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Preparation of (*S*)-4-(1-(3,4-dichlorophenyl)-2-methoxyethyl)piperidine

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ABSTRACT

The novel triple reuptake inhibitor (*S*)-4-(1-(3,4-dichlorophenyl)-2-methoxyethyl)piperidine monohydrochloride **1** possesses a unique 2-phenyl-2-(piperidin-4-yl)ethanol moiety with a stereogenic center at the benzyl position. To synthesize **1** as the (*S*)-isomer, three possible routes were investigated; (1) the lipase-catalyzed kinetic resolution of *tert*-butyl 4-(1-(3,4-dichlorophenyl)-2-hydroxyethyl)piperidine-1-carboxylate **2** utilizing PS-IM from *Pseudomonas* sp. as the lipase; (2) the asymmetric hydrogenation of *tert*-butyl 4-(1-(3,4-dichlorophenyl)-2-oxoethyl)piperidine-1-carboxylate **5** utilizing dynamic kinetic resolution; and (3) the resolution of racemic [1-(*tert*-butoxycarbonyl)piperidin-4-yl](3,4-dichlorophenyl)acetic acid **8** with (*S*)-phenylethylamine. The design of the asymmetric reaction using retrosynthesis, as well as the extensive exploration of enzymes, asymmetric hydrogenation catalysts, and resolving reagents, were all important to afford the optically active compound **1** in excellent yield.

1. Introduction

Depression is a common mental disease, characterized by sadness, loss of interest in activities, and decreased energy, which affects more than 350 million people worldwide.[1] Among the numerous hypotheses put forward for the mechanism of depression, the monoamine hypothesis is one of the most prominent. Currently, many drugs based on the monoamine hypothesis are widely used, such as the tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin noradrenaline reuptake inhibitors. As an extension of the hypothesis, 'triple reuptake inhibitors', which inhibit the reuptake of serotonin, norepinephrine, and dopamine, have emerged as broad-spectrum antidepressants. Triple reuptake inhibitors are expected to show high efficacy, including for the refractory population and those in remission, with less side effects of sexual dysfunction, and early onset of action.[2]

Optically active 2-phenyl-2-substituted ethanol derivatives are common structural motifs found in a variety of active pharmaceutical ingredients, such as the serotonin–norepinephrine reuptake inhibitor EffexorXR[3] and the triple reuptake inhibitor (*S*)-4-(1-(3,4-dichlorophenyl)-2-methoxyethyl)piperidine monohydrochloride **1**, which was created as a candidate novel antidepressant agent after extensive optimization efforts. The identification of a more potent stereoisomer of **1** using a mice tail suspension test, and the determination of its absolute configuration by X-ray single crystal structure analysis, revealed that the potent isomer has an (*S*)-configuration[4] (Fig. 1).

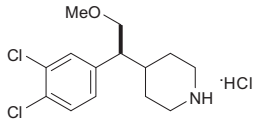

Figure 1. The structure of triple reuptake inhibitor **1**.

Our primary concept was to synthesize the enantiomerically pure compound **1** by appropriately designing a substrate, selecting reagents, and optimizing the reaction conditions and/or procedures. The design of the substrate was conducted based on a retrosynthesis approach, as depicted in Figure 2.

Various synthetic methods, such as asymmetric epoxidation, asymmetric hydrogenation, diastereomeric salt resolution, enzymatic resolution, chiral pool synthesis, and optical resolution using preparative HPLC, were all worth considering to effectively obtain

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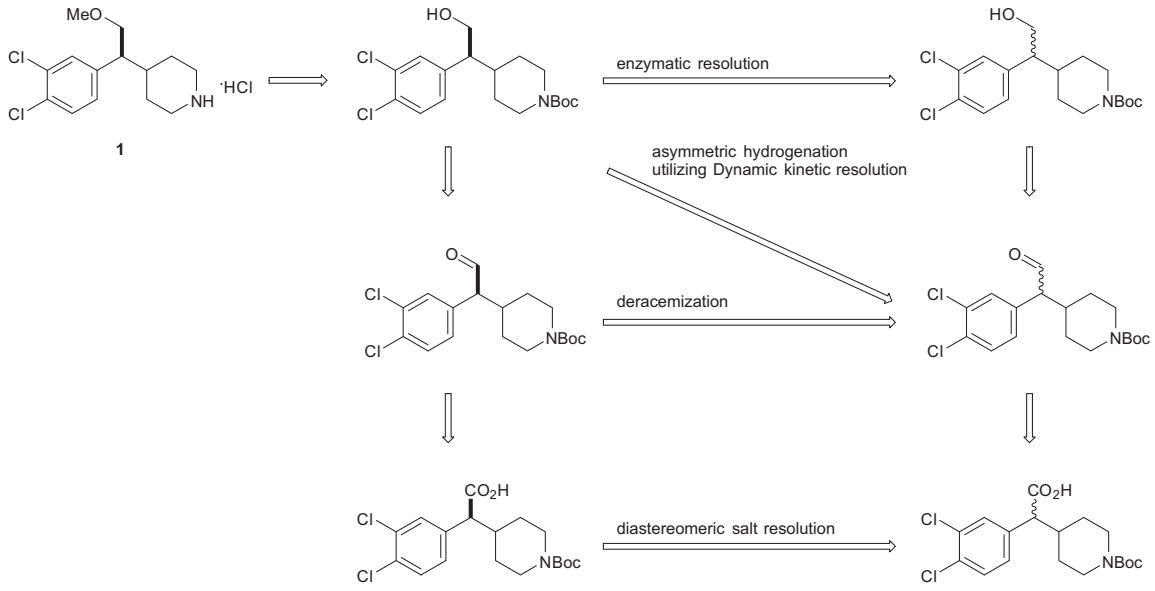


