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CATALYTIC ASYMMETRIC SYNTHESIS OF (–)-RITODRINE HYDROCHLORIDE *VIA* SILYL ENOL ETHER AMINATION USING DIRHODIUM(II) TETRAKIS [TETRAFLUOROPHTHALOYL-(*S*)-*TERT*-LEUCINATE]

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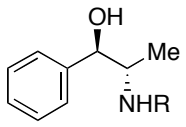
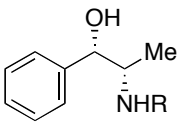
Abstract – A catalytic asymmetric synthesis of (–)-ritodrine hydrochloride was achieved, incorporating an enantioselective amination of (*Z*)-silyl enol ether derived from 4-benzyloxypropiophenone with [(2-nitrophenylsulfonyl)imino]-phenyliodinane (NsN=IPh) and a chelation-controlled reduction of the ketone carbonyl group with $Zn(BH_4)_2$ as the key steps. The use of dirhodium(II) tetrakis[tetrafluorophthaloyl-(*S*)-*tert*-leucinate] as a catalyst produced the targeted α-amino ketone in 94% yield with 91% ee.

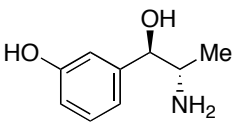
2-Amino-1-aryl-1-propanols (**1**) are important and versatile intermediates in the synthesis of a wide variety of natural products and pharmaceuticals, such as ephedrine (**1a**),[1] norephedrine (**1b**),[2] pseudoephedrine (**1c**),[3] norpseudoephedrine (**1d**),[4] the α_1-adrenergic receptor agonist metaraminol (**1e**),[5] and the antianginal agent oxyfedrine (**1f**).[6] Further interest stems from their use as chiral auxiliaries and ligands.[7] Because of their importance, several strategies have been developed to achieve the catalytic asymmetric synthesis of **1**, including asymmetric nitroaldol (Henry) reaction,[8,9] dynamic kinetic resolution of racemic α-amino ketones,[10] and asymmetric reduction of α-oxoketoxime ethers.[11]



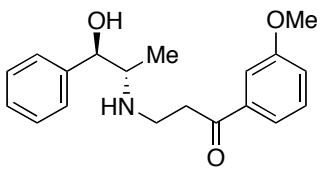
R = Me: ephedrine (**1a**)
R = H: norephedrine (**1b**)



R = Me: pseudoephedrine (**1c**)
R = H: norpseudoephedrine (**1d**)



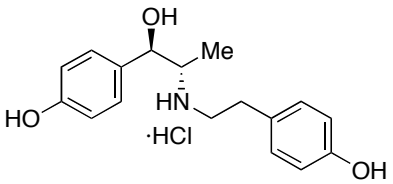
metaraminol (**1e**)



oxyfedrine (**1f**)

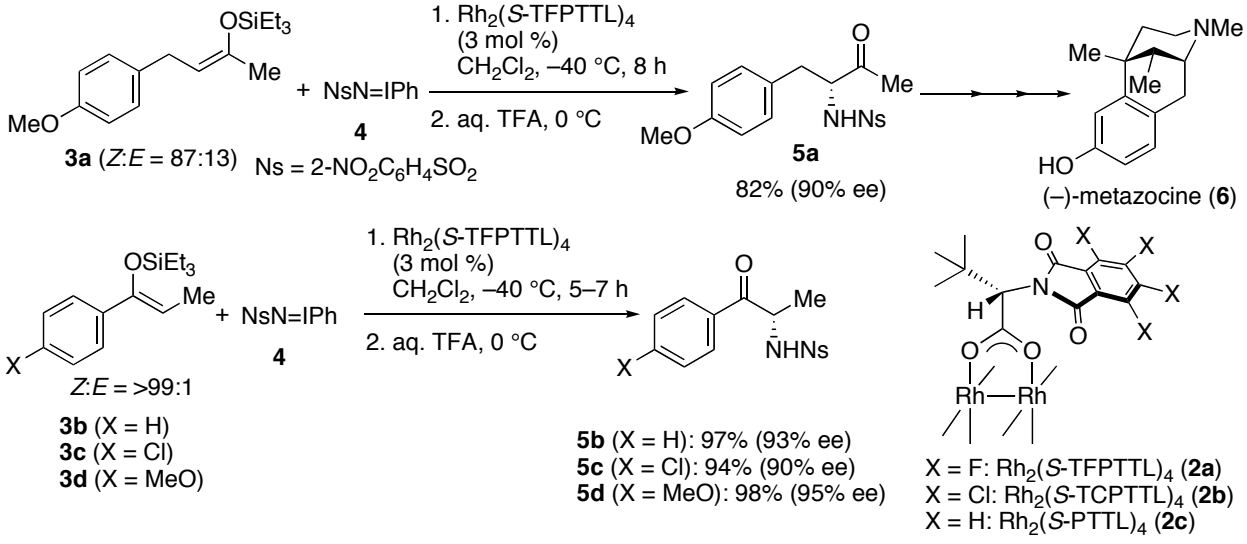
† Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

