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Synthesis of Chiral 1,2-Amino Alcohol-Containing Compounds Utilizing Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation of Unprotected α-Ketoamines

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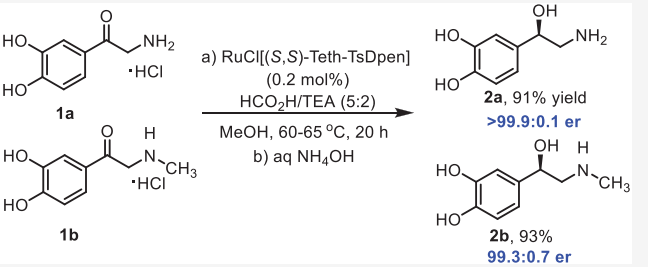
ABSTRACT: Herein, we disclose a facile synthetic strategy to access an important class of drug molecules that contain chiral 1,2-amino alcohol functionality utilizing highly effective ruthenium-catalyzed asymmetric transfer hydrogenation of unprotected α-ketoamines. Recently, the COVID-19 pandemic has caused a crisis of shortage of many important drugs, especially norepinephrine and epinephrine, for the treatment of anaphylaxis and hypotension because of the increased demand. Unfortunately, the existing technologies are not fulfilling the worldwide requirement due to the existing lengthy synthetic protocols that require additional protection and deprotection steps. We identified a facile synthetic protocol via a highly enantioselective one-step process for epinephrine and a two-step process for norepinephrine starting from unprotected α-ketoamines **1b** and **1a**, respectively. This newly developed enantioselective ruthenium-catalyzed asymmetric transfer hydrogenation was extended to the synthesis of many 1,2-amino alcohol-containing drug molecules such as phenylephrine, denopamine, norbudrine, and levisoprenaline, with enantioselectivities of >99% ee and high isolated yields.



INTRODUCTION

The synthesis of enantiomerically pure 1,2-amino alcohols using catalytic asymmetric hydrogenation or transfer hydrogenation reactions has distinct advantages over the resolution methods for economic and environmental benefits.[1] More importantly, asymmetric transfer hydrogenation has a tremendous advantage over pressurized hydrogenation reactions due to nonaccessibility of the pressurized equipment. Chiral 1,2-amino alcohols are prevalent structural motifs in many pharmaceutical molecules, such as epinephrine, whose indication is for emergency treatment of Type I allergic reactions, including anaphylaxis, and for increasing mean arterial blood pressure in patients with hypotension associated with cardiac arrest or septic shock.[2] The other drugs include Norepinephrine for the treatment of patients in vasodilatory shock states such as septic shock and neurogenic shock.[3] (*R*)-Phenylephrine is applied for the treatment of hypotension caused by shock or anesthesia.[4] (*R*)-Salbutamol is a β-2 adrenergic receptor agonist used to treat asthma, bronchitis, and COPD, as well as prevent exercise-induced bronchospasms,[5] and (*R*)-denopamine is a catecholamine neurotransmitter used to treat hemodynamic imbalances, low cardiac output, and hypotension[6] (Figure 1). The chiral 1,2-amino alcohol functionality is also present in a large number of natural products.[7] However, an efficient synthesis of enantiomerically pure amino alcohols remains one of the most challenging tasks in organic synthesis, especially the phenol or catechol-containing subunits. Therefore, we envisage a facile

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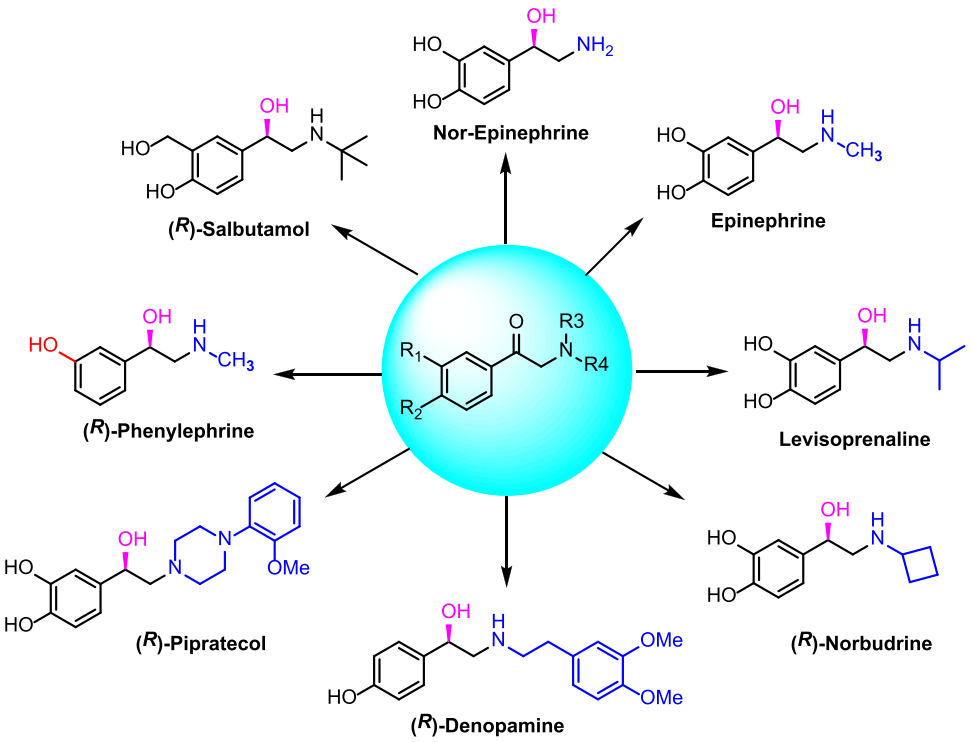

Figure 1. Selected natural products and active pharmaceutical ingredients containing chiral 1,2-amino alcohols

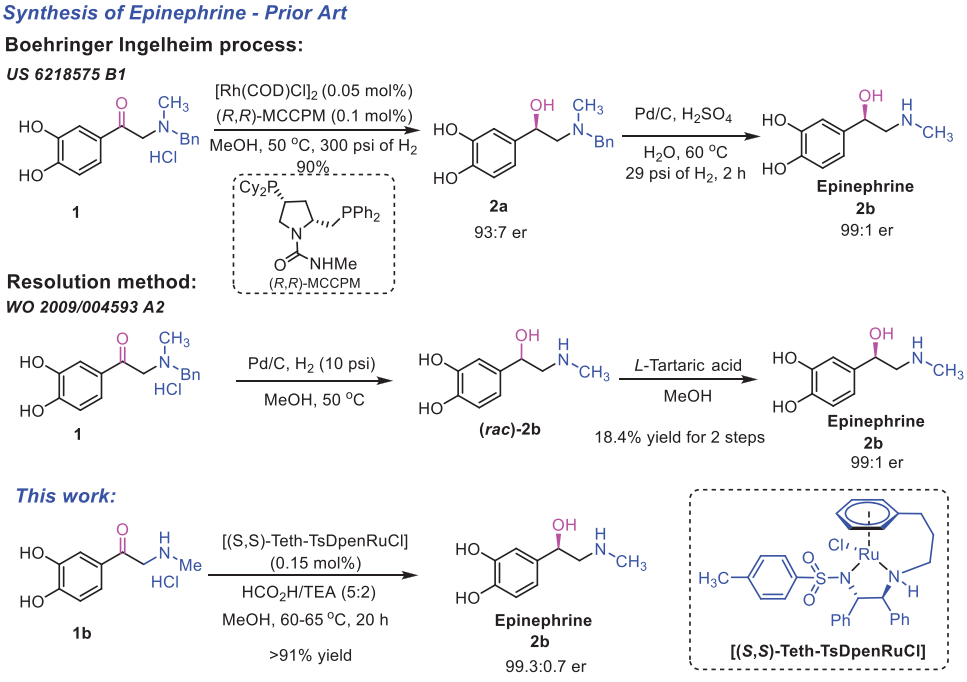

Figure 2. Prior art and this work on reduction of catechol-containing α-amino ketones

and simplified synthetic strategy enabling expedient accessibility to these important drugs, which would be a highly important goal for humankind.

The synthesis of chiral 1,2-amino alcohols by asymmetric hydrogenation of the corresponding α-amino ketones utilizing rhodium, iridium, or ruthenium catalysis represents one of the most effective approaches.[8] However, protection of the amines is required to generate tertiary or *N*-benzyl amino ketones prior to Rh-catalyzed hydrogenation to prevent the coordination of metal to the nitrogen atom and to increase the reactivity and enantioselectivity.[8] Furthermore, direct asymmetric hydrogenation of unprotected primary and secondary α-amino ketones containing catechol and phenol moieties has been studied less, with surprisingly limited substrate scope,[9] due to the labile functionality of catechol and phenol groups.[10] For example, the existing synthetic methodologies of epinephrine require benzyl protection of the amino group prior to high-pressure (~500 psi) asymmetric hydrogenation[15] and its subsequent removal of the benzyl-protecting group via Pd-catalyzed hydrogenolysis resulting in a longer synthetic

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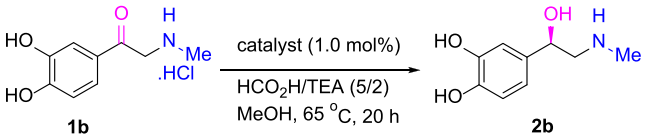
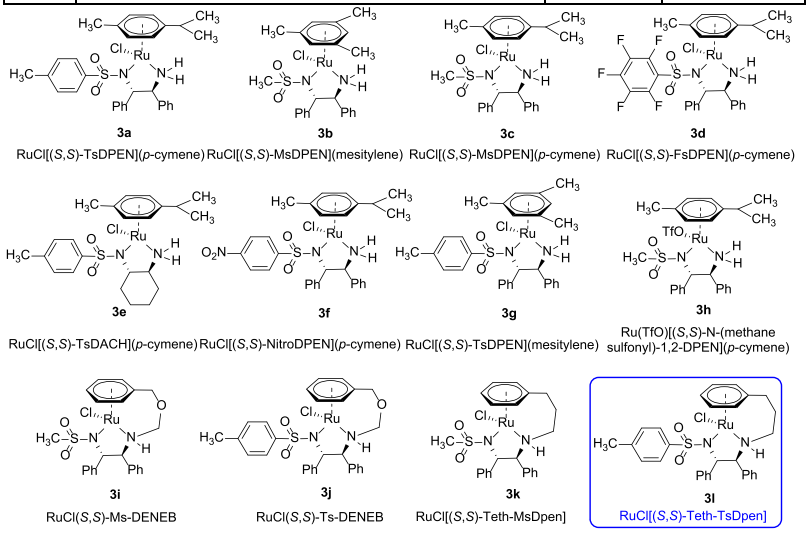
Table 1. Catalyst Screening for Asymmetric Transfer Hydrogenation of 1b[a]



Entry	Catalyst	Conv to **2b**	er (**2b**)
1	RuCl[(*S*,*S*)-TsDPEN](*p*-cymene) (**3a**)	15%	86:14
2	RuCl[(*S*,*S*)-MsDPEN](*p*-mesitylene) (**3b**)	6%	81:19
3	RuCl[(*S*,S)-MsDPEN](*p*-cymene) (**3c**)	5%	91:9
4	RuCl[(*S*,S)-FsDPEN](*p*-cymene) (**3d**)	10%	86:14
5	RuCl[(*S*,S)-TsDACH](*p*-cymene) (**3e**)	5%	66:34
6	RuCl[(*S*,*S*)-NitroDPEN](*p*-cymene) (**3f**)	5%	89:11
7	RuCl[(*S*,S)-TsDPEN](mesitylene) (**3g**)	7%	77:23
8	Ru(OTf)[(*S*,*S*)-MsDPEN](*p*-cymene) (**3h**)	11%	65:35
9	RuCl(*S*,*S*)-Ms-DENEB (**3i**)	100%	97:3
10	RuCl(*S*,*S*)-Ts-DENEB (**3j**)	100%	96:4
11	RuCl(*S*,*S*)-Teth-MsDpen (**3k**)	100% 91%[b]	98:2
12	RuCl(*S*,*S*)-Teth-TsDpen (**3l**)	100% 94%[b]	99.3:0.7 >99.9:0.1[c]



[a]Reaction conditions: **1b** (1.0 mmol), catalyst (1 mol %) in 2 mL of MeOH, HCO_2H/triethylamine (TEA) (5/2, 0.2 mL). The conversion was monitored by high-performance liquid chromatography (HPLC), and the enantiomeric ratio was determined by HPLC with a chiral stationary phase after dilution to become a homogeneous solution. [b]Isolated yield. [c]Er after neutralization/crystallization with 28% NH_4OH.

sequence to the preparation of epinephrine. It is important to note that the presence of the amino alcohol functionality complicates the Pd removal process. Extensive efforts are required to scavenge the residual Pd content; therefore, the overall yield suffers (Figure 2).[15]

Asymmetric transfer hydrogenation without the usage of high-pressure H_2 gas has been utilized for asymmetric amino ketone reductions; however, all of the literature reports displayed the universal requirement for the amino group to be protected to enable successful ketone reduction, which added unnecessary steps.[11] Herein, we demonstrated that catechol- or phenol-containing unprotected α-amino ketones are reduced in high enantioselectivity under asymmetric transfer hydrogenation conditions by proper selection of the ruthenium−diamine catalyst. The enantioselectivity of >99% ee was accomplished with high yields, which represents a concise and cost-effective synthesis for many important drugs, including epinephrine and norepinephrine.