Figure 2. The design of substrates via a retrosynthetic approach.

optically active 2-phenyl-2-substituted ethanol derivatives. Among them, three key methods, enzymatic resolution, asymmetric hydrogenation, and diastereomeric salt resolution, were selected in anticipation of scale-up synthesis.

Enzymatic resolution has attracted much attention due to its ability for stereo-recognition, which enables enantiomerically pure compounds such as alcohols and amino acids to be prepared.[5] This method is also advantageous for green chemistry because of the reduced use of metal catalysts and the formation of by-products.

Asymmetric hydrogenation is also an attractive and straightforward technique to obtain enantiomerically enriched compounds due to the fact that there is little wasted substrate, and it was envisioned that recent advancements in the design of substrates with good anchor groups for metals and ligand selection might enable us to synthesize optically active 2-phenyl-2-substituted ethanol derivatives with both high enantioselectivity and yield.

Resolution via diastereomeric salt formation is still a useful technique on an industrial scale, since it is generally simple, clean, and easy to reproduce laboratory-scale data on an industrial scale. In fact, many chiral drugs on the pharmaceutical market are produced by the diastereomeric salt formation method using resolving reagents.[6]

Herein we describe the process for establishing an efficient synthetic method to afford the novel triple reuptake inhibitor (*S*)-4-(1-(3,4-dichlorophenyl)-2-methoxyethyl)piperidine monohydrochloride **1**.

2. Results and discussion

2.1. Enzymatic resolution

Enzymatic resolution in a later step can be beneficial to minimize the chance for racemization. Furthermore, it has been reported that lipases are able to resolve primary alcohols.[7] These facts encouraged us to investigate the enzymatic resolution of compound **2**,[4] which was a straightforward substrate for the synthesis of compound **1**. A preliminary enzyme screen was conducted using 38 lipases; those with an *E*-value of over 10 are shown in Table 1.

As a result, lipases from *Pseudomonas* sp. were found to have a high potential for resolution (Table 1, entries 5–9), and lipase PS on diatomite (Amano Enzyme Inc.) gave an efficient *E*-value of 243 (Table 1, entry 7). Considering the availability of the lipases as well as the conversions and selectivity, we selected lipase PS-IM (Amano enzyme) for further optimization and scale-up synthesis.

The solubility of compound **2** and the results of the reaction in various solvents are summarized in Table 2. Among the solvents tested, diisopropyl ether (IPE) gave the highest *E*-value for esterification (Table 2, entry 1). Although the solubility of compound **2** in IPE is moderate, the excellent *E*-value encouraged us to choose IPE as the solvent. The addition of acetone as a co-solvent was an attractive idea to improve the solubility and obtain high enantiomeric excess, but feasibility trials indicated that acetone inhibited the progress of the reaction.

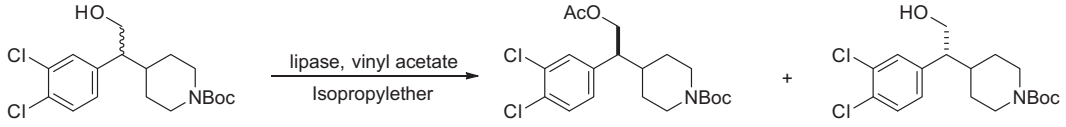
Preliminary optimization of the reaction on a 10 g scale synthesis showed that the reaction rate dropped drastically after forty hours. It was surmised that the major reason for this decrease in the reaction rate was that the lipase becomes deactivated when the essential water from it is withdrawn by the hygroscopic nature of the organic solvent.[8] However, it was then found that a stepwise addition of lipase and vinyl acetate could keep the high reaction rate with an excellent *E*-value.

After the enzymatic resolution, compound **3** was isolated by a simple extraction work-up using sulfur trioxide pyridine in 96% ee with 98% purity.[9] Hydrolysis of the acetyl group followed by methylation, according to the established method, afforded compound **1**[4] (Scheme 1).