Ritodrine, (±)-(1*R**,2*S**)-1-(4-hydroxyphenyl)-2-[*N*-[2-(4-hydroxyphenyl)ethyl]amino]-1-propanol, is a selective β_2-adrenergic receptor agonist, and its hydrochloride is currently one of the most commonly used drugs for the treatment of preterm labor.[12] Ritodrine binds to β_2-receptors located on the outer surface of the myometrium, triggering the conversion of adenosine 5'-triphosphate (ATP) to cyclic adenosine 3',5'-monophosphate (cAMP), which leads to relaxation of myometrial tissues. Although ritodrine is used as a racemate, it has been disclosed that the (1*R*,2*S*)-(–)-enantiomer (**1g**) is primarily responsible for the pharmacological effects.[13] Very recently, Shibasaki and co-workers described the first highly efficient, catalytic asymmetric synthesis of (–)-ritodrine (**1g**) hydrochloride by developing an *anti*- and enantio-selective nitroaldol reaction catalyzed by a heterobimetallic Pd/La/Schiff base complex.[14]



(–)-ritodrine (**1g**) hydrochloride

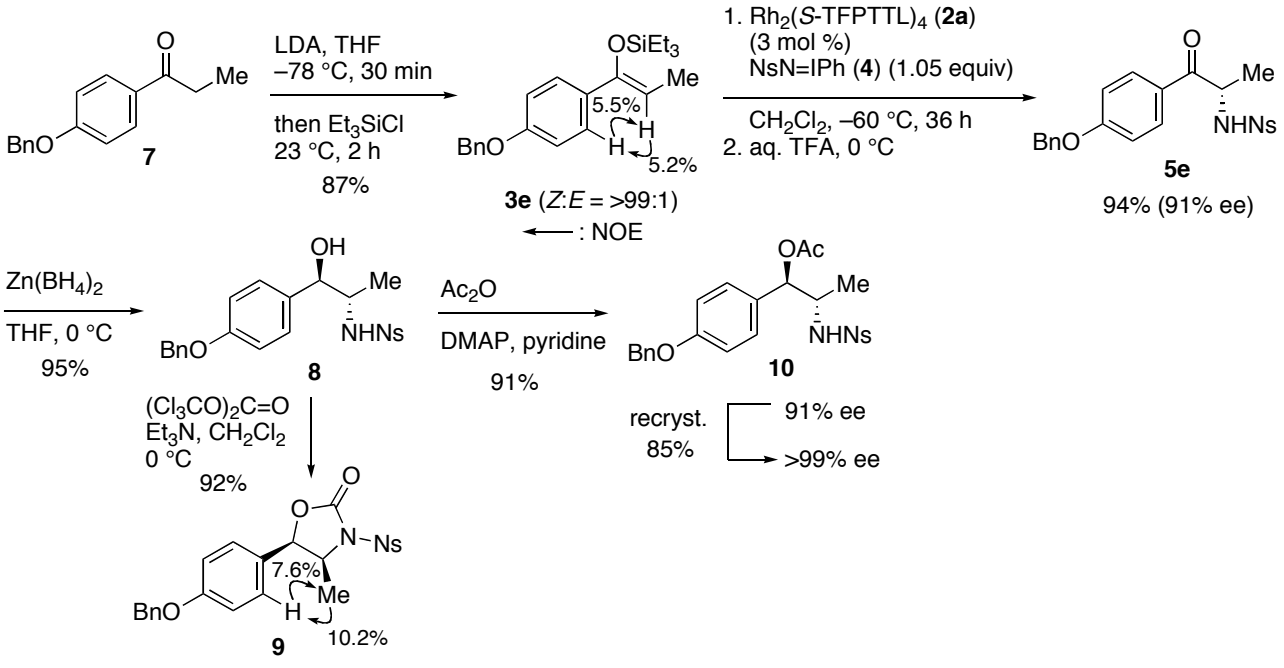
We have recently documented the utility of Rh_2(*S*-TFPTTL)$_4$ (**2a**) and Rh_2(*S*-TCPTTL)$_4$ (**2b**),[15] characterized by the substitution of fluorine or chlorine atoms for four hydrogen atoms on the phthalimido group in the parent dirhodium(II) complex, [Rh_2(*S*-PTTL)$_4$] (**2c**),[16,17] in the catalysis of enantioselective nitrene transfer reactions[18] such as C–H amination[19,20] and olefin aziridination.[21] More recently, we have reported that Rh_2(*S*-TFPTTL)$_4$-catalyzed enantioselective amination of silyl enol ethers with [(2-nitrophenylsulfonyl)imino]phenyliodinane (NsN=IPh) (**4**) provides *N*-(2-nitrophenylsulfonyl)-α-amino ketones with enantioselectivities of up to 95% ee,[22] the effectiveness of which has been demonstrated by an asymmetric formal synthesis of (–)-metazocine (**6**), a benzomorphan analgesic (Scheme 1). In this process, the use of NsN=IPh (**4**) as a nitrene precursor is not only crucial for high levels of enantioselection but also synthetically advantageous since the alkylation of resultant *N*-



Scheme 1

monosubstituted Ns-amides and deprotection proceed under mild conditions.[23] In order to further broaden the utility of this catalytic protocol, we envisioned that stereocontrolled reduction of the 1-phenyl-2-[*N*-(2-nitrophenylsulfonyl)amino]propan-1-one derivatives thus obtained would provide facile access to optically active 2-amino-1-aryl-1-propanols (**1**).[24,25] Based on this scenario, we have now addressed the catalytic asymmetric synthesis of (–)-ritodrine (**1g**) hydrochloride.