RESULTS AND DISCUSSION

Unprotected compound **1b** was prepared using modified literature procedures.[16] The reaction of 4-(chloroacetyl)-catechol with methyl amine produced the free base, which was subsequently treated with 12 M aqueous hydrochloric acid to

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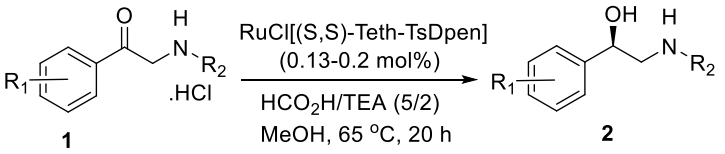
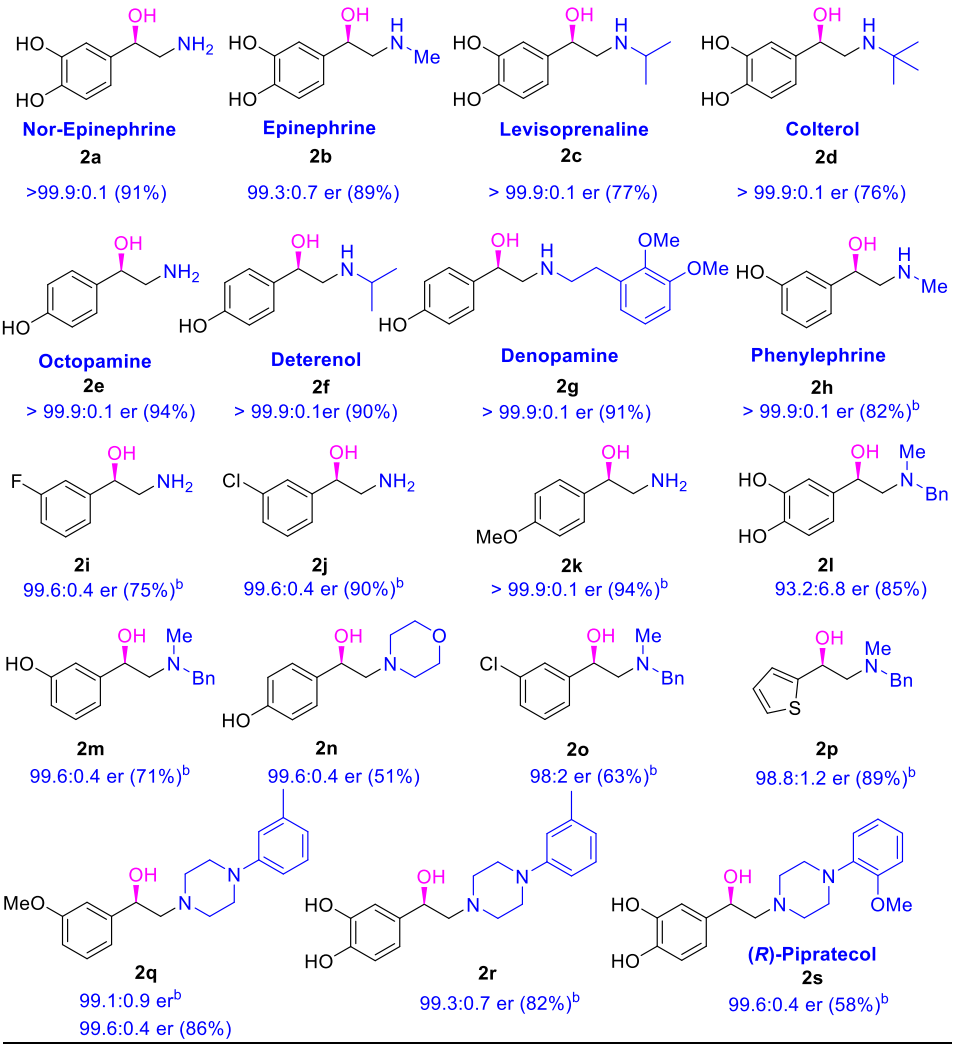
Scheme 1. Asymmetric Transfer Hydrogenation of α-Amino Ketones[a]





[a]Reaction conditions: RuCl[(*S*,*S*)-Teth-TsDpen] catalyst 0.13−0.2 mol % and formic acid/triethylamine (5:2), 60−65 °C for 16 h. The numbers in parentheses are isolated yields by direct crystallization after the addition of aqueous 28% NH_4OH unless specified otherwise. [b]The enantiomeric ratio of the crude reaction mixture and isolated yield obtained after silica gel purification.

generate the hydrochloride salt **1b**. Our initial testing was performed on substrate **1b** using $[Rh(COD)Cl]_2$ (0.5 mol %) and (*R*,*R*)-MCCPM ligand (1.0 mol %) previously utilized by Boehringer Ingelheim Pharmaceutical under the asymmetric hydrogenation conditions with 300 psi H_2 pressure; however, only 80:20 enantiomeric ratio was observed for product **2b**. Interestingly, when the amine was protected with a benzyl group, the enantiomeric ratio was improved significantly to the reported results of 93:7,[15] which confirms the requirement of protection on the amino group for Rh-catalyzed asymmetric hydrogenation of the keto functionality. Nevertheless, we are interested in identifying a cost-effective and readily accessible method without the need for protection and deprotection steps for epinephrine synthesis. Ruthenium-catalyzed asymmetric transfer hydrogenation is a powerful technology that can be operated without the need for pressurized equipment. Furthermore, ruthenium is among the most inexpensive noble metal elements with high accessibility. They are almost 10 to 15 times less expensive than iridium and rhodium.[12] The direct asymmetric reduction of the unprotected α-amino ketone **1b** was first tested with Noyori's ruthenium−diamine catalyst systems.[13] Low reactivity (up to 15%) and low enantioselectivity were observed with most of the diphenyldiamine-substituted Ru−arene catalysts (**3a**−**3h**) at a 1 mol % catalyst with a 5:2 mixture of formic acid and triethylamine in MeOH at 65 °C (Table 1, entries 1−8). We then turned our attention to Will's tethered arene catalyst systems, which have been reported with improved reactivity and selectivity,[14] though the catalysts have not been reported on the asymmetric transfer hydrogenation of *unprotected* amino ketones. Gratifying, the Ru-tethered catalytic

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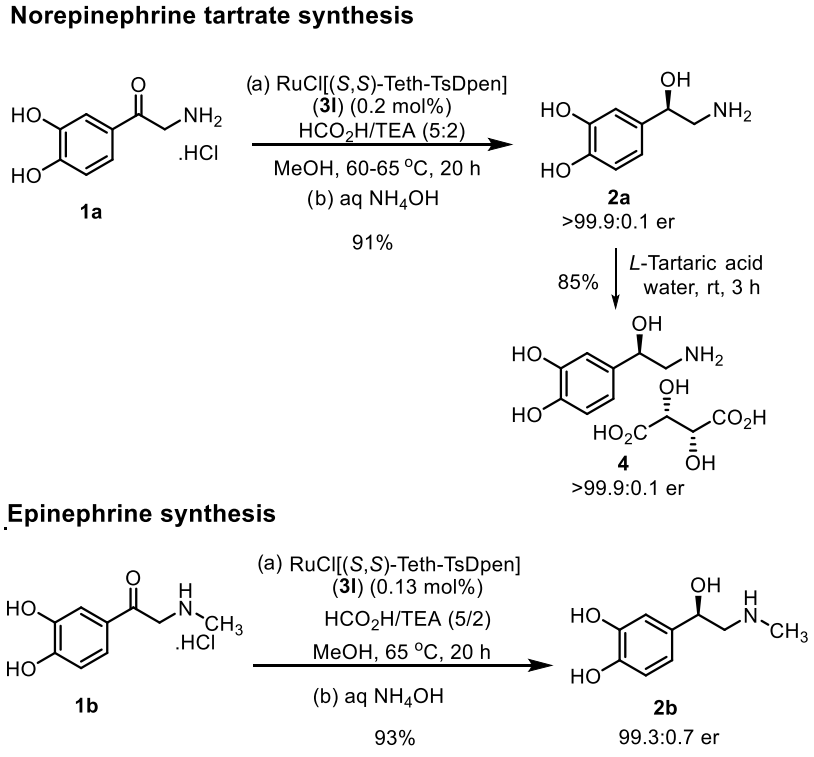
Scheme 2. Synthesis of Epinephrine and Norepinephrine on Decagram Scales



systems gave high reactivity and high enantioselectivity for the asymmetric transfer hydrogenation reaction of α-amino ketone **1b**. The methanesulfonyl amide-containing catalyst RuCl(*S*,*S*)-Ms-DENEB (**3i**) with an ether linkage provided a 97:3 er. The corresponding tosylsulfonylamide catalyst RuCl(*S*,*S*)-Ts-DENEB (**3j**) yielded a 96:4 er. The tethered catalysts with an all-carbon linker RuCl(*S*,*S*)-Teth-MsDpen (**3k**) produced a 98:2 er, and the best enantioselectivity was obtained with RuCl(*S*,*S*)-Teth-TsDpen (**3l**) at a 99.3:0.7 er. The product **2b** can be directly crystallized out in 94% yield in >99.9:0.1 er after neutralization with aqueous 28% NH_4OH.

Furthermore, the catalyst load of **3l** can be decreased to 0.13 mol % with a complete conversion of compound **1b** in 20 h at 60 °C. Asymmetric transfer hydrogenation of a number of α-amino ketone HCl salts, including the substitution of both aryl and heteroaryl functionality on the aromatic ring, was achieved. As shown in Scheme 1, unprotected amine ketones could be converted to the corresponding chiral 1,2-amino alcohol products in high yields with excellent enantioselectivities. We applied this powerful technology for the synthesis of various chiral 1,2-amino alcohol-containing pharmaceutical drugs. For example, previous synthetic efforts toward norepinephrine required the resolution of D,L-artenol using tartrate salt[3] or ruthenium-catalyzed transfer hydrogenation of an *N*-benzylamine derivative followed by Pd-catalyzed hydrogenolysis.[3b] Using our method, norepinephrine **2a** was produced in one synthetic step with a high enantiomeric ratio of >99.9:0.1 er after simple isolation in 94% yield. The synthesis toward levisoprenaline **2c** could also be simplified by utilizing this method. It was reported by Corey and co-workers utilizing CBS reduction of ketone to produce **2c** in the total 6-step protocol.[17] Other methods include asymmetric Henry reaction with macrocyclic salen ligands[18] or chromium complexes[19] or Sharpless asymmetric dihydroxylation.[20] A clear benefit of the direct asymmetric transfer hydrogenation of the unprotected α-amino ketone is the reduced number of synthetic steps with levisoprenaline being isolated in >99.9:0.1 er and 77% yield.

This methodology can also be applied to sterically hindered substrates, such as compound **2d** with an adjacent *t*-butylamine group, which was achieved in 76% yield and high enantioselectivity of >99.9:0.1 er. The compound **2d** was reported only in racemic synthesis from hydrogenation of a benzyl-protected derivative.[21] Next, we investigated other drug candidates having the monohydroxy substitution on the aromatic ring with the free amines, as in octopamine (**2e**). Enantiomerically pure octopamine has been synthesized previously using enzymatic catalysis,[22] dual-enzymatic parallel kinetic resolution approach,[23] or a Rh-catalyzed asymmetric transfer hydrogenation of the 2-tosyloxy ketone intermediate before converting to 1,2-amino alcohol via an azido intermediate.[24] By using this transfer hydrogenation methodology, octopamine **2e** was successfully obtained in >99.9:0.1 er and 94% yield. Octopamine was also applied as a reductive amination partner in the manufacture of deterenol (**2f**),[25] while our method provided compound **2f** in 90% yield with >99.9:0.1 er under transfer hydrogenation conditions. (*R*)-Denopamine, a β-receptor agonist used to treat congestive heart failure, was also synthesized in >99.9:0.1 er and 91% isolated yield with 0.2 mol % of catalyst **3l**. The literature method for the synthesis of (*R*)-denopamine employed a CBS reduction[26] or iridium-catalyzed asymmetric hydrogenation under 40 atm H_2 pressure, which is a less practical methodology.[27]

Phenylephrine (**2h**) was originally synthesized by kinetic resolution on a styrene oxide derivative.[28] Another method involved the use of a whole-cell biocatalyst to reduce 2-chloro-1-(3-nitrophenyl)ethenone to produce (*R*)-2-chloro-1-(3-nitrophenyl)ethanol, which was later converted to phenylephrine.[29] Alternatively, the Ru-PPhos catalyst was applied for asymmetric hydrogenation in the presence of hydrogen gas.[30] By applying the Ru-catalyzed asymmetric transfer hydrogenation

