O. The resulting solution was treated with 300 kg of 48% aq NaOH and extracted with 1080 kg of toluene twice. The separated organic layer was concentrated and distilled at 115–120 °C under reduced pressure (90–240 Pa) to afford 252 kg of (*S*)-**5** (CP >99.9% (GC), enantiomeric purity 99.4% ee, yield 68.9% on the basis of **4**). The ^{1}H NMR spectrum of (*S*)-**5** was consistent with those in the literature.[12,25] IR (neat) 3381, 3062, 3028, 2944, 2797, 1604, 1585, 1494, 1477, 1454, 1376, 1347, 1254, 1208, 1128, 1094, 1028, 1001, 971, 909, 883, 850, 828, 751, 699, 632, 476, 468, 467. ^{1}H NMR ($CDCl_3$) δ (ppm) 7.31–7.22 (m, 5 H), 4.31–4.28 (m, 1H), 3.61 (s, 2H), 2.86–2.80 (m, 1H), 2.64 (d, 1H, J = 10 Hz), 2.52 (dd, 1H, J = 10.2 Hz, 5.4 Hz), 2.29 (dd, 1H, J = 15.6 Hz, 8.0 Hz), 2.21–2.12 (m, 1H), 1.74–1.67 (m, 1H).

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23. Ts-(*S*)-Phe was prepared according to *J. Am. Chem. Soc.* **1937**, *59*, 1116. Ts-(S)-Phe: Mp 164–165 °C. IR (KBr) 3319, 3259, 3064, 3027, 2926, 2658, 2584, 1714, 1694, 1597, 1496, 1456, 1423, 1389, 1344, 1331, 1309, 1294, 1224, 1189, 1157, 1091, 1030, 1020, 935, 903, 846, 819, 758, 751, 730, 704, 666, 556, 493. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.59 (d, 2H, J = 8.4 Hz), 7.24–7.20 (m, 5H), 7.09–7.07 (m,2H), 4.19 (t, 1H, J = 6 Hz), 3.09 (dd, 1H, J = 14 Hz, 5.2 Hz), 2.99 (dd, 1H, J = 14 Hz, 5.2 Hz), 2.40 (s, 3H).
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