2.2. Asymmetric hydrogenation

Next, we investigated an asymmetric hydrogenation reaction to obtain compound **1**. A great deal of effort has been devoted to the development of efficient and potent chiral ligands for use in asymmetric hydrogenation.[10] To elicit high performance from these sophisticated ligands, it is necessary to design substrates with suitable anchor groups, which enable the substrate to chelate to a metal, adjacent to the desired stereogenic center.[11] Thus, we were encouraged to investigate the synthesis of **1** via asymmetric hydrogenation using dynamic kinetic resolution, considering structures with a stereogenic center at the benzylic position, which can readily be epimerized by bases. As a catalyst system, we investigated Ru-diphosphine–diamine, which is widely utilized for the

Table 1
Enzyme screening for primary alcohol **2**[a]



2 **3** **4**

Entry	Lipase	Ee (%)[b]		Conversion (%)[b]	*E*-value
		3	**4**		
1	QLG[c]	73	>99	58	47
2	AH[d]	91	6	6	25
3	AH-S[d]	76	>99	56	45
4	AK-20[d]	92	11	11	30
5	P[d]	98	16	14	123
6	PS[d]	97	28	23	100
7	PS on diatomite[d]	94	>99	52	243
8	PS on Toyonite[d]	89	>99	53	100
9	PS-C[d]	81	>99	55	74

[a] Reaction conditions: **2** (1.0 mg), vinyl acetate (0.005 mL), lipase (5 mg) in solvent (IPE (1 mL)) at 35 °C for 24 h.
[b] Determined by HPLC analysis (CHIRALCEL OD-H column).
[c] Meito Sangyo Co., Ltd.
[d] Amano Enzyme Inc.

asymmetric hydrogenation of ketones and imines[12] and also dynamic kinetic resolution.[13]

As shown in the Table 3, some Ru-diphosphine–diamine catalysts gave high to moderate enantiomeric excesses and chemical yields.

For homogeneous ruthenium catalysts it has been shown that the combination of diphosphines and diamines is critical to obtain excellent enantiomeric excesses and chemical yields. Tuning the structural and electronic properties of the diphosphines and diamines is pivotal for the outcome of the reaction. In our case, the absolute configuration of the diphosphines and the diamines is the key to obtain high enantiomeric excess, while the structure of the diamine ligands also seems to be important for the catalysts' overall performance (Table 3).

The fact that the yields exceed 50% with high enantiodiscrimination clearly indicates that epimerization of the substrate must have occurred in the reaction, thus indicating dynamic kinetic resolution. As a result, we focused on the optimization of the reaction conditions to improve the yields and ee's.

The use of potassium *tert*-butoxide (*t*-BuOK) as a base was essential to the reaction (Table 4, entry 2 vs entry 3). Low hydrogen pressure gave a low conversion (Table 4, entry 4) and high reaction temperature did not affect the outcome of the reaction (Table 4, entry 5). It was expected that additional investigation would further improve the enantiomeric excesses and chemical yields.

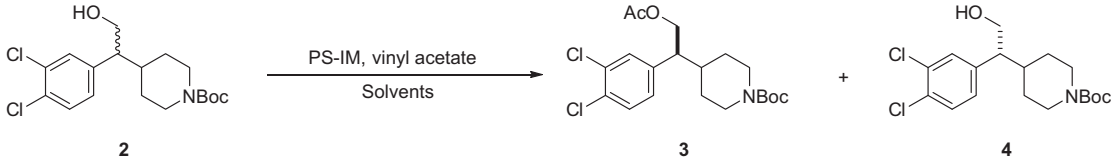
2.3. Diastereomeric salts resolution

Finally, we devoted our efforts to the diastereomeric salt resolution of compound **8**.[4] To make the resolution highly attractive both in terms of the yield and cost, we carefully conducted the screening of different resolving reagents. A preliminary screening of 28 resolving reagents indicated that (+)-dehydroabietyl amine (82% ee), (*S*)-phenylethylamine (75% ee), quinine (12% ee), (*R*)-1-(*p*-tolyl)ethylamine (54% ee), (*S*)-cyclohexylamine (26% ee), (1*R*,2*S*)-*cis*-2-benzylamino-cyclohexanemethanol (28% ee) and hydroquinine (22% ee) formed diastereomeric salts with considerable ee's. Among them, (*S*)-phenylethylamine was chosen as a promising resolving reagent due to it having some substructural similarity with the substrate[14] and, more importantly, its ready availability.

Over the course of the optimization, we conducted solvent screening; Table 5 shows that the enantiomeric excess of the salt obtained from acetonitrile was up to 97% ee, with a moderate yield (Table 5, entry 1). The volume of solvent is very important for diastereomeric salt resolution, especially on an industrial scale. In order to reduce the volume of solvent while keeping the high enantiomeric excess, it was found that the addition of ethanol to acetonitrile was effective (Table 5, entries 6 and 7).