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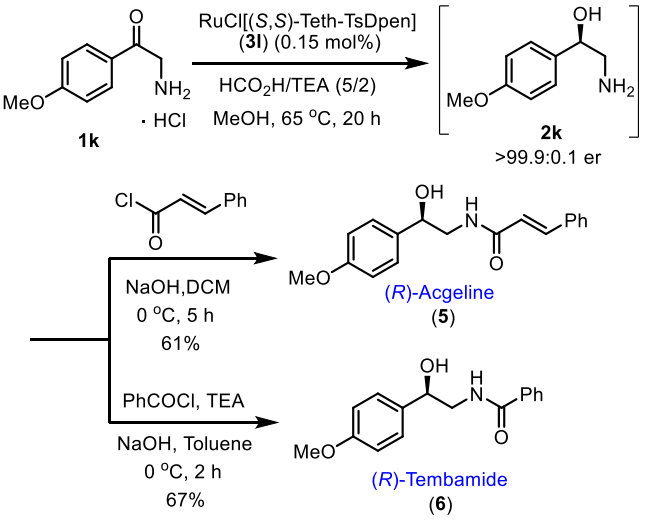
conditions, phenylephrine was produced with >99.9:0.1 er and 82% yield. Encouraged by these results, we explored the syntheses of fluoro, chloro-, and methoxy-substituted phenyl-containing amino alcohols from their corresponding amino ketones. Compounds **2i**−**2k** were synthesized by using the optimized conditions of 0.15 mol % catalyst **3l** to obtain the desired enantiomerically pure 1,2-amino alcohols in 99.6:0.4 er and >99.9:0.1 er, respectively. Higher yield and higher enantioselectivity were obtained compared to the literature conditions for the known compound **2k**.[6a31]

The identified conditions are also effective for the substituted α-amino ketones. Zhang's group previously reported the synthesis of compound **2p** by iridium/f-amphox-catalyzed asymmetric hydrogenation that was applied to various *N*-Me derivatives.[8a] Zhou's group also successfully synthesized compounds **2m** and **2o** by using chiral spiro iridium catalysts under asymmetric hydrogenation reactions.[32] By using the newly developed Ru-catalyzed asymmetric transfer hydrogenation conditions, compound **2l** was obtained in a 93.2:6.8 er and 86% yield; compound **2m** was generated in a 99.6:0.4 er in 88% yield; compound **2n** was produced in a 99.6:0.4 er and 55% yield; **2o** was synthesized in a 98:2 er and 63% yield; and heteroaryl thiophene 1,2-amino alcohol **2p** was created in a 98.8:1.2 er and 89% yield. Furthermore, the piperazine containing amino alcohol **2q** was obtained in a 99.1:0.9 er in the crude mixture and 99.6:0.4 er in 86% yield after direct crystallization. Compound **2r** was obtained in 99.3:0.7 er in 82% yield. The vasodilator, (*R*)-Pipratecol (**2s**), was synthesized in an excellent enantioselectivity of 99.6:0.4 er with 58% yield.

To demonstrate the practicality of the asymmetric transfer hydrogenation process, syntheses of norepinephrine and epinephrine were demonstrated on 10 g scales (Scheme 2). The asymmetric transfer hydrogenation of **1a** in the presence of 0.2 mol % RuCl[(*S*,*S*)-Teth-TsDpen] (**3l**) furnished the product **2a** with 99.3:0.7 er in the crude mixture, upon isolation by direct crystallization from the reaction mixture with the addition of aqueous 28% NH_4OH, compound **2a** was isolated in 91% yield and >99.9:0.1 er. Then, tartrate salt formation and the charcoal treatment generate the final compound **4** in a >99.9:0.1 er and 85% yield. The asymmetric transfer hydrogenation of 10 g **1b** in the presence of 0.13 mol % catalyst **3l** proceeded to full conversion to **2b** in 12 h with 99.3:0.7 er and 93% yield after direct isolation from the reaction mixture.

The syntheses of the ritaceae family natural products, such as tembamide and acgeline,[33] were also demonstrated using this asymmetric transfer hydrogenation technology. These chiral hydroxy amide derivatives exhibit both adrenaline-like activity and anti-HIV activity.[34] The reported process involves the intermediate cyanohydrin, which requires the handling of hydrogen cyanide or trimethylsilyl cyanide as the cyanide source.[35] The two natural products were synthesized using asymmetric hydrogenation or asymmetric transfer hydrogenation of the corresponding keto amides.[36] With a modular approach, after obtaining the crude enantiomerically pure **2k** (>99.9:0.1 er), it was coupled with the corresponding acid chlorides, (*R*)-acgeline (**5**) was obtained in 61% yield and (*R*)-tembamide (**6**) was generated in 88% yield in one pot with the same enantiomeric ratios of >99.9:0.1 (Scheme 3).

Scheme 3. Synthesis of two Natural Products (*R*)-Tembamide and (*R*)-Acgeline



CONCLUSIONS

We have developed the first protection-free economical synthesis of important drugs, such as epinephrine and norepinephrine, utilizing readily accessible and effective ruthenium-catalyzed asymmetric transfer hydrogenation technology. High enantioselectivities of >99.9:0.1 enantiomeric ratios were observed for the catechol- or phenol-containing α-hydroxy amines. A number of enantiomerically pure drugs and natural products were also synthesized employing this technology, including colterol, octopamine, deterenol, denopamine, pipratecol, acgeline, and tembamide. Ruthenium-catalyzed asymmetric transfer hydrogenation of unprotected α-amino ketones is a safer, operationally simpler, most inexpensive methodology and a green chemistry alternative to the existing resolution and asymmetric hydrogenation processes utilizing the required protection and deprotection on the amino groups. This method enables an ideal synthesis for these important pharmaceutical drugs.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, all reactions were performed under a nitrogen atmosphere. Analytical thin-layer chromatography was performed on silica gel 60 F254 plates. **1l** and **1n** were purchased without further purification. NMR spectra were recorded on 400 or 600 MHz instruments. The chemical shifts given in ppm were referenced to the residual proton signal of the deuterated solvent with the residual solvent peak used as an internal standard δ $^1H/^{13}C$ (solvent); 7.26/77.2 ($CDCl_3$); 2.50/39.5 (DMSO-d_6); 3.31/49.0 (CD_3OD); 4.79 (D_2O). The D_2O samples were prepared with 0.1% H_3PO_4. The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; m, multiplet. High-resolution mass spectra (TOF analyzer) were recorded using either electron impact (EI) or electrospray ionization (ESI) techniques. Chiral HPLC was conducted using different chiral columns with different eluents. All of the catalysts (**3a**−**3l**) were purchased from Strem Chemicals.

Synthesis of 2-Amino-1-(3,4-dihydroxyphenyl)ethan-1-one hydrochloride, 1a.[3] A 3-neck round-bottom flask was charged with 2-chloro-1-(3,4-dihydroxyphenyl)ethan-1-one (5.0 g, 26.7 mmol) and MeCN (10.0 mL). To the reaction mixture, 28% NH_4OH (30.1 mL, 241.1 mmol) was added. The reaction mixture was stirred for 16 h at room temperature. The slurry was filtered and washed with MeOH (3 × 20 mL), and the product (2-amino-1-(3,4-dihydroxyphenyl)ethan-1-one) was obtained as an off-white solid (2.69 g, 60% yield). To a 2-neck round-bottom flask, 2-amino-1-(3,4-dihydroxyphenyl)ethan-1-one (10.0 g, 167.2 mmol) and MeOH (40 mL) were charged. To the reaction mixture, 3 M HCl in MeOH (79.7 mL, 239.3 mmol) was added slowly. The reaction mixture was stirred for 10 min, filtered

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through a charcoal bed, and washed with methanol (3 × 20 mL). The filtrate was concentrated, and MTBE (100 mL) was added. The slurry was stirred for 30 min, filtered, and washed with MTBE (20 mL) to afford an off-white solid (9.6 g, 86% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.43−8.67 (br s, 4H), 7.40 (t, J = 7.2 Hz, 2H), 6.92 (d, J = 8.4 Hz, 1H), 4.41 (s, 2H); ^{13}C{H} NMR (150 MHz, DMSO-d_6) δ 190.7, 152.0, 145.5, 125.5, 121.7, 115.4, 114.8, 44.1.

*Synthesis of (R)-4-(2-Amino-1-hydroxyethyl)benzene-1,2-diol, **2a**.*[3] A 3-neck round-bottom flask was charged with compound **1a** (10 g, 49.11 mmol), methanol (100 mL, 10 V), and catalyst **3l** (45.6 mg, 0.15 mol %), followed by HCOOH/TEA (5:2) (13 mL). The reaction mixture was stirred at 60−65 °C (oil bath) for 20 h. After taking a sample and HPLC showed that the reaction was completed, it was cooled to rt, treated with 12.5 mL of 28% NH_4OH, and the slurry was stirred for 15 min. Water (10 V) was added and stirred for 30 min. The slurry was filtered and washed with water (10 V) and MeOH (4 V). The solid was dried under vacuum at 50 °C for 16 h. Product **2a** was obtained as an off-white solid (7.86 g, 91% yield); er ratio >99.9:0.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.71 (s, 1H), 6.65 (d, J = 8.0 Hz, 1H), 6.54 (d, J = 6.8 Hz, 1H), 4.26 (q, J = 4.0 Hz, 1H), 2.56 (m, 2H); ^{13}C NMR{H} (100 MHz, DMSO-d_6) δ 145.4, 144.6, 135.7, 117.2, 115.5, 113.9, 74.6, 50.5. The enantiomeric ratio was determined by SFC (CBH, 4.0 mm × 100 mm, particle size: 5 μm, 10 mM sodium phosphate monobasic, pH 5.8/isopropyl alcohol = 98/2, flow rate 0.75 mL/min, 230 nm), t_R = 18.6 min (major).

*Synthesis of Norepinephrine Tartrate Salt, **4**.*[3d] A 3-neck round-bottom flask was charged with water (5 V) and *L*-tartaric acid (9.78 g, 1.12 equiv, 65.1 mmol). The mixture was stirred to get a clear solution. Compound **2a** (10.1 g, 59.7 mmol) was charged, rinsed with water (1 V), aged at rt for 0.5 h, warmed up to 35−40 °C (oil bath) to complete the salt formation, and a dark black colored solution was observed. To remove the undissolved dark-colored mass, the solution was passed through a filter. The filter was washed with water (1 V). The solution was passed through a 20 wt % 1:1 Solka-Floc and Norit CGP carbon column. A light brown solution was observed. The solution was washed with water (1 V). The aqueous salt solution was distilled to ∼2 vol at 50−55 °C (oil bath) at 80 mbar vacuum. The slurry was cooled down to rt in 1 h, filtered, and washed with 3 × 3 V ethanol. Product **4** was obtained as a white solid (17.0 g, 85% yield, 97.5% purity (HPLC)); mp 95.6 °C; $[\alpha]_D^{25}$ = −9.0° (H_2O); ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.79 (s, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 4.64 (d, J = 8.8 Hz, 1H), 4.04 (s, 2H), 2.94 (d, J = 11.8 Hz, 1H), 2.76 (t, J = 11.1 Hz, 1H). ^{13}C {H} NMR (150 MHz, DMSO-d_6): δ 175.3, 145.7, 145.4, 133.4, 117.2, 115.9, 114.0, 72.6, 69.4, 46.4.

*Synthesis of 1-(3,4-Dihydroxyphenyl)-2-(methylamino)ethan-1-one Hydrogen Chloride, **1b**.*[2a] A 250 mL 3-neck round-bottom flask equipped with an internal thermometer, addition funnel, and N_2 line was charged with 2-chloro-1-(3,4-dihydroxyphenyl)ethan-1-one (10.0 g, 53.6 mmol) and MeCN (6 V). The reaction mixture was treated dropwise with 40% CH_3NH_2/H_2O (32.4 mL, 7.0 equiv) over a period of 25 min. During the addition, the slurry changed color from dark beige to greyish green, and the internal temperature increased from 18.5 to 23.7 °C before cooling back to 18.5 °C. The slurry was heated to 35 °C for 1 h. After cooling to room temperature, the reaction mixture was treated with 1 V MeCN, filtered, and washed with 1 V MeCN, 1 V of water, and 1 V of MeCN. The cake was suction-dried and dried in a vacuum oven at 40 °C for 12 h. The product 1-(3,4-dihydroxyphenyl)-2-(methylamino)ethan-1-one was collected as a light green solid (8.25 g, 85% yield). A 1L flask with an overhead stirrer, internal thermometer, addition funnel, and N_2 line was charged with 1-(3,4-dihydroxyphenyl)-2-(methylamino)ethan-1-one (10.0 g, 55.0 mmol) and MeOH (6 V). To this slurry, 3 M HCl in MeOH (73.5 mL) was added at rt, followed by 2 V water. During the addition, the slurry changed from greyish/green to a dark brown solution. After 1 h, distillation was performed under reduced pressure to remove methanol (70 mL). The reaction mixture was charged with isopropyl alcohol (IPA, 20 mL), and the mixture was filtered and washed with 3 V IPA. Product **1b** was obtained as an off-white solid (8.5 g, 71% yield). ^{1}H NMR (400 MHz, D_2O) δ 7.45 (dd, J = 8.4, 2.0 Hz, 1H), 7.41 (d, J = 2.0 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 4.62 (s, 2H), 2.79 (s, 3H); ^{13}C {H} NMR (100 MHz, D_2O) δ 191.4, 151.4, 144.2, 125.8, 123.2, 115.7, 115.2, 53.6, 32.7.