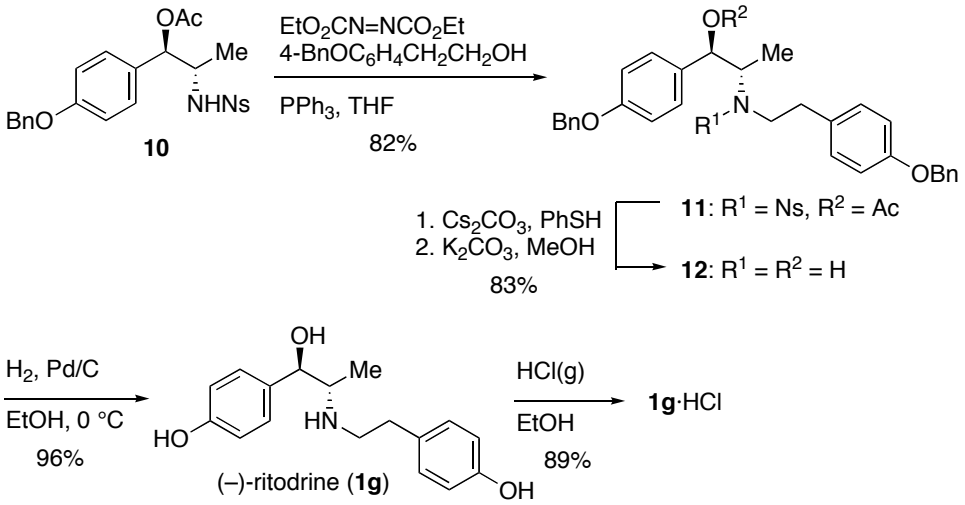
Toward this end, we selected (*Z*)-1-(4-benzyloxyphenyl)-1-triethylsiloxy-1-propene (**3e**) as a substrate on the basis of our previous finding that only (*Z*)-silyl enol ethers are responsible for the formation of α-amino ketones.[22,26] (*Z*)-Silyl enol ether (**3e**) was readily prepared from 4-benzyloxypropiophenone (**7**)[27] by treatment with LDA at –78 °C followed by the addition of Et_3SiCl (Scheme 2).[28] The (*Z*)-stereochemistry of **3e** was established by the ^{1}H NOE between C2–H and *ortho* protons on the benzene ring. The reaction of **3e** with NsN=IPh (**4**) in CH_2Cl_2 in the presence of 3 mol % of Rh_2(*S*-TFPTTL)$_4$ proceeded at –40 °C to completion in 5 h, and, after treatment with 90% aqueous trifluoroacetic acid, gave α-amino ketone (**5e**), $[\alpha]_D^{23}$ +4.65° (*c* 1.27, $CHCl_3$), in 92% yield. The enantioselectivity of this reaction was determined to be 82% ee by HPLC analysis (Daicel Chiralpak IA column). The preferred absolute configuration of **5e** was assigned as *S* by its conversion to **1g**·HCl (*vide infra*). Gratifyingly, the enantioselectivity was further enhanced up to 91% ee by lowering the reaction temperature to –60 °C without affecting product yield, although much longer reaction times (36 h) were necessary to reach completion. Chelation-controlled reduction of the ketone carbonyl group in **5e** with $Zn(BH_4)_2$ led to the exclusive formation of the desired *anti*-amino alcohol (**8**) in 95% yield.[25b,c,29] The *anti*-stereochemistry of **8** was established by its transformation to the 1,3-oxazolidin-2-one (**9**),[30] which



Scheme 2

showed an NOE correlation between the C4-methyl group and *ortho* protons on the benzene ring. No signs of the *syn*-amino alcohol could be detected in the crude reaction mixture by NMR spectroscopy.[31] Acetylation of **8** under standard conditions provided amino acetate (**10**) in 93% yield as a white solid. Fortunately, we found that a single recrystallization of **10** from MeOH gave crystals with 3% ee {11%, mp 130.5–131.5 °C, $[\alpha]_D^{23}$ –1.46° (*c* 1.12, $CHCl_3$)}, while the mother liquor contained **10** with >99% ee {84%, mp 50.0–51.0 °C, $[\alpha]_D^{23}$ –41.2° (*c* 1.05, $CHCl_3$)}.

With enantioenriched amino acetate (**10**) (>99% ee) in hand, we proceeded to the elaboration of the target molecule (Scheme 3). *N*-Alkylation of **10** with 2-(4-benzyloxyphenyl)ethanol[32] under Mitsunobu conditions gave the *N*,*N*-disubstituted amine derivative (**11**) in 82% yield.[33,34] Removal of the Ns group under standard Fukuyama conditions[23] followed by removal of the acetyl group with K_2CO_3 in MeOH gave β-amino alcohol (**12**) in 83% yield. Hydrogenolysis of the benzyl ethers over 10% Pd/C in EtOH furnished (–)-ritodrine (**1g**), $[\alpha]_D^{21}$ –5.33° (*c* 1.43, EtOH), in 96% yield, which upon treatment with HCl in EtOH afforded (–)-ritodrine (**1g**) hydrochloride[13,14] in 89% yield. The synthetic material (**1g**·HCl) had an optical rotation, $[\alpha]_D^{23}$ –13.6° (*c* 0.30, EtOH), in good agreement with the literature value {lit.,[13] $[\alpha]_D^{20}$ –13.2° (*c* 0.24, EtOH)}. Thus, the preferred absolute configuration of α-amino ketone (**5e**) was established as *S*.