It has been reported that a hydrogen bond network exists in less soluble diastereomeric salts,[15] and that there would be a hydrogen bond network between the carboxyl group at (*S*)-**8** and the

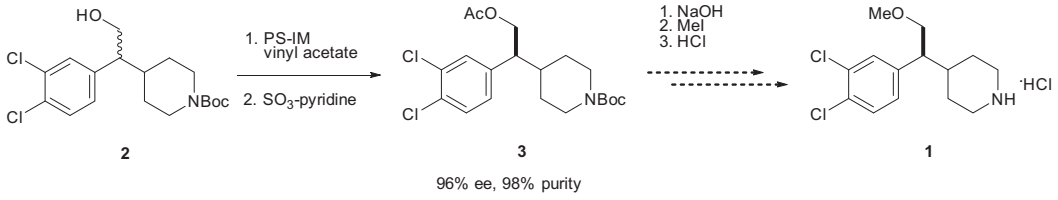
Table 2
Investigation of the reaction solvents[a]



2 3 4

Entry	Solvent	Solubility (mg/mL)	Reaction time (h)	Ee (%)[b]	Conversion (%)[b]	*E*-value[b]
1	IPE	>25	24	98	48	525
2	THF	>300	48	98	7	178
3	Acetone	>300	48	93	20	37
4	Acetonitirile	>100	48	92	48	66
5	DMF	>300	24	-[c]	-	-
6	*t*-BME	>100	40	91	52	107

[a] Reaction conditions: **2** (100 mg), vinyl acetate (2 equiv), PS-IM (10 mg)) in solvent (4 mL) at 35 °C.
[b] Determined by HPLC analysis (CHIRALCEL OD-H column).
[c] Not detected.



2 3 1

96% ee, 98% purity

Scheme 1. Synthesis of **1** via enzymatic resolution.

amino group at (*S*)-phenylethylamine to form a 2_1-column. The substructural similarity of compound **8** and phenylethylamine suggests that van der Waals interactions between the 2_1-columns may stabilize the diastereomeric salt.

The robustness of the diastereomeric salt resolution method was confirmed by a 612 g scale experiment, in which 97% ee with 41% yield was obtained. After recrystallization of the diastereomeric salt **9**, 224 g of **9** were obtained successfully with >99.9% ee. According to the established method,[4] compound **1** was successfully synthesized without any deterioration of the enantiomeric excess (>99.9% ee) (Scheme 2).

3. Conclusion

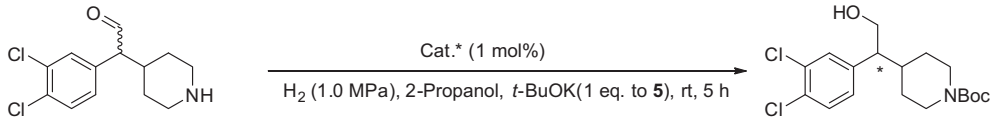
Excellent enantiomeric excess has been achieved for the novel triple reuptake inhibitor (*S*)-4-(1-(3,4-dichlorophenyl)-2-methoxyethyl)piperidine monohydrochloride **1**, using three approaches; enzymatic resolution (up to 98% ee, 48%), asymmetric hydrogenation (up to 85% ee, 73%), and diastereomeric salt resolution (up to 98% ee, 40%). Each approach has scientific insights and is worth developing for scale-up synthesis. The success of a greater than 200 g scale synthesis of **1** indicates that diastereomeric salt resolution is a promising approach for large scale production. We have also shown that the careful design of substrates, based on retro-synthesis and the knowledge of resolution and asymmetric synthesis, as well as screening for optimization, can lead to an effective synthetic procedure for chiral compounds.

4. Experimental

4.1. General

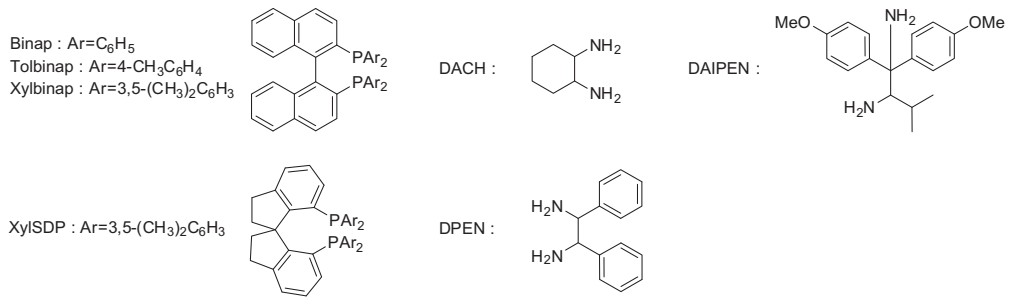
The proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AVANCE 300 (300 MHz) or Varian Gemini 200 (200 MHz) or Ultra-300spectrometer (300 MHz) or JEOL JMTC0400/5 (400 MHz). Chemical shifts are given in δ values (ppm) using tetramethylsilane as the internal standard. Reactions were followed by TLC on Silica gel 60 F 254 pre-coated TLC plates (E. Merck) or NH TLC plates (Fuji Silysia Chemical Ltd). Chromatographic separations were carried out on silica gel 60 (0.063–0.200 or 0.040–0.063 mm, E. Merck) or basic silica gel (Chromatorex® NH, 100–200 mesh, Fuji Silysia Chemical Ltd) using the indicated eluents. High-performance liquid chromatography (HPLC) was performed with Agilent 1200 System equipped with a G1365B MWD. Elemental analyses were carried out by Takeda Analytical Laboratories, Ltd and were within 0.4% of theoretical values unless otherwise noted. HPLC–MS measurements were performed on Waters HPLC–MS system ZMD-1. Asymmetric