*Synthesis of (R)-4-(1-Hydroxy-2-(methylamino)ethyl)benzene-1,2-diol, **2b**.*[2a] A 3-neck round-bottom flask was charged with compound **1b** (10 g, 217.6 mmol), catalyst **3l** (37 mg, 0.13 mol %), and MeOH (100 mL, 10 V). This solution was treated with formic acid/TEA (5:2) (10.5 mL). The reaction mixture was stirred at reflux for 20 h. The reaction mixture was cooled to rt and treated with 28% NH_4OH (15 mL). The slurry was stirred for 15 min before adding water (150 mL) and then stirred for another 30 min. The slurry was filtered and washed with water (20 V). The cake was suction-dried under vacuum, and product **2b** was obtained as an off-white solid (7.5 g, 89% yield); mp 215−217 °C; er ratio 99.3:0.7; $[\alpha]_D^{25}$ = −55.1° (0.6 N HCl (aq.)); ^{1}H NMR (400 MHz, D_2O) δ 6.90−6.88 (m, 2H), 6.81 (dd, J = 8.2, 2.1 Hz, 1H), 4.87 (dd, J = 7.1, 5.8 Hz, 1H), 3.22 (d, J = 6.4 Hz, 2H), 2.71 (s, 3H); ^{13}C{H} NMR (100 MHz, D_2O): δ 144.2, 144.1, 132.0, 118.5, 116.3, 113.8, 68.2, 54.4, 32.9. The enantiomeric ratio was determined by SFC (CBH, 4.0 mm × 100 mm, particle size: 5 μm, 10 mM sodium phosphate monobasic, pH 5.8/isopropyl alcohol = 98/2, flow rate 0.75 mL/min, 230 nm), t_R = 2.3 min (major), 2.8 min (minor).

*Synthesis of 1-(3,4-Dihydroxyphenyl)-2-(isopropylamino)ethan-1-one Hydrogen Chloride, **1c**.*[39c] 2-Chloro-1-(3,4-dihydroxyphenyl)-ethan-1-one (5.03 g, 26.95 mmol) in MeCN (25.0 mL) was treated with the dropwise addition of isopropylamine (6.55 mL, 80.4 mmol). The reaction mixture was heated to 65 °C (oil bath). After 2 h, liquid chromatography−mass spectrometry (LCMS) indicated reaction completion. The reaction mixture was treated with IPA (50 mL) and concentrated to 35 mL. The precipitate was filtered and washed with H_2O (6 V). NMR showed residual isopropylamine. The cake was washed with H_2O (10 V) and IPA (10 V). NMR indicated <1% isopropylamine remaining. The yellow solid was suspended in IPA (5 V) and treated with 12 M HCl (2 equiv, 4.5 mL). After stirring for 1 h, the suspension was filtered and washed with acetone (10 V) and heptane (5 V). The cake was transferred to the vacuum oven for further drying (35 °C, 14 h). The amino ketone salt **1c** (1.61 g, 24%) was collected as an off-white solid. ^{1}H NMR (400 MHz; DMSO-d_6) δ 7.45 (dd, J = 8.4, 2.0 Hz, 1H), 7.40 (d, J = 2.0 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 3.48 (sept, J = 6.6 Hz, 1H), 1.33 (d, J = 6.6 Hz, 1H); ^{13}C{H} NMR (101 MHz; DMSO-d_6) δ 191.5, 151.3, 144.2, 125.8, 123.2, 115.7, 115.2, 50.9, 49.4, 18.1.

*Synthesis of (R)-4-(1-Hydroxy-2-(isopropylamino)ethyl)benzene-1,2-diol, **2c**.*[9] A 3-neck round-bottom flask was charged with compound **1c** (0.250 g, 1.02 mmol) and MeOH (10 V, 2.5 mL). The suspension was treated with **3l** (0.20 mol %, 1.26 mg) in formic acid/TEA (5:2) (1 V, 0.25 mL). The reaction mixture was stirred at 62 °C (oil bath) under N_2 sparging for 19 h. After cooling to rt, the reaction mixture was treated with 28% NH_4OH (1 V, 0.25 mL) and H_2O (5 V, 1.0 mL) and stirred for 20 min. The precipitate was filtered and rinsed with MTBE (5 V). The amino alcohol **2c** was collected as a beige solid (165 mg, 77% yield); *er* ratio >99.9:0.1. ^{1}H NMR (400 MHz; DMSO-d_6): δ 6.73 (d, J = 2.0 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 6.56 (dd, J = 8.0, 2.0 Hz, 1H), 4.42 (dd, J = 8.6, 4.0 Hz, 1H), 2.77 (sept, J = 6.2 Hz, 1H), 2.63−2.52 (m, 2H), 0.98 (app t, J = 6.6 Hz, 6H); ^{13}C{H} NMR (101 MHz; DMSO-d_6): δ 144.9, 144.2, 135.3, 116.7, 115.1, 113.5, 71.1, 54.9, 48.1, 22.5, 22.4. The enantiomeric ratio was determined by SFC (IC-3, 4.6 mm × 150 mm, particle size: 3 μm, temperature: 40 °C, CO_2/ethanol with 0.05% of diethylamine = 88/12, flow rate 1.5 mL/min, 215 nm), t_R = 12.4 min (major).

*Synthesis of 2-(tert-Butylamino)-1-(3,4-dihydroxyphenyl)ethan-1-one Hydrogen Chloride, **1d**.*[21] A sealed tube was charged with 2-chloro-1-(3,4-dihydroxyphenyl)ethan-1-one (2.0 g, 10.72 mmol, 1.0 equiv) and dioxane (2 V). The reaction mixture was treated with the dropwise addition of *t*-butylamine (9.01 mL, 85.75 mmol, 8.0 equiv) over a period of 10 min at rt. The slurry was heated to 70−75 °C (oil bath) for 4 h. The reaction mixture was cooled, diluted with acetone (40 mL), filtered, and washed with 2 V acetone. The crude filtrate was dried, and acetone (50 mL) was added. After stirring for 1 h, the filtered solid compound was vacuum oven-dried at 25 °C for 12 h. The product 2-(*tert*-butylamino)-1-(3,4-dihydroxyphenyl)ethan-1-one was collected

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as a brown-colored solid (2.25 g, 94% crude yield). A 50 mL 3-neck RBF equipped with an internal thermometer, addition funnel, and N_2 line was charged with 2-(*tert*-butylamino)-1-(3,4-dihydroxyphenyl)-ethan-1-one (1.0 g, 4.48 mmol, 1.0 equiv) and MeOH (6 V). The reaction mixture was treated with the dropwise addition of 3 M HCl in MeOH (2.98 mL, 8.96 mmol 2.0 equiv) at 0−5 °C over a period of 5 min. The reaction mixture was stirred at rt for 1 h. The crude reaction mixture MTBE (100 mL) was added and stirred for 3 h. The crystallized salt was filtered and washed with MTBE (20 mL) and dried in a vacuum oven at rt for 12 h to afford **1d** (0.97 g, 84% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 9.54 (s, 1H), 8.92 (t, J = 6.6 Hz, 2H), 7.54 (dd, J = 8.3, 2.2 Hz, 1H), 7.48 (d, J = 2.2 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 4.53 (t, J = 6.2 Hz, 2H), 3.36 (s, 2H), 1.35 (s, 9H); ^{13}C NMR{H} (101 MHz, DMSO-d_6) δ 190.9, 152.7, 146.1, 126.0, 122.7, 115.8, 115.5, 56.7, 46.9, 25.6.

Synthesis of (R)-4-(2-(tert-Butylamino)-1-hydroxyethyl)benzene-1,2-diol, ***2d****.*[21] A sample vial equipped with a stir bar and N_2 line was charged with compound **1d** (200 mg, 0.81 mmol), MeOH (2 mL, 10 V), **3l** (0.15 mol %), and formic acid/TEA (5:2) (1 V). The reaction mixture was stirred at 62 °C (oil bath). After 20 h, the reaction mixture was cooled to rt (100% conversion). The reaction mixture was cooled to rt and neutralized with aq NH_4OH (1 V). The reaction mixture was filtered and washed with H_2O (1 mL), followed by MeOH (5 mL). The filtrate was evaporated to dryness, and the crude compound was treated with MeOH (2 mL) and EtOAc (10 mL), followed by heating at 70−75 °C (oil bath). The crude compound was slowly cooled to rt. The crystallized material was filtered and washed with EtOAc (2 mL). The filtered solid was dried in a vacuum oven at 45 °C for 16 h to afford compound **2d** as a cream color solid (132 mg, 76% yield); *er* ratio >99.9:0.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.84 (d, J = 1.7 Hz, 1H), 6.77−6.67 (m, 2H), 4.73 (dd, J = 10.1, 3.1 Hz, 1H), 3.08−2.88 (m, 2H), 1.34 (s, 9H); ^{13}C {H} NMR (101 MHz, DMSO-d_6) δ 145.2, 145.2, 132.5, 117.1, 115.0, 112.8, 69.2, 56.7, 48.5, 24.4. The enantiomeric ratio was determined by SFC (IC-3, 4.6 mm × 150 mm, particle size: 3 μm, temperature: 35 °C, CO_2/ethanol with 0.1% of diethylamine = 82/18, flow rate 0.8 mL/min, 230 nm), t_R = 26.2 min (major).

Synthesis of 2-Amino-1-(4-hydroxyphenyl)ethan-1-one Hydrogen Chloride, ***1e****.*[24] A 3-neck RBF was charged with 2-bromo-1-(4-hydroxyphenyl)ethan-1-one (4.0 g, 0.014 mol), HMTA (3.0 g, 0.016 mol), IPA (4 V), and MeCN (4 V). An immediate formation of a creamy white solid was observed. The reaction mixture was stirred for 2 h. The cake was washed with IPA (90 mL) and dried under vacuum to afford hexamine salt (6.4 g, 96% yield). A 25 mL single-neck round-bottom flask equipped with a stirrer, internal thermometer, and N_2 line was charged with hexamine salt (3.0 g, 8.5 mmol) and MeOH (6 V). The reaction mixture was treated with the dropwise addition of 12 M HCl (2 mL, 2.0 equiv) at rt over a period of 5 min. During the addition, the slurry changed from pale white to a light-yellow solution over a period of 24 h. The solvent was evaporated, and the solid was washed with cold MeOH to give compound **1e** as a white solid (1.5 g, 98% yield). ^{1}H NMR (400 MHz, D_2O) δ 7.96 (d, J = 8.9 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 4.65 (s, 2H); ^{13}C{H} NMR (101 MHz, DMSO-d_6) δ 190.7, 163.4, 130.8, 125.1, 115.6, 44.1.

Synthesis of (R)-4-(2-Amino-1-hydroxyethyl)phenol, ***2e****.*[24] A 10 mL vial equipped with a stirrer and N_2 line was charged with compound **1e** (0.1 g, 0.54 mmol), MeOH (3 mL), Ru catalyst (0.5 mg, 0.15 mol %), and formic acid/TEA (5:2) (1 V). The reaction mixture was stirred at 62 °C. After 24 h, the reaction mixture was cooled to room temperature, and the solvent was reduced and neutralized with 28% aq NH_4OH (1 V). The slurry was stirred for 15 min, filtered, and dried in a vacuum oven at 45 °C for 16 h to yield compound **2e** as a white solid (78.0 mg, 94% yield); *er* ratio >99.9:0.1. ^{1}H NMR (400 MHz, CD_3OD) δ 7.19 (d, J = 8.6 Hz, 2H), 6.76 (d, J = 8.5 Hz, 2H), 4.69 (dd, J = 8.9, 4.0 Hz, 1H), 3.00−2.81 (m, 2H); ^{13}C {H} NMR (101 MHz, CD_3OD) δ 157.1, 132.0, 126.9, 115.0, 70.1, 46.5. The enantiomeric ratio was determined by SFC (AD3, 4.6 mm × 150 mm, particle size: 3 μm, temperature: 40 °C, CO_2/isopropyl alcohol with 0.1% of diethylamine = 85/15, flow rate 1.0 mL/min, 218 nm), t_R = 23.0 min (major).

Synthesis of 1-(4-Hydroxyphenyl)-2-(isopropylamino)ethan-1-one Hydrogen Chloride, ***1f****.*[25] A 25 mL single-neck RBF equipped with a stirrer, internal thermometer, and N_2 line was charged with 1-(4-hydroxyphenyl)-2-(isopropylamino)ethan-1-one (0.3 g, 4.8 mmol) and MeOH (12 V). The reaction mixture was treated with the dropwise addition of 12 M HCl (0.260 mL, 2.0 equiv) in H_2O (3 V) at rt over a period of 5 min. During the addition, the slurry changed from dark orange to a pale-yellow solution. The slurry was stirred at rt for 1 h. The solvent was evaporated, and the solid was washed with cold MeOH to give compound **1f** as a pale-yellow solid (325 mg, 92% yield). The solid was carried forward to the next steps. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 8.99 (s, 2H), 7.93 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 4.61 (d, J = 5.8 Hz, 2H), 1.29 (d, J = 6.5 Hz, 6H); ^{13}C{H} NMR (101 MHz, DMSO-d_6) δ 190.4, 163.5, 163.5, 131.0, 130.9, 125.1, 115.6, 49.7, 49.1, 49.0, 18.5.

Synthesis of (R)-4-(1-Hydroxy-2-(isopropylamino)ethyl)phenol, ***2f****.*[25] A 10 mL reactor equipped with a stirrer and N_2 line was charged with compound **1f** (150 mg, 0.66 mmol), MeOH (2 mL), **3l** (0.69 mg, 0.15 mol %), and formic acid/TEA (5:2) (1 V). The reaction mixture was stirred at 62 °C. After 20 h, the reaction mixture was cooled to room temperature, and the solvent was reduced and neutralized with aq NH_4OH (1 V). The slurry was stirred for 15 min, filtered, and dried in a vacuum oven at 45 °C for 16 h to give compound **2f** as a white solid (115.0 mg, 90% yield); *er* ratio >99.9:0.1. ^{1}H NMR (400 MHz, D_2O) δ 7.33 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.6 Hz, 2H), 4.95 (dd, J = 7.3, 5.9 Hz, 1H), 3.50 (hept, J = 6.6 Hz, 1H), 3.27 (d, J = 7.2 Hz, 2H), 1.34 (dd, J = 6.6, 2.2 Hz, 6H); ^{13}C NMR {H} (101 MHz, D_2O) δ 155.9, 131.5, 127.7, 115.7, 68.8, 51.0, 50.1, 18.3, 17.9. The enantiomeric ratio was determined by SFC (AD3, 4.6 mm × 150 mm, particle size: 3 μm, temperature: 40 °C, CO_2/isopropyl alcohol with 0.1% of diethylamine = 85/15, flow rate 1.0 mL/min, 210 nm), t_R = 7.9 min (major).

Synthesis of 2-((2,3-Dimethoxyphenethyl)amino)-1-(4-hydroxyphenyl)ethan-1-one Hydrogen Chloride, ***1g****.*[27] To a stirred solution of 2-bromo-1-(4-hydroxyphenyl)ethan-1-one (3.0 g, 1.0 equiv) in THF (27.0 mL) was added 2-(3,4-dimethoxyphenyl)ethan-1-amine (5.057 g, 2.0 equiv) at 0 °C over a period of 1 h and stirred at the same temperature for 2 h. The resulting precipitate was filtered, the solid was washed with THF (3.0 mL), and the filtrate was concentrated. The residue was dissolved in acetone (60.0 mL), treated with 2 N HCl in Et_2O (15 mL) at 0 °C, and stirred for 30 min. The precipitated solid was filtered and washed with acetone (3 × 5 mL) to obtain compound **1g** as a white solid (2.7 g, 55% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.89 (br s, 1H), 9.29 (br s, 2H), 7.89 (d, J = 9.2 Hz, 2H), 6.97 (d, J = 8.2 Hz, 2H), 6.92−6.88 (m, 2H), 6.78 (dd J = 8, 2.5 Hz, 1H), 4.68 (s, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 3.20−3.16 (m, 2H), 2.99−2.95 (m, 2H); ^{13}C {H} NMR (100 MHz, DMSO-d_6) δ 190.7, 164.1, 149.3, 148.2, 131.4, 130.0, 125.5, 121.0, 116.2, 113.0, 112.6, 56.0, 55.9, 52.1, 48.5, 31.4.

Synthesis of (R)-4-(2-((2,3-Dimethoxyphenethyl)amino)-1-hydroxyethyl)phenol, ***2g****.*[27] To a stirred solution of **1g** (0.2 g, 0.568 mmol) in MeOH (2.0 mL) was added the Ru catalyst (0.71 mg, 0.00113 mmol) followed by a mixture of HCO_2H/TEA (0.2 mL) at rt. The reaction mixture was warmed to 65 °C (oil bath) and stirred for 12 h. MeOH was evaporated from the reaction mixture, and the residue was neutralized with aq NH_4OH solution and extracted with DCM (3 × 2 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford crude compound **2g**. The crude compound was recrystallized with MeOH to afford the desired product **2g** as an off-white solid (0.164 g, 91% yield); *er* ratio >99.9:0.1; $[\alpha]_D^{25}$ = −29.1° (MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (br s, 1H), 7.16 (d, J = 7.1 Hz, 2H), 6.90−6.82 (m, 2H), 6.72−6.70 (m, 3H), 5.09 (br s, 1H), 4.574.51 (m, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 2.84−2.72 (m, 2H), 2.71−2.60 (m, 4H); ^{13}C{H} NMR (100 MHz, DMSO- d_6) δ 156.7, 149.1, 147.5, 135.3, 133.4, 127.5, 120.8, 115.1, 113.0, 112.3. 71.7, 58.1, 56.0, 55.8., 51.4, 36.0. The enantiomeric ratio was determined by SFC (IC-3, 4.6 mm × 150 mm, particle size: 3 μm, temperature: 35 °C, CO_2/methanol with 0.1% of diethylamine = 8/155, flow rate 1.2 mL/min, 230 nm), t_R = 41.8 min (major).

Synthesis of 1-(3-Hydroxyphenyl)-2-(methylamino)ethan-1-one Hydrogen Chloride ***1h****.*[30] To the cooled solution of $MeNH_2$ in THF

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(35.0 mL, 70.0 mmol, 3.0 equiv), was added 2-bromo-1-(3-hydroxyphenyl)ethan-1-one (5.0 g, 23.2 mmol, 1.0 equiv) in THF (15.0 mL) slowly at 0 °C under nitrogen. After the resulting solution was stirred at this temperature for 30−60 min, the crude was filtered to remove $MeNH_2$·HBr salt, and THF solution was cooled to 0 °C and 3 M HCl in MeOH was added slowly and stirred for 1 h at rt. After this time, the crude reaction mixture was filtered, and the cake was washed with MTBE (5 mL) and dried under vacuum to afford HCl salt **1h** as a white solid (1.7 g, 36% yield over 2 steps). ^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (m, 1H), 7.43−7.33 (m, 3H), 7.12 (m, 1H), 4.69 (s, 2H), 2.81 (s, 3H); ^{13}C {H} NMR (100 MHz, CD_3OD) δ 192.8, 159.4, 136.2, 131.3, 123.0, 120.5, 115.3, 55.4, 33.5.

Synthesis of (R)-3-(1-Hydroxy-2-(methylamino)ethyl)phenol, ***2h.***[30] A 40 mL vial was charged with compound **1h** (0.3 g, 1.49 mmol), catalyst Ru-TsDPEN (1.42 mg, 0.15 mol %), and MeOH (10 V). To the above reaction flask, HCOOH/TEA mixture (0.3 mL) was added at rt and stirred at 60−65 °C (oil bath) for 5 h. After completion of the starting material from HPLC, the reaction mixture was neutralized with 28% NH_4OH (1 V). The organic solvent (MeOH) was concentrated, and the crude was dissolved in DCM (1.0 mL). The crude compound was purified by column chromatography (DCM/MeOH/NH_4OH = 80:18:2), providing **2h** as an off-white solid (206 mg, 82% yield); *er* ratio >99.9:0.1; $[\alpha]_D^{25} = -30.4°$ (MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.16 (t, J = 7.8 Hz, 1H), 6.87−6.79 (m, 2H), 6.73−6.66 (m, 1H) 4.75 (dd, J = 5.03 Hz, 1H), 2.88−2.77 (m, 2H), 2.49 (s, 3H); ^{13}C {H} NMR (101 MHz, CD_3OD) δ 158.8, 145.5, 130.5, 118.0, 115.7, 113.8, 72.2, 59.0, 35.3. The enantiomeric ratio was determined by SFC (AD3, 4.6 mm × 150 mm, particle size: 3 μm, temperature: 40 °C, CO_2/isopropyl alcohol with 0.5% diethylamine = 78/22, flow rate 1.4 mL/min, 218 nm), t_R = 5.0 min (major).

Synthesis of 2-Amino-1-(3-fluorophenyl)ethan-1-one Hydrogen Chloride, ***1i.***[39ab] (a) A 100 mL RB flask was charged with the bromo-keto starting material (4.2 g, 19.53 mmol) and $CHCl_3$ (10 V). To the reaction mixture, HMTA (2.73 g, 19.53 mmol) was added. The reaction mixture was stirred for 2 h at 50 °C (oil bath), and the reaction was monitored by thin-layer chromatography (TLC). The reaction was completed and filtered, and the solid was washed with $CHCl_3$ (10 V) and dried under vacuum to afford hexamine salt as a white solid (6.4 g, 92% yield). (b) A 100 mL RB flask was charged with hexamine salt (6 g, 16.79 mmol), EtOH (10 V), and conc HCl (8.39 mL, 100.7 mol). The reaction mixture was refluxed for 4 h. After completion of the reaction (TLC), the reaction mixture was cooled to room temperature (RT), the solid was filtered, and the filtrate was concentrated to get a crude compound. The crude compound was triturated with MTBE (20 mL), and the resulting solid was filtered. The solid was washed with MTBE (30 mL) to get a pale-yellow solid **1i** (3.3 g, 65% yield, qNMR 62.6%). The product contains NH_4Cl as a byproduct (observed by ^{1}H NMR). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.51 (s, 3H), 7.88−7.82 (m, 2H), 7.67−7.58 (m, 2H), 7.37 (t, J = 51 Hz, 3H, NH4+), 4.61 (d, J = 5.4 Hz, 2H); ^{13}C {H}NMR (150 MHz, DMSO-d_6) 192.1, 162.2 (d, $J_{19F\text{-}13C}$ = 244.5 Hz), 135.8 (d, $J_{19F\text{-}13C}$ = 6 Hz), 131.4 (d, $J_{19F\text{-}13C}$ = 160.5 Hz), 124.6 (d, $J_{19F\text{-}13C}$ = 157.5 Hz), 121.5 (d, $J_{19F\text{-}13C}$ = 171 Hz), 114.8 (d, $J_{19F\text{-}13C}$ = 181.5 Hz), 44.7 (d, $J_{19F\text{-}13C}$ = 135 Hz).

Synthesis of (R)-2-Amino-1-(3-fluorophenyl)ethan-1-ol, ***2i.***[1h] A 100 mL RBF was charged with compound **1i** (1.0 g, 5.27 mmol, qNMR: 62.6%) and MeOH (10 V). The catalyst (TsDPEN: 6.53 mg, 0.2 mol %) and HCOOH/TEA mixture (1 mL) were added to the reaction mixture at RT. The reaction mixture was stirred at 60−65 °C (oil bath) for 7 h. The starting material was not completely consumed, then 0.3 mL of HCOOH/TEA was added and the reaction was continued overnight. The reaction was completed (monitored by HPLC). The reaction mixture was cooled to rt, neutralized with NH_4OH (1 V), and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude compound. The crude compound was purified by column chromatography (on SiO_2, 15 to 20% MeOH in DCM) to afford **2i** as a tan solid (385 mg, 74.7% yield), *er* ratio 99.6:0.4. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.37−7.33 (m, 1H), 7.16−7.12 (m, 2H), 7.04 (t, J = 8.4 Hz, 1H), 4.48−4.46 (m, 1H), 2.70−2.67 (m, 1H), 2.59−2.56 (m, 1H); ^{13}C {H} NMR (150 MHz, DMSO-d_6) δ 162.6 (d, $J_{19F\text{-}13C}$ = 241.5 Hz), 148.1(d, $J_{19F\text{-}13C}$ = 7.5 Hz), 130.2 (d, $J_{19F\text{-}13C}$ = 7.5 Hz), 122.4 (d, $J_{19F\text{-}13C}$ = 1.5 Hz), 113.7 (d, $J_{19F\text{-}13C}$ = 21 Hz), 113.0 (d, $J_{19F\text{-}13C}$ = 21 Hz), 74.3, 50.4. The enantiomeric ratio was determined by SFC (IA-3, 4.6 mm × 150 mm, particle size: 3 μm, temperature: 25 °C, CO_2/methanol with 0.1% of diethylamine = 90/10, flow rate 2.0 mL/min, 218 nm), t_R = 8.4 min (major), 8.2 min (minor).

Synthesis of 2-Amino-1-(3-chlorophenyl)ethan-1-one Hydrogen Chloride ***1j.***[39a] A 3-neck round-bottom flask was charged with 2-bromo-1-(3-chlorophenyl)ethan-1-one (4 g, 0.014 mol), HMTA (3 g, 0.016 mol), IPA (4 V), and MeCN (4 V). Immediate formation of a creamy white solid was observed. The reaction mixture was stirred for 2 h, and the cake was washed with IPA (90 mL). The cake was dried under vacuum to afford hexamine salt (3.0 g, 94% yield). A 25 mL single-neck round-bottom flask equipped with a stirrer, internal thermometer, and N_2 line was charged with the above hexamine salt (3.0 g, 8.5 mmol) and MeOH (6 V). The reaction mixture was treated with the dropwise addition of 12 M HCl (2 mL, 2.0 equiv) at rt over a period of 5 min. During the addition, the slurry changed from pale white to a light-yellow solution over a period of 24 h. After 24 h, the solvent was evaporated, and the solid was washed with cold MeOH, filtered, and dried to give **1j** as an off-white solid (1.1 g, 71% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63−8.38 (s, 3H), 8.04 (t, J = 1.85 Hz, 1H), 7.97 (m, 1H), 7.8 (m, 1H), 7.62 (m, 1H), 4.61 (s, 2H); ^{13}C {H} NMR (100 MHz, DMSO-d_6) δ 192.1, 135.5, 134.1, 133.9, 131.0, 127.9, 126.8, 44.9.