Table 3
Asymmetric hydrogenation of compound **5** with various catalysts[a]



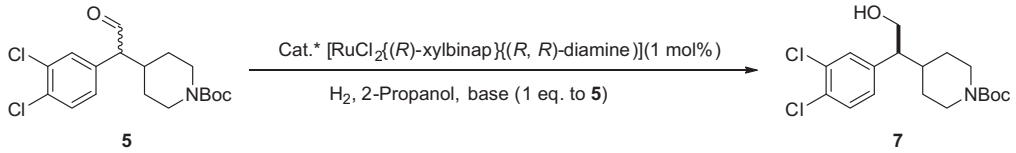
5 **6**

Entry	Cat.*		Ee (%)[b]	Yield (%)[b]
	diphosphine	diamine		
1	(*R*)-Binap	(*R*, *R*)-DACH	65	76
2		(*R*, *R*)-DPEN	71	79
3		(*R*)-DAIPEN	30	80
4		(*S*, *S*)-DACH	7	66
5		(*S*, *S*)-DPEN	rac	86
6		(*S*)-DAIPEN	20	80
7	(*R*)-Tolbinap	(*R*, *R*)-DACH	66	70
8		(*R*, *R*)-DPEN	46	68
9		(*R*)-DAIPEN	38	80
10		(*S*, *S*)-DACH	4	87
11		(*S*, *S*)-DPEN	2	84
12		(*S*)-DAIPEN	26	81
13	(*R*)-Xylbinap	(*R*, *R*)-DACH	80	69
14		(*R*, *R*)-DPEN	77	86
15		(*R*)-DAIPEN	50	84
16		(*S*, *S*)-DACH	35	73
17		(*S*, *S*)-DPEN	26	84
18		(*S*)-DAIPEN	8	85
19	(*R*)-XylSDP	(*R*, *R*)-DACH	10	56
20		(*R*, *R*)-DPEN	5	80
21		(*R*)-DAIPEN	6	70
22		(*S*, *S*)-DACH	35	70
23		(*S*, *S*)-DPEN	31	75
24		(*S*)-DAIPEN	3	79



[a] Reaction conducted on a 0.1 mmol scale at room temperature under 1.0 MPa of H_2. Cat.* were generated in situ using $[RuCl_2(binaps)](dmf)_n$ and diamines.
[b] Determined by HPLC analysis using CHIRALPAK AD-H column.

Table 4
Asymmetric hydrogenation of compound **5** with various bases and conditions[a]

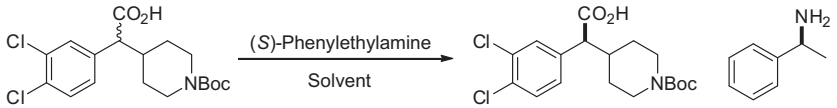


5 **7**

Entry	(*R*, *R*)-Damine	Base	H_2 (MPa)	Other conditions	Ee (%)[b]	Yield (%)[b]
1	DACH	*t*-BuOK	1.0	rt, 2h	82	77
2	DPEN	*t*-BuOK	1.0	rt, 2h	85	68
3	DPEN	K_2CO_3	1.0	rt, 2h	---	no reaction
4	DPEN	*t*-BuOK	0.2	rt, 5h	80	17[c]
5	DPEN	*t*-BuOK	1.0	50°C, 2h	85	73

[a] Reaction conducted on 0.1 mmol-scale under 1.0 MPa of H_2.
[b] Determined by HPLC analysis (CHIRALPAK AD-H column).
[c] Compound **5** remained unchanged.

Table 5
Diastereomeric salt resolution of **8** with various solvents[a]



8 **9**

Entry	Solvent	Volume (mL)	Ee (%)[b]	Yield (%)[b]	Resolution efficiency [c]
1	CH_3CN	50	97	39	76
2	MeOH	5	93	41	76
3	EtOH	10	95	43	82
4	Acetone	15	37	68	50
5	5%H_2O/EtOH	5	96	33	63
6	EtOH/CH_3CN (1/1)	10	90	46	83
7	EtOH/CH_3CN (2/1)	15	98	40	78