Synthesis of (R)-2-Amino-1-(3-chlorophenyl)ethan-1-ol, ***2j.***[37] A 40 mL vial was charged with compound **1j** (0.3 g, 1.456 mmol), catalyst **3l** (1.39 mg, 0.15 mol %), and MeOH (10 V). To the above reaction flask, the HCOOH/TEA mixture (0.3 mL) was added at RT and stirred at 60−65 °C (oil bath) for 5 h. The reaction was completed (monitored by HPLC). After completion of the starting material, the reaction mixture was neutralized with NH_4OH (1 V). The organic solvent (MeOH) was concentrated, and the crude was dissolved in DCM (1.0 mL). The crude compound was directly purified by column chromatography, providing **2j** as an off-white solid (226 mg, 90% yield), *er* ratio: 99.6:0.4. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39−7.31 (m, 2H), 7.30−7.23 (m, 2H), 4.46 (dd, J = 4.3 Hz, 1H), 2.69 (m, 1H), 2.58 (m, 1H);^{13}C {H} NMR (101 MHz, DMSO-d_6) δ 147.0, 132.7, 129.8, 126.6, 125.8, 124.6, 73.6, 49.8. *er* ratio 99.6:0.4. The enantiomeric ratio was determined by SFC (AD3, 4.6 mm × 150 mm, particle size: 3 μm, temperature: 25 °C, A: CO_2/Isopropyl alcohol with 0.1% diethylamine = 0 min-5%, 3 min-5% and 10 min-30%, flow rate 2.0 mL/min, 218 nm), t_R = 8.4 min (major), 8.2 min (minor).

Synthesis of 2-Amino-1-(4-methoxyphenyl)ethan-1-one Hydrogen Chloride, ***1k.***[31] This compound was synthesized by using a literature protocol.[1] A 3-neck round-bottom flask was charged with urotropine (6.12 g, 43.65 mmol) and dichloromethane (150 mL, 15 V), and then 2-bromo-1-(4-methoxyphenyl)ethan-1-one (10 g, 43.65 mmol) was added portion wise. Immediate formation of a creamy white solid was observed, and the reaction mixture was stirred at room temperature for 24 h. The reaction mass was filtered through a sintered funnel, washed with DCM (2 × 20 mL), MTBE (2 × 50 mL), and dried under vacuum to give an off-white hexamine salt (11.0 g, 68.5% yield). A 100 mL three-neck round-bottom flask equipped with a stirrer and an internal thermometer was charged with hexamine salt (5.0 g, 13.58 mmol) and MeOH (25 mL, 5 V). The reaction mixture was treated with the dropwise addition of 12 M HCl (2.26 mL, 2.0 equiv) at room temperature over a period of 5 min. During the addition, the mixture changed from an off-white slurry to a light-yellow solution over a period of 24 h. The solvent was evaporated, and the solid was washed with cold MeOH (5 mL, 1 V). The solid **1k** (2.0 g, 73% yield) was carried forward to the next step. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.25 (br s, 3H), 7.95−8.04 (m, 2H), 7.03−7.14 (m, 2H), 4.53 (s, 2H), 3.88 (s, 3H); ^{13}C {H} NMR (101 MHz, DMSO-d_6) δ 191.7, 164.6, 131.1, 127.0, 114.7, 56.2, 44.9.

Synthesis of (R)-2-Amino-1-(4-methoxyphenyl)ethan-1-ol, ***2k.***[31] A stirred solution of 2-amino-1-(4-methoxyphenyl)ethan-1-one hydrochloride **1k** (1.0 g, 4.97 mmol, 1.0 equiv) in MeOH (8.0 mL, 8 V) was treated with catalyst **3l** (0.15 mol %, 4.83 mg) followed by formic acid/TEA (5:2) (1.0 mL, 1.0 V). The reaction mixture was stirred at 60 °C

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(oil bath) under N_2 sparging for 8 h. After cooling to rt, the reaction mixture was treated with NH_4OH (2.0 mL, 2.0 V) and stirred at RT for 30 min. Most of the MeOH was evaporated under vacuum in a rotavapor, and the reaction mass was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with H_2O (1 × 5 mL), brine (1 × 5 mL), and evaporated to dryness to get the desired amino alcohol **2k** as a brown solid (780 mg, 94% yield); *er* ratio >99.9:0.1; $[\alpha]_D^{25}$ = −37.6° (MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.25−7.19 (m, 2H), 6.90−6.84 (m, 2H), 4.53−4.38 (m, 1H), 3.73 (s, 3H), 3.16−2.94 (m, 1H), 2.66−2.54 (m, 1H); ^{13}C {H} NMR (100 MHz, DMSO-d_6): δ 158.5, 136.0, 127.3, 113.6, 73.2, 55.2, 49.4. The enantiomeric ratio was determined by HPLC (AD3, 4.6 mm × 150 mm, particle size: 3 μm, temperature: 35 °C, *n*-hexane with 0.1% isopropylamine/isopropyl alcohol: 0 min-20% to 10 min-55%, flow rate 1.2 mL/min, 218 nm), t_R = 6.3 min (major).

Synthesis of (R)-4-(2-(Benzyl(methyl)amino)-1-hydroxyethyl)-benzene-1,2-diol, ***2l****.*[12] A 3-neck RBF was charged with compound **1l** (5.0 g, 16.26 mmol), catalyst (14.5 mg, 0.13 mol %), and MeOH (100 mL, 10 V). This solution was charged with formic acid and TEA (5:2) (10.5 mL). The reaction mixture was stirred at reflux for 20 h. The reaction mixture was cooled to RT and treated with 15 mL of NH_4OH. The slurry was stirred for 15 min, treated with water (150 mL), and stirred for another 30 min. The slurry was filtered, washed with water (20 V), and dried under vacuum. The product **2l** was obtained as an off-white solid (3.74 g, 85% yield); *er* ratio: 93.2:6.8; $[\alpha]_D^{25}$ = −43.7° (MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30−7.20 (m, 5H), 6.72 (s, 1H), 6.64 (d, J = 8.0 Hz, 1H), 6.54 (d, J = 7.6 Hz, 1H), 4.55 (dd, J = 7.6, 4.6 Hz, 1H), 2.52−2.47 (m, 1 H), 2.37 (dd, J = 12.5, 4.4 Hz, 1H), 2.17 (s, 3 H); ^{13}C {H} NMR (100 MHz, DMSO-d_6) δ 144.9, 144.2, 139.1, 135.6, 128.8, 128.1, 126.8, 117.0, 115.1, 113.7, 70.1, 65.4, 61.9, 42.4, 39.5. The enantiomeric ratio was determined by SFC (AD3, 4.6 mm × 150 mm, particle size: 3 μm, temperature: 30 °C, CO_2/Isopropyl alcohol with 0.1% diethylamine = 70/30, flow rate 1.5 mL/min, 230 nm), t_R = 4.4 min (major), 4.0 min (minor).

Synthesis of (R)-3-(2-(Benzyl(methyl)amino)-1-hydroxyethyl)-phenol, ***2m****.*[32] A 3-neck RBF was charged with 2-(benzyl(methyl)-amino)-1-(3-hydroxyphenyl)ethan-1-one hydrochloride salt (1.0 g, 3.4 mmol), MeOH (10 mL), Ru catalyst (2.7 mg, 0.13 mol %), and HCO_2H/TEA (5:2, 1 mL), and heated to 60 °C (oil bath) for 18 h. The crude mixture was analyzed by HPLC, which showed 100A% conversion of the starting material. The mixture was cooled, filtered through charcoal/celite, and the bed was washed with methanol. This crude mixture was charged with aq NH_3 (2.0 mL) and water (5 mL). The solvent was removed under reduced pressure, passed through a silica bed, and evaporated to dryness to obtain **2m** as an off-white solid (0.62 g, 71% yield); *er* ratio >99.9:0.1. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.26 (s, 1H), 7.29−7.23 (m, 5H), 7.09 (dd, J = 6.7, 3.8 Hz, 1H), 6.76 (s, 1H), 6.73 (s, 1H), 6.63−6.62 (m, 1H), 4.94 (s, 1H), 4.65 (s, 1H), 3.56 (s, 2H), 2.51 (s, 1H), 2.44−2.42 (m, 1H), 2.21 (d, J = 2.5 Hz, 3H); ^{13}C {H} NMR (151 MHz, DMSO-d_6) δ 157.5, 146.7, 139.5, 129.2, 129.2, 128.5, 127.2, 117.2, 114.1, 113.4, 70.7. 65.7, 62.3, 42.8. The enantiomeric ratio was determined by SFC (IK, 4.6 mm × 150 mm, particle size: 3 μm, temperature: 30 °C, CO_2/methanol with 0.1% of DEA, flow rate 2.5 mL/min, 260 nm), t_R = 8.9 min (major).

Synthesis of 1-(4-Hydroxyphenyl)-2-morpholinoethan-1-one Hydrogen Chloride, ***1n****.*[38] To a mixture of 2-bromo-1-(4-hydroxyphenyl)ethan-1-one (4.0 g, 18.6 mmol) in acetonitrile was added morpholine (3 equiv) at room temperature. The mixture was allowed to stir at room temperature for 1 h. The formation of a white precipitate was observed during the course of the reaction. The precipitate was filtered, and the cake was washed with water followed by acetonitrile and dried under air followed by vacuum to obtain the product as a white solid (3.8 g, 92% yield). To a suspension of 1-(4-hydroxyphenyl)-2-morpholinoethan-1-one (3.7 g, 16.7 mmol) in MeOH (5 V) at room temperature was added a solution of 3 M HCl in MeOH (11.15 mL, 33 mmol). The resulting suspension was stirred at room temperature for 3 h and filtered, and the cake was washed with MeOH and dried to obtain **1n** (3.9 g, 91% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 10.74 (br s, 1H), 7.87 (d, J = 8 Hz, 2H), 6.98 (d, J = 12 Hz, 2H), 5.02 (s, 2H), 3.95−3.92 (br m, 4H), 3.45−3.25 (m overlapping with the water peak, 7 H). ^{13}C {H} NMR (100 MHz, DMSO-d_6) δ 189.6, 164.2, 132.3, 125.6, 116.2, 63.4, 60.5, 52.6.

Synthesis of (R)-4-(1-Hydroxy-2-morpholinoethyl)phenol, ***2n****.*[38,39] To a mixture of hydrochloride salt **1n** (500 mg, 1.94 mmol, 1 equiv) and Ru catalyst **3l** (1.8 mg, 2.9 μmol, 0.15 mol %) in MeOH (10 V) was added formic acid/triethylamine complex (5:2) (2 V). The reaction mixture was stirred at 60 °C (oil bath) for 14 h while a slow stream of N_2 was bubbled through the reaction mixture. HPLC after 14 h indicated the complete consumption of the starting material. Then, the reaction mixture was cooled to room temperature and MeOH was evaporated. The crude mixture was then treated with aq NH_4OH and stirred. The resulting suspension was filtered, and product **2n** was obtained as a light brown solid (220 mg, 51% yield) and the presence of additional material (not quantified) was observed in the mother liquor; *er* ratio: 99.6:0.4; $[\alpha]_D^{25}$ = −48.1° (MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (s, 1H), 7.06 (d, J = 8 Hz, 2H), 6.63 (d, J = 8 Hz, 2H), 4.78 (s, H), 4.55−4.53 (m, 1H), 3.51−3.49 (m, 4H), 2.44−2.26 (overlapping m, 6H); ^{13}C {H} NMR (100 MHz, DMSO-d_6) δ 156.7, 135.2, 127.6, 115.1, 69.6, 67.2, 66.6, 54.1; HRMS (ESI) $[M + H]^+$ *m*/*z* calcd for $[C_{12}H_{18}NO_3]^+$ 224.1287, found 224.1308. The enantiomeric ratio was determined by HPLC (AD3, 4.6 mm × 150 mm, particle size: 3 μm, temperature: 35 °C, *n*-heptane with 0.1% diethylamine/isopropyl alcohol with 0.1% of diethylamine = 30/70, v/v, flow rate 1.0 mL/min, 230 nm), t_R = 2.9 min (major), 3.2 min (minor).