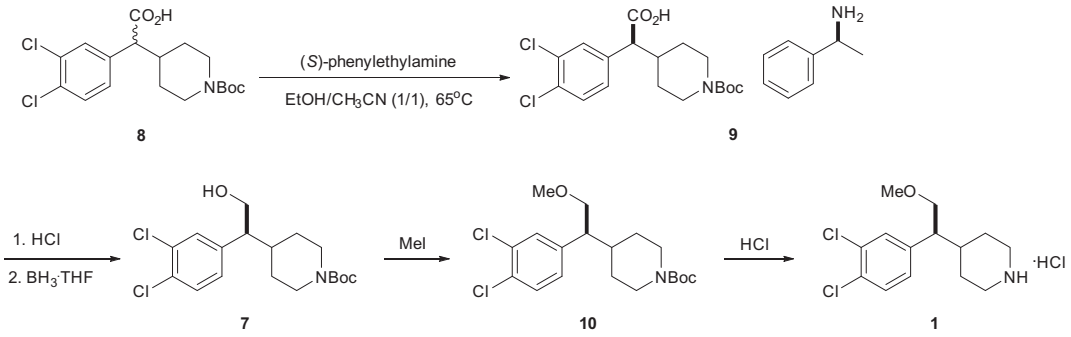
[a] Reaction conducted on 1.0-g scale with 1.0 equiv of (*S*)-phenylethylamine at room temperature.
[b] Determined by HPLC analysis (CHIRACEL OJ-RH column).
[c] Resolution efficiency = enantiomeric excess (% ee) × yield (%) × 2/100.

hydrogenation was carried out using standard Schlenk techniques. Compounds **2** and **8** were synthesized by the reported method.[4]

4.2. Enzymatic resolution

4.2.1. *tert*-Butyl 4-((1*S*)-2-acetoxy-1-(3,4-dichlorophenyl)ethyl) piperidine-1-carboxylate 3

To a solution of **2** (1000 mg, 2.67 mmol) and vinyl acetate (0.495 mL, 2.0 equiv) in IPE (20 mL) was added lipase (PS-IM™, Amano Co. Ltd) (50 mg) at 35 °C. The resulting mixture was stirred for 40 h at 35 °C. To this solution were added vinyl acetate (0.248 mL, 1.0 equiv) and lipase (PS-IM™, Amano Co. Ltd) (25 mg) at 35 °C. The resulting mixture was stirred for 24 h at 35 °C. The lipase was filtered off and washed with IPE. The same scale reactions were repeated three times. The resulting filtrate and washings were combined and concentrated under reduced pressure to give crude **3** (4.0 g, 96% ee). To a solution of crude **3** in pyridine (16 mL) was added SO_3-pyr (2.73 g, 3.0 equiv) at room temperature. The resulting mixture was stirred for 2.5 h at room temperature and cooled to 0 °C. After the addition of water



Scheme 2. Synthesis of **1** via diastereomeric salt resolution.

(32 mL), the whole mixture was extracted with IPE (20 mL, twice). The organic layers were combined and washed successively with a 10% aqueous NaCl solution (20 mL, three times), a 10% aqueous citric acid solution (20 mL, twice) and a 10% aqueous NaCl solution (20 mL), and concentrated under reduced pressure to give (*S*)-**3** (2.11 g, purity 98%) as an oil. Enantiomeric excess (96%) was determined by HPLC analysis using racemic **3** as the external standard. (CHIRALCEL OD-H, eluted with *n*-hexane/EtOH = 95/5 (v/v); flow rate, 1.0 mL/min; detection, 220 nm; temperature, 40 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24–1.28 (m, 2H), 1.41 (s, 9H), 1.64–1.90 (m, 3H), 1.97 (s, 3H), 2.65–2.70 (m, 4H), 3.95–4.20 (m, 1H), 4.24–4.37 (m, 2H), 7.00 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.24–7.29 (m, 1H), 7.38 (d, *J* = 8.0 Hz, 1H). MS: 315 $[M-Boc+H]^+$.

4.3. Asymmetric hydrogenation

4.3.1. *tert*-Butyl 4-(1-(3,4-dichlorophenyl)-2-oxoethyl)piperidine-1-carboxylate 5

Dess–Martin reagent (4.00 g, 9.43 mmol) was added portionwise at 0 °C to a solution of *tert*-butyl 4-(1-(3,4-dichlorophenyl)-2-hydroxyethyl)piperidine-1-carboxylate (2.21 g, 5.90 mmol) in CH_3CN (50 mL). The mixture was stirred at room temperature for 1 h and then poured into satd $NaHCO_3$ aq and satd $Na_2S_2O_3$ aq. After being stirred for 30 min, the mixture was extracted with EtOAc and washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 9/1 to 2/1) to afford **5** (1.67 g, 76%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91–1.09 (m, 1H), 1.14–1.35 (m, 2H), 1.43 (s, 9H), 1.77–1.88 (m, 1H), 2.12–2.28 (m, 1H), 2.57–2.83 (m, 2H), 3.31 (dd, *J* = 9.5, 2.3 Hz, 1H), 3.98–4.18 (m, 2H), 7.01 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.28 (d, *J* = 2.1 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 9.70 (d, *J* = 2.3 Hz, 1H). MS: 272 $[M-Boc+H]^+$.