Synthesis of 2-(Benzyl(methyl)amino)-1-(3-chlorophenyl) ethan-1-one Hydrochloride, ***1o****.*[32] A single-neck RBF equipped with a magnetic stir bar was charged with *N*,*N*-dimethylacetamide (11 mL, 10 V) and 2-chloro-1-(3-chlorophenyl)ethan-1-one (a) (1.1 g, 5.82 mmol) at 10 °C. *N*-Benzylmethylamine (0.79 mL, 6.11 mmol, 1.05 equiv) was charged dropwise over 5 min, resulting in a clear brown color solution, followed by the dropwise addition of triethylamine (0.85 mL, 6.11 mmol, 1.05 equiv), resulting in the thickening of the reaction mixture. Cooling was removed, and the reaction mixture was heated to 35 °C (oil bath) using a water bath. The reaction mixture was stirred at this temperature for 2.5 h until complete conversion of the starting material was confirmed by TLC. Afterward, the reaction mixture was diluted with 30 mL of water and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were then washed with water, dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography using a 5−40% ethyl acetate/hexane solvent system to give 2-(benzyl(methyl)amino)-1-(3-chlorocyclohexa-1,5-dien-1-yl)ethan-1-one (1.1 g, 4.02 mmol, 69% yield) as a yellow oil. A single-neck RBF equipped with a magnetic stir bar was charged with methanol (10 mL, 10 V) and 2-(benzyl(methyl)amino)-1-(3-chlorocyclohexa-1,5-dien-1-yl)ethan-1-one (1.0 g, 3.65 mmol) at room temperature. 3 M HCl in MeOH (4.9 mL, 14.61 mmol, 4.0 equiv) was charged in one portion, and the reaction mixture was stirred at room temperature for 1 h. TLC confirmed a complete consumption of the starting material. Afterward, the reaction mixture was evaporated to dryness to get a yellow oil. Heptane (10 mL, 10 V) was charged to the flask and evaporated again to get a yellow solid. Finally, the yellow solid was recrystallized with the ethyl acetate/heptane solvent system to get **1o** as an off-white solid (1.11 g, 98% yield). ^{1}H NMR (600 MHz, CD_3OD) δ 8.03 (s, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.66−7.56 (m, 3H), 7.51 (s, 3H), 5.10 (d, J = 17.7 Hz, 1H), 4.97 (d, J = 17.8 Hz, 1H), 4.57 (d, J = 12.8 Hz, 1H), 4.29 (d, J = 12.8 Hz, 1H), 2.96 (s, 3H); ^{13}C {H} NMR (150 MHz, CD_3OD) δ 191.4, 136.6, 136.4, 135.9, 132.4, 131.9, 131.5, 130.6, 130.5, 129.2, 127.8, 61.9, 41.9 (one carbon merging).

Synthesis of (R)-2-(Benzyl(methyl)amino)-1-(3-chlorophenyl)-ethan-1-ol, ***2o****.* A 50 mL 3-neck round-bottom flask equipped with a magnetic stir bar, nitrogen line, and a reflux condenser was charged with MeOH (5 mL, 10 V) and 3-chloro *N*-benzylmethyl adrenalone hydrochloride **1o** (0.5 g, 1.61 mmol). The reaction mixture was purged with N_2 for 10 min before charging with **3l** (1.3 mg, 0.002 mmol, 0.0013 equiv), followed by charging with formic acid/triethylamine (5:2) complex (0.65 mL, 1.3 V). The reaction mixture was refluxed at 65−70 °C (oil bath) for 9 h, in which 99% conversion was observed. The reaction mixture was stirred for another hour and then cooled to room temperature. Charged water (2.5 mL, 5 V) and ammonium hydroxide

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(1 mL, 2 V) to see oiling out of the reaction mixture. The reaction mixture was concentrated to dryness, diluted with water, and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography using 25−30% ethyl acetate/hexane solvent to give (*R*)-2-(benzyl(methyl)amino)-1-(3-chlorophenyl)ethan-1-ol **2o** as a colorless oil (0.28 g, 63% yield), *er* ratio 98.0:2.0. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30−7.25 (m, 3H), 7.25−7.19 (m, 3H), 7.19−7.12 (m, 3H), 4.63 (dd, J = 9.1, 5.0 Hz, 1H), 3.66 (d, J = 13.1 Hz, 1H), 3.46 (d, J = 13.1 Hz, 1H), 2.54−2.39 (m, 2H), 2.24 (s, 3H); ^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 144.5, 138.1, 134.4, 129.7, 129.2, 128.6, 127.7, 127.6, 126.2, 124.1, 68.9, 65.4, 62.5, 41.9; HRMS (ESI) $[M + H]^+$ m/z calcd for $[C_{16}H_{19}ClNO]^+$ 276.1150, found 276.1138; the enantiomeric ratio was determined by SFC (IA, 4.6 mm × 150 mm, particle size: 3 μm, temperature: 30 °C, CO_2/methanol = gradient: 5% of methanol, flow rate 2.0 mL/min, 210 nm), t_R = 5.2 min (major), 6.7 min (minor).

Synthesis of 2-(Benzyl(methyl)amino)-1-(thiophen-2-yl)ethan-1-one Hydrogen Chloride, ***1p****.*[32] To 1.0 g of bromo compound dissolved in anhydrous toluene (10 mL) was added *N*-methylbenzylamine dropwise (2.0 equiv) at 0 °C. The reaction mixture was brought to ambient temperature and stirred at the same temperature for 2 h. The solids were filtered, and the filtrate was concentrated under vacuum to afford 1.2 g of 2-(benzyl(methyl)amino)-1-(thiophen-2-yl)ethan-1-one crude thick brown liquid. 1.0 g of crude 2-(benzyl(methyl)amino)-1-(thiophen-2-yl)ethan-1-one was dissolved in 10.0 mL of MTBE, and 5.0N HCl in IPA (1.5 equiv) was added dropwise. The solid material was observed, and the reaction mixture was allowed to stir at ambient temperature for 1 h. The solid material was filtered, washed with MTBE, and dried under vacuum to afford crude **1p** (1.0 g, 73% yield), which was carried to the next step with no further purification. ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (dd, J = 4.9, 1.0 Hz, 1H), 8.00 (dd, J = 3.9, 1.0 Hz, 1H), 7.62−7.58 (m, 2H), 7.51−7.44 (m, 4H), 7.28 (dd, J = 4.9, 3.9 Hz, 1H), 5.02 (d, J = 17.4 Hz, 1H), 4.88 (d, J = 17.2 Hz, 1H), 4.57 (d, J = 12.8 Hz, 1H), 4.33 (d, J = 12.8 Hz, 1H), 2.96 (s, 3H).

Synthesis of (S)-2-(Benzyl(methyl)amino)-1-(thiophen-2-yl)-ethan-1-ol, ***2p****.*[32] A 10.0 mL sealed tube was charged with compound **1p** (250 mg, 1.0 mmol), MeOH (2.5 mL, 10 V), catalyst **3l** (0.15 mol %), and formic acid/TEA (5:2) (1 V) with nitrogen bubbling. The reaction mixture was stirred at 62 °C (oil bath) under nitrogen bubbling. After 3 h, the reaction mixture was monitored for conversion by LC-MS/HPLC. Both showed completion of SM. After 3 h, the reaction mixture was cooled to room temperature and neutralized with aq NH_4OH (1 V). The volatiles were removed under vacuum and diluted with DCM (20 mL). The organic layer was washed with water (2 × 5 mL), dried over Na_2SO_4, and reduced under vacuum to afford crude, which was purified using 10% DCM in MeOH as an eluent to afford **2p** as a brown viscous oil (150 mg, 89% yield), *er* ratio 98.8:1.2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.23−7.40 (m, 6H), 6.94−7.06 (m, 2H), 5.11 (m, 1H), 4.94 (br s, 1H), 3.65 (q, 2H, J = 18.32 Hz), 2.66−2.86 (m, 2H), 2.34 (s, 3H); ^{13}C {H} NMR (100 MHz, DMSO-d_6): δ 138.9, 130.0, 120.9, 119.7, 118.7, 117.9, 115.8, 115.3, 58.9, 56.6, 54.0, 33.4. The enantiomeric ratio was determined by SFC (IC-3, 4.6 mm × 150 mm, particle size: 3 μm, temperature: 35 °C, CO_2/methanol with 0.1% diethylamine = 88/12, flow rate 1.0 mL/min, 230 nm), t_R = 7.5 min (major), 7.9 min (minor).

Synthesis of 1-(3-Methoxyphenyl)-2-(4-(m-tolyl)piperazin-1-yl)-ethan-1-one Hydrochloride, ***1q****.* To a stirred solution of 1-(*m*-tolyl) piperazine (750 mg, 4.26 mmol, 1.0 equiv) in acetonitrile (18 mL, 24 V) was added K_2CO_3 (706 mg, 5.11 mmol, 1.2 equiv) under a N_2 atmosphere at 0 °C. The mixture was stirred for 5 min at 0 °C before the addition of 2-bromo-1-(3-methoxyphenyl) ethan-1-one (975 mg, 4.26 mmol, 1.0 equiv). After complete consumption of the starting materials, the reaction mixture was quenched by the addition of H_2O (4.5 mL, 6 V) and diluted with DCM (4.5 mL, 6 V). The aqueous layer was extracted with DCM (2 × 4.5 mL, 12 V), and the collected organic layers were washed with brine (4.5 mL, 6 V), dried over Na_2SO_4, filtered, and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography to afford the product as a colorless oil (1.22 g, 88.4% yield). A solution of 1-(3-methoxyphenyl)-2-(4-(*m*-tolyl)piperazin-1-yl)ethan-1-one (158 mg, 0.49 mmol, 1.0 equiv) in MeOH (5.6 mL, 36 V) was treated with the dropwise addition of 12 M HCl (0.10 mL, 1.22 mmol, 2.5 equiv) in H_2O (0.47 mL, 3 V) over a period of 5 min at 22 °C. The resulting mixture was stirred for 1 h at 22 °C. Upon completion, the reaction mixture was filtered through a charcoal bed and Solka-Floc. The collected filtrate was distilled to remove MeOH, charged with IPA (0.96 mL, 6 V), and the distillation was continued. The product suspension in IPA was filtered and washed with IPA (0.16 mL, 1 V). The solid was suction-filtered and dried in a vacuum oven at 35 °C for 18 h to afford product **1q** as a red solid (150 mg, 89.3% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.67 (dt, J = 7.6, 1.2 Hz, 1H), 7.60 (dd, J = 2.6, 1.5 Hz, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.33 (dd, J = 8.0, 2.6 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 7.11 (t, J = 1.9 Hz, 1H), 7.06 (dd, J = 8.1, 2.4 Hz, 1H), 6.95 (d, J = 7.5 Hz, 1H), 5.16 (s, 2H), 3.91 (s, 3H), 3.82−3.59 (m, 8H), 2.38 (s, 3H); ^{13}C{H} NMR (101 MHz, CD_3OD) δ 190.3, 160.3, 147.7, 139.5, 134.8, 130.0, 129.2, 124.0, 120.8, 120.5, 118.3, 114.7, 112.4, 60.9, 54.7, 52.2, 47.5, 20.3.

Synthesis of (R)-1-(3-Methoxyphenyl)-2-(4-(m-tolyl)piperazin-1-yl)ethan-1-ol, ***2q****.* To a stirred solution of 1-(3-methoxyphenyl)-2-(4-(*m*-tolyl) piperazin-1-yl) ethan-1-one hydrochloride (**1q**) (80 mg, 0.2318 mmol, 1.0 equiv) in MeOH (0.8 mL, 10 V) were added **3l** (0.22 mg, 0.3477 μmol, 0.15 mol %) and a 5:2 mixture of formic acid and triethylamine (0.08 mL, 1 V) under a N_2 atmosphere at 22 °C. The reaction mixture was heated to 62 °C and agitated for 6 h at the same temperature. After 6 h of stirring at 62 °C (oil bath) (reaction progress was monitored by HPLC), the reaction mixture was cooled to 22 °C and neutralized by the addition of aq NH_4OH (0.08 mL, 1 V). The resulting slurry was filtered, and the wet cake was successively washed with HPLC grade H_2O (0.48 mL, 6 V), MeOH (0.40 mL, 5 V), and *n*-heptane (0.16 mL, 2 V). The cream-colored wet cake was first dried via vacuum suction and then in a vacuum oven at 35 °C for 48 h to afford **2q** as a white solid (65.0 mg, 86.0% yield), *er* ratio 99.6:0.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, J = 7.9 Hz, 1H), 7.11−7.04 (m, 1H), 6.92−6.84 (m, 2H), 6.74 (ddd, J = 8.2, 2.6, 1.0 Hz, 1H), 6.70−6.59 (m, 3H), 4.68 (dd, J = 9.8, 4.1 Hz, 1H), 3.73 (s, 3H), 3.13 (pt, J = 7.4, 3.3 Hz, 4H), 2.81 (ddd, J = 10.7, 6.4, 3.4 Hz, 2H), 2.56−2.45 (m, 4H), 2.24 (s, 3H); ^{13}C{H} NMR (101 MHz, $CDCl_3$) δ 159.8, 151.3, 143.9, 138.9, 129.4, 129.0, 120.9, 118.2, 117.1, 113.4, 113.2, 111.3, 68.8, 66.2, 55.3, 53.1, 49.4, 21.8; HRMS (ESI) $[M + H]^+$ m/z calcd for $[C_{20}H_{27}N_2O_2]^+$ 327.2067, found 327.2058. The enantiomeric ratio was determined by SFC (AD3, 4.6 mm × 150 mm, particle size: 3 μm, temperature: 30 °C, CO_2/isopropyl alcohol with 0.1% of diethylamine = 0 min—20%, 8 min—50%,15 min—50%, flow rate 0.5 mL/min, 210 nm), t_R = 11.1 min (major), 13.3 min (minor).