4.3.2. *tert*-Butyl 4-[(1*S*)-(3,4-dichlorophenyl)-2-hydroxyethyl] piperidine-1-carboxylate 7

To *tert*-butyl 4-(1-(3,4-dichlorophenyl)-2-oxoethyl)piperidine-1-carboxylate **5** (37 mg, 0.1 mmol), $RuCl_2$\{(*R*)-xylBINAP\}\{(*R*,*R*)-DPEN\}(1.1 mg, 1 mol %) in a glass autoclave was added a solution of *tert*-BuOK (0.1 mL, 1.0 M in *tert*-BuOH) in 2-propanol (1.5 mL). Hydrogen (1.0 MPa) was then introduced, and the reaction mixture stirred at 50 °C. After 2 h, the enantiomeric excess (85%) and chemical yield (73%) were determined by HPLC analysis using racemic **7** as the external standard. (CHIRALPAK AD-H, eluted with *n*-hexane/2-propanol = 900/100 (v/v); flow rate, 1.0 mL/min; detection, 220 nm; room temperature).

4.4. Diastereomeric resolution

4.4.1. [(1*S*)-(*tert*-Butoxycarbonyl)piperidin-4-yl](3,4-dichlorophenyl)acetic acid (*S*)-1-phenyl ethylamine salt 9

To a solution of [1-(*tert*-butoxycarbonyl)piperidin-4-yl](3,4-dichlorophenyl)acetic acid **8** (612 g, 1.58 mol) in ethanol (3,060 mL) and acetonitrile (3,060 mL) was added (*S*)-(−)-1-phenyl ethylamine (194 g, 1.60 mol) at 65 °C. The mixture was stirred at 65 °C for 3 h, and then at room temperature for 3 h. The solids were collected and washed with 50% EtOH in acetonitrile (800 mL) and dried under reduced pressure to give colorless solids (331 g, 41%, 97% ee).

To a solution of **9** (248 g, 487 mmol) in 5% aqueous EtOH (3700 mL) was added acetonitrile (3700 mL) at 75 °C and stirred at 50 °C for 1 h, and then at room temperature for 14 h. The resulting solid was filtered and washed with 50% EtOH in acetonitrile (500 mL) and then concentrated under reduced pressure at 40 °C to give **9** as a colorless solid (224 g, 90%, 99.9% ee). Enantiomeric excess was determined by HPLC analysis using **8** as the external standard. (CHIRALCEL OJ-RH, eluted with 20 mM $KHPO_4$ (pH 2.1) adjusted by phosphoric acid/acetonitrile = 1/1 (v/v); flow rate, 1.0 mL/min; detection, 220 nm; temperature, 30 °C). $[\alpha]_D^{25}$ = +36.9 (*c* 0.9310, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 0.57–0.93 (1H, m), 0.94–1.14 (2H, m), 1.22–1.47 (12H, m), 1.69–1.84 (1H, m), 1.93–2.01 (1H, m), 2.70 (br s, 2H), 2.97–3.59 (4H, m), 3.67–4.01 (2H, m), 4.14 (1H, q, *J* = 6.4 Hz), 7.13–7.39 (6H, m) 7.43–7.69 (2H, m).

4.4.2. *tert*-Butyl 4-[(1*S*)-(3,4-dichlorophenyl)-2-hydroxyethyl] piperidine-1-carboxylate 7

To a suspension of **9** (224 g, 440 mmol) in ethyl acetate (2,250 mL) was added 0.2 M hydrochloric acid (2500 mL) at 5–10 °C. After stirring for 30 min, the organic layer was separated and aqueous layer was extracted with ethyl acetate (1200 mL). The combined organic layer was washed with brine (1700 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give (*S*)-**8** as a colorless solid (171 g, quantitative, 99.9% ee).

The part of the solid (146 g, 376 mmol) was dissolved in THF (1,020 mL) and to the solution was added a 1.1 M BF_3·THF complex in THF (450 mL, 495 mmol) at 3–5 °C. After being stirred at room temperature for 1 h, to the solution was added 30% aqueous citric acid (470 mL) at 10–15 °C. The mixture was then concentrated under reduced pressure and the residue was diluted with EtOAc (1000 mL) and water (500 mL). The organic layer was separated and washed with brine (1000 mL), dried over Mg_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10–90% ethyl acetate in *n*-hexane) to

give **7** (138 g, 98%, 99.9% ee) as a colorless oil. Enantiomeric excess was determined by HPLC analysis using racemic **7** as the external standard. (CHIRALPAK AD, eluted with *n*-hexane/2-propanol = 900/100 (v/v); flow rate, 1.0 mL/min; detection, 220 nm; temperature, 40 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00–1.36 (m, 4H), 1.43 (s, 9H), 1.67–1.90 (m, 2H), 2.50–2.76 (m, 3H), 3.78–3.94 (m, 2H), 3.95 (br s, 1H), 4.00–4.16 (m, 1H), 7.04 (dd, J = 2.2, 8.3 Hz, 1H), 7.30 (d, J = 2.2 Hz, 1H), 7.40 (d, J = 8.3 Hz, 1H). MS: 318 $[M-t\text{Bu}+H]^+$.