Synthesis of 1-(3,4-Dihydroxyphenyl)-2-(4-(m-tolyl)piperazin-1-yl)ethan-1-one Hydrochloride, ***1r****.*[39d] A stirred solution of 2-chloro-1-(3,4-dihydroxyphenyl)ethan-1-one (0.514 g, 2.68 mmol) in acetonitrile (3 mL, 6 V) was treated with 1-(3-Methylphenyl)piperazine (0.582 g, 2.68 mmol) and TEA (0.747 mL, 5.36 mmol). The reaction mixture was stirred under N_2 for 16 h at 45 °C (oil bath). LCMS was used to track reaction progress. The reaction mixture was cooled to rt, filtered, rinsed with MeCN (5 V), and suction-filtered. The solid collected was triethylamine hydrochloride salt. The filtrate was concentrated and purified by flash column chromatography (0−10% MeOH in CH_2Cl_2). The collected fractions were dissolved in 3 mL of MeOH and treated with 12 M HCl (0.5 mL). Upon stirring for 1 h, the precipitate was filtered and rinsed with MeOH. The product **1r** was collected as a cream-colored solid (725 mg, 75% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 7.42 (d, J = 2.1 Hz, 1H), 7.38 (dd, J = 8.3, 2.1 Hz, 1H), 7.15 (app t, J = 7.76 Hz, 1H), 6.96 (d, J = 8.2 Hz, 1H), 6.85−6.81 (m, 2H), 6.70 (d, J = 7.4 Hz, 1H), 5.02 (s, 2H), 3.82−3.78 (m, 2H), 3.62−3.59 (m, 2H), 3.31−3.21 (m, 4H), 2.27 (s, 3H); ^{13}C {H} NMR (100 MHz, DMSO-d_6) δ 189.3, 152.5, 149.5, 145.7, 138.3, 129.0, 125.5, 121.8, 120.8, 116.6, 115.5, 114.9, 113.1, 59.7, 51.8, 45.1, 21.4.

Synthesis of (R)-4-(1-Hydroxy-2-(4-(m-tolyl)piperazin-1-yl)ethyl)-benzene-1,2-diol, ***2r****.* A solution of **1r** (0.203 g, 0.560 mmol) in MeOH (2.0 mL, 10 V) was treated with Ru cat (1.05 mg, 0.30 mol %) in formic acid/TEA (5:2) (0.2 mL, 1 V). The reaction mixture was stirred at 62 °C (oil bath) under N_2 sparging for 4 h, and more formic acid/TEA (5:2) (0.2 mL, 1 V) was added. After an additional 4 h of stirring, HPLC

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indicated >98% conversion and the reaction mixture was cooled to rt and treated with NH_4OH (0.3 mL, 1.5 V). The solution was treated with brine (5 mL) and EtOAc (5 mL). The biphasic layers were stirred for 5 min, transferred to a separatory funnel, and separated. The aqueous layer was extracted with EtOAc (2 × 8 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (on SiO_2, 0−10% MeOH in CH_2Cl_2), and the amino alcohol **2r** was collected as a white solid (154 mg, 82% yield), *er* ratio 99.3:0.7. ^{1}H NMR (400 MHz; CD_3OD): δ 8.44 (s, 1 H), 7.15 (app t, J = 7.8 Hz, 1 H), 6.89−6.74 (m, 6 H), 4.93 (dd, J = 7.7, 3.3 Hz, 1 H), 3.45−3.23 (m, 8 H), 3.14 (dd, J = 13.0, 10.4 Hz, 1 H), 3.04 (dd, J = 13.0, 3.3 Hz, 1 H), 2.31 (s, 3 H). ^{13}C{H} NMR (101 MHz; CD_3OD): δ 151.7, 146.6, 146.5, 140.1, 134.2, 130.1, 122.9, 118.7, 118.6, 116.3, 115.0, 114.3, 69.2, 64.9, 53.7, 21.7; HRMS (ESI) $[M + H]^+$ m/z calcd for $[C_{19}H_{25}N_2O_3]^+$ 329.1860, found 329.1870. The enantiomeric ratio was determined by SFC (AD3, 4.6 mm × 150 mm, particle size: 3 μm, temperature: 50 °C, CO_2/ethanol with 0.05% of DEA = 68/32, flow rate 1.2 mL/min, 210 nm), t_R = 7.8 min (major), 7.0 min (minor).

*Synthesis of 1-(3,4-Dihydroxyphenyl)-2-(4-(2-methoxyphenyl)-piperazin-1-yl)ethan-1-one Hydrochloride, **1s**.*[39d] To a solution of 2-chloro-1-(3,4-dihydroxyphenyl)ethan-1-one (2 g, 10.7 mmol, 1.0 equiv) in MeCN (10 mL, 5 V) and DMF (4 mL, 2 V) was added a solution of 1-(2-methoxyphenyl)piperazine (6.2 g, 31.2 mmol, 3.0 equiv) in MeCN (10 mL, 5 V) at rt. The reaction mixture was heated to 60 °C (oil bath) and stirred under nitrogen for 3 h. Then, the reaction mixture was cooled to rt and filtered to remove insoluble salts. The filter cake was rinsed with MeCN (10 mL × 2). Then, combined organic solutions were concentrated under reduced pressure to afford the crude product. The crude product was purified by flash column chromatography (EtOAc/hexanes = 20:80 to 80:20) to afford 1-(3,4-dihydroxyphenyl)-2-(4-(2-methoxyphenyl)piperazin-1-yl)ethan-1-one as a brown solid (3.17 g, 86% yield). To a slurry of 1-(3,4-dihydroxyphenyl)-2-(4-(2-methoxyphenyl)piperazin-1-yl)ethan-1-one (1.03 g, 3 mmol, 1.0 equiv) in MeOH (5 mL, 5 V) was added conc HCl (0.55 mL, 6.6 mmol, 2.2 equiv) at rt. The slurry was dissolved immediately after HCl addition, and then the precipitate was formed after stirring at rt for about 20 s. The slurry was stirred for an additional 1 h and then filtered. The filter cake was washed with MeOH (2.0 mL, 2 V) and dried overnight under vacuum at 40 °C to afford hydrochloride salt **1s** as an off-white solid (1.06 g, 85% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.65 (br s, 1H), 7.43 (d, J = 2.1 Hz, 1H), 7.38 (dd, J = 8.3, 2.1 Hz, 1H), 7.08−6.97 (m, 4H), 6.92 (td, J = 7.2, 1.4 Hz, 1H), 6.36 (br s, 3H), 5.04 (s, 2H), 3.79 (s, 3H), 3.34 (br s, 2H), 3.63−3.50 (m, 4H), 3.40−3.26 (m, 4H). ^{13}C {H} NMR (101 MHz, DMSO-d_6) δ 189.3, 152.5, 152.0, 145.8, 138.6, 125.6, 124.3, 121.9, 121.0, 118.8, 115.6, 115.0, 112.3, 59.8, 55.6, 52.1, 48.7, 46.9.

*Synthesis of (R)-4-(1-Hydroxy-2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)benzene-1,2-diol, **2s**.* To a mixture of hydrochloride salt **1s** (208 mg, 0.5 mmol, 1 equiv) and **3l** (0.62 mg, 1.0 μmol, 0.2 mol %) in MeOH (1.1 mL, 5 V) was added formic acid/triethylamine complex (5:2) (0.2 mL, 1 V). The reaction mixture was stirred at 60 °C (oil bath) for 4 h. Then, the reaction mixture was treated with formic acid/TEA (5:2) (0.06 mL, 0.3 V) again and stirred at 60 °C for 4 h. The reaction mixture was cooled to rt, basified with 28% aq NH_4OH (0.2 mL, 1 V), and concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (2 mL, 10 V) and washed with water (2 mL, 10 V). The reaction mixture was concentrated under reduced pressure and purified by column chromatography (CH_2Cl_2/MeOH = 98:2 to 94:6) to afford **2s** (101 mg, 58% yield) as an off-white solid, *er* ratio 99.6:0.4. ^{1}H NMR (400 MHz, CD_3OD) δ 7.03−6.88 (m, 4H), 6.84 (d, J = 1.9 Hz, 1H), 6.74 (d, J = 8.2 Hz, 1H), 6.70 (dd, J = 8.2, 2.0 Hz, 1H), 4.89 (br s, 3H), 4.72 (dd, J = 9.3, 3.6 Hz, 1H), 3.84 (s, 3H), 3.07 (br s, 4H), 2.80−2.79 (m, 2H), 2.72 (br s, 2H), 2.68 (partially obscured dd, J = 13.0, 9.2 Hz, 1H), 2.51 (dd, J = 12.8, 3.5 Hz, 1H). ^{13}C{H} NMR (101 MHz, CD_3OD): δ 153.9, 146.3, 145.8, 142.3, 136.2, 124.6, 122.2, 119.4, 118.7, 116.1, 114.4, 112.8, 71.5, 67.5, 55.9, 54.6, 51.7; HRMS (ESI) $[M + H]^+$ m/z calcd for $[C_{19}H_{25}N_2O_4]^+$ 345.1809, found 345.1847. The enantiomeric ratio was determined by HPLC (AD3, 4.6 mm × 150 mm, particle size: 3 μm, temperature: 35 °C, *n*-heptane with 0.1% diethylamine/isopropyl alcohol with 0.1% diethylamine = 70/30, flow rate 1.0 mL/min, 230 nm), t_R = 4.7 min (major), 4.3 min (minor).

*Synthesis of (R)-Acgeline, **5**.*[36b] A 40 mL reaction vial equipped with a stirrer bar and N_2 line was charged with compound **1k** (0.5 g, 2.479 mmol), MeOH (5 mL), **3l** (2.31 mg, 0.15 mol %), and formic acid/TEA (5:2) (0.5 mL, 1 V). The reaction mixture was stirred at 62 °C. After 16 h, the reaction mixture was cooled to room temperature and neutralized with aq. NH_4OH (1 V), and the solvent was removed under reduced pressure and extracted with isopropyl acetate (2 × 10 mL). The crude **2k** was carried forward to the next step to couple with cinnamoyl chloride. To a solution of **2k** (0.2 g, 1.196 mmol) in dry CH_2Cl_2 (4 mL), a solution of NaOH (0.143 g, 3.59 mmol) in water (3.3 mL) was added at 0−5 °C. The mixture was stirred for 10 min. A solution of cinnamoyl chloride (239 mg, 1.43 mmol) in anhydrous toluene (1.0 mL) was added dropwise to the reaction mixture while vigorously stirring. After the addition was complete, the reaction mixture was stirred for a further 5 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was separated and washed with brine. The solvent was evaporated, and then the resulting solid was recrystallized from ethanol/water (v/v = 80:20) to afford the natural product (*R*)-(−)-acgeline, **5** (450 mg, 61% yield); $[\alpha]_D^{25} = -65.0°$ ($CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (t, J = 5.8 Hz, 1H), 7.54 (d, J = 6.5 Hz, 2H), 7.45−7.33 (m, 4H) 7.27 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.72 (d, J = 15.8 Hz, 1H), 5.44 (d, J = 3.0 Hz, 1H), 4.61 (m, 1H), 3.73 (s, 3H), 3.47−3.36 (m, 1H), 3.28−3.17 (m, 1H); ^{13}C{H} NMR (101 MHz, DMSO-d_6) δ 165.1, 158.3, 138.5, 135.7, 134.9, 129.4, 128.9, 127.5, 127.1, 122.4, 113.4, 70.9, 55.0, 47.0.

*Synthesis of (R)-Tembamide, **6**.*[36b] To a stirred solution of 2-amino-1-(4-methoxyphenyl)ethan-1-one hydrochloride **1k** (1.0 g, 4.97 mmol, 1.0 equiv) in MeOH (8.0 V, 8 mL), Ru cat (0.15 mol %, 4.83 mg) followed by formic acid/TEA (5:2) (1.0 V, 1.0 mL) were added. The reaction mixture was stirred at 60 °C (oil bath) under N_2 sparging for 8 h. After cooling to rt, the reaction mixture was treated with NH_4OH (2.0 mL, 2 V) and stirred at RT for 30 min. Next, most of the MeOH was evaporated under vacuum in a rotavapor, and the reaction mass was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with H_2O (1 × 5 mL) and brine (1 × 5 mL) and evaporated to dryness to get the desired amino alcohol **2k** (870 mg) as a brown semisolid. To the crude compound **2k**, toluene (20 mL) and aq NaOH (10%, 4 mL, 4.0 equiv) were added and cooled to 0 °C with an ice bath. Benzoyl chloride (0.635 mL, 5.467 mmol, 1.1 equiv) in toluene (2 mL) was added dropwise at 0 °C and the reaction mass was stirred for 2 h at 0−10 °C. Reaction progress was monitored by TLC, and after confirming complete consumption of amino alcohol, the reaction mass was diluted with EtOAc (15 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (5 mL). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL) and then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford **6** as an off-white solid (0.9 g, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.67 (d, J = 7.3 Hz, 2H), 7.41 (d, J = 7.3 Hz, 1H), 7.28−7.38 (m, 2H), 7.19−7.28 (m, J = 8. Five Hz, 2H), 6.72−6.90 (m, J = 8.6 Hz, 2H), 6.61 (br s, 1H), 4.81 (dd, J = 7.9, 3.3 Hz, 1H), 3.78 (ddd, J = 10.5, 7.0, 3.4 Hz, 1H), 3.73 (s, 3H), 3.36−3.48 (m, 1H), 3.27 (br s, 1H); ^{13}C{H} NMR (101 MHz, $CDCl_3$) δ 168.6, 159.3, 134.1, 133.9, 131.7, 128.6, 127.1, 127.0, 114.0, 73.3, 55.3, 47.8

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c00045.

Experimental procedures, NMR spectra, and chromatograms (PDF)

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Notes

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