4.4.3. *tert*-Butyl 4-[(1*S*)-(3,4-dichlorophenyl)-2-methoxyethyl] piperidine-1-carboxylate 10

To a suspension of NaH (60% in oil, 18.4 g, 460 mmol) in DMF (430 mL) was added a solution of *tert*-butyl 4-[(1*S*)-(3,4-dichlorophenyl)-2-hydroxyethyl]piperidine-1-carboxylate **7** (144 g, 384 mmol) and methyl iodide (109 g, 767 mmol) in DMF (430 mL) at 0–10 °C. After being stirred at room temperature for 2 h, to the mixture was added water (500 mL) at 0–10 °C. After being stirred for 30 min at 10 °C, the mixture was diluted with water (1000 mL) and extracted by ethyl acetate (1500 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (750 mL). The combined organic layer was washed successively with 10% aqueous citric acid (750 mL) and brine (750 mL), dried over $MgSO_4$, and concentrated under a reduced pressure. The residue was recrystallized from toluene (300 mL) and diisopropyl ether (150 mL). The collected crystals were washed with diisopropyl ether (150 mL) and dried under reduced pressure to give **10** (61 g, 41%). The mother liquid was concentrated under reduced pressure and the residue was suspended with *tert*-butyl methylether (150 mL) and filtered. The solid was washed with a small amount of *tert*-butyl methylether and dried under reduced pressure to give a 2nd crop of crystals (52 g, 35%). The mother liquid was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (10–90% ethyl acetate in *n*-hexane) to give a 3rd crop of crystals (17 g, 11%) (total yield 130 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98–1.36 (m, 3H), 1.43 (s, 9H), 1.67–1.90 (m, 2H), 2.45–2.76 (m, 3H), 3.28 (s, 3H), 3.52–3.67 (m, 2H), 4.01 (br s, 1H), 4.12 (br s, 1H), 7.02 (dd, J = 2.2 and 8.3 Hz, 1H), 7.28 (d, J = 2.2 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H). MS: 374 $[M-Me+H]^+$.

4.4.4. 4-[(1*S*)-1-(3,4-Dichlorophenyl)-2-methoxyethyl]piperidine monohydrochloride 1

To a solution of *tert*-butyl 4-[(1*S*)-(3,4-dichlorophenyl)-2-methoxyethyl]piperidine-1-carboxylate **10** (130 g, 336 mmol) in *tert*-butyl methylether (650 mL) was added 4 M HCl/ethyl acetate solution (910 mL) at 23 °C. After being stirred at room temperature for 3 h, to the resulting suspension was added *n*-heptane (1,040 mL). The resulting suspension was stirred at room temperature for 1 h, and then stirred at 10 °C for 30 min, and filtered. The solid was washed successively with *tert*-butyl methylether/*n*-heptane = 1/1 (1000 mL) and *n*-heptane (500 mL × 2 times), and dried under reduced pressure to give crude **1** as a colorless solid (101 g, yield 93%, purity 99.7% (HPLC area%)).

Crude **1** (210 g, 647 mmol, combined with the other crude **1**) was dissolved in 2-propanol (1800 mL) at 70 °C; to this solution was added *n*-heptane (1000 mL) at 65 °C. After being stirred at 50 °C for 2 h, to the suspension was added *n*-heptane (900 mL) at 50 °C. The resulting suspension was stirred at room temperature for 2 h and then at 5 °C for 2 h. The suspension was filtered and the solid was washed with *n*-heptane (1000 mL) and dried under reduced pressure to give **1** as colorless crystals (202 g, yield 96%, purity 99.8% (HPLC area %), >99.9% ee. Enantiomeric excess was determined by SFC analysis using racemic **1** as the external standard. (CHIRALPAK AD-H, eluted with CO_2/MeOH/2-propanol = 920/80/3 (v/v/v); flow rate, 2.35 mL/min; pressure, 150 bar; detection, 220 nm; temperature, 30 °C). Chemical purity was determined by HPLC analysis. (Imtact Cadenza C18, eluted with (A) 50 mmol/L $HClO_4$ aq (pH 2.5) (B) acetonitrile; flow rate, 1 mL/min; gradient program, 0 min: (B) 38%, 10 min: (B) 38%, 15 min: (B) 90%, 24.5 min: (B) 90%; detection, 220 nm; temperature, 40 °C). $[\alpha]_D^{22}$ = +31.3 (*c* 0.5234, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.10–1.31 (m, 1H), 1.31–1.52 (m, 2H), 1.73–1.99 (m, 2H), 2.63–2.87 (m, 3H), 3.00–3.29 (m, 5H), 3.51–3.67 (m, 2H), 7.24 (dd, J = 8.3 and 1.9 Hz, 1H), 7.52 (d, J = 1.9 Hz, 1H), 7.54–7.61 (m, 1H), 8.96 (br s, 2H). MS: 288 $[M+H]^+$. Anal. Calcd for $C_{14}H_{20}Cl_3NO$: C, 51.79; H, 6.21; N, 4.31. Found: C, 51.81; H, 6.32; N, 4.23.

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