Scheme 3

In summary, we have achieved the catalytic asymmetric synthesis of (–)-ritodrine hydrochloride in 10 steps and with 35% overall yield from 4-benzyloxypropiophenone. The present protocol provides ready access to its novel analogues for biological and pharmacological investigations.

EXPERIMENTAL

General. Melting points were determined on a Büchi 535 digital melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer and absorbance bands are

reported in wavenumber (cm^{-1}). ^1H NMR spectra were recorded on JEOL JNM-ECX 400 (400 MHz) spectrometer or JEOL JNM-ECA 500 (500 MHz) spectrometer. Chemical shifts are reported relative to the internal standard (tetramethylsilane; δ_H 0.00, $CDCl_3$; δ_H 7.26 or DMSO-d_6; δ_H 2.50). Data are presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant and integration. ^{13}C NMR spectra were recorded on JEOL JNM-ECX 400 (100 MHz) spectrometer or JEOL JNM-ECA 500 (125 MHz) spectrometer. The following internal references were used ($CDCl_3$; δ 77.0, CD_3OD; δ 49.8 or DMSO-d_6; δ 39.7). Optical rotations were measured on a JASCO P-1030 digital polarimeter at the sodium D line (589 nm). EI-MS spectra were obtained on a JEOL JMS-FABmate spectrometer, operating with ionization energy of 70 eV. FAB-MS spectra were obtained on a JEOL JMS-HX 110 spectrometer. Column chromatography was carried out on Kanto silica gel 60 N (63–210 mesh) or Wakogel® C-200 (75–150 mesh). Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates with visualization by UV light, anisaldehyde stain solution or phosphomolybdic acid stain solution. Analytical high performance liquid chromatography (HPLC) was performed on a JASCO PU-1580 intelligent HPLC pump with JASCO UV-1575 intelligent UV/vis detector. Detection was performed at 254 nm. Chiralpak AD-H (0.46 cm × 25 cm) or Chiralpak IA column (0.46 cm × 25 cm) from Daicel were used. Retention times (t_R) and peak ratios were determined with JASCO-Borwin analysis system.

All non-aqueous reactions were carried out in flame-dried glassware under an argon atmosphere unless otherwise noted. Reagents and solvents were purified by standard means. Dehydrated stabilizer-free CH_2Cl_2 and THF were purchased from Kanto Chemical Co., Inc. Diisopropylamine and *N*,*N*-dimethylformamide (DMF) were distilled from calcium hydride prior to use. Rh_2(*S*-TFPTTL)$_4$·2EtOAc (**2**) was prepared from L-*tert*-leucine according to literature procedure.[15,17] [*N*-(2-nitrophenylsulfonyl)imino]phenyliodinane (**4**) was prepared from the corresponding sulfonamide according to literature procedure.[35] Diethyl azodicarboxylate (2.2 M in toluene) was purchased from Tokyo Chemical Industry Co., Ltd. Cesium carbonate was purchased from Wako Pure Chemical Industries, Ltd.

(*Z*)-1-(4-Benzyloxyphenyl)-1-triethylsiloxy-1-propene (3e). BuLi (1.6 M in hexane, 6.8 mL, 11.0 mmol) was added to a solution of diisopropylamine (1.31 g, 1.82 mL, 12.0 mmol) in THF (20 mL) at –78 °C. After stirring at this temperature for 0.5 h, 4-benzyloxypropiophenone[27] (2.40 g, 10.0 mmol) in THF (15 mL) was added to the mixture over a period of 1 h. The solution was stirred for 0.5 h and chlorotriethylsilane (1.85 mL, 11.0 mmol) was added. The mixture was allowed to warm to rt over 0.5 h and stirred for 1 h. The mixture was diluted with 5% triethylamine in hexane (60 mL), and the mixture was washed with saturated aqueous $NaHCO_3$ (3 × 30 mL) and brine (2 × 30 mL), and dried over

anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude product, which was purified by Kugelrohr distillation (3 mmHg, 180 °C) to provide **3e** (2.81 g, 81% yield, *Z*/*E* = >99:1) as a colorless oil; R_f = 0.48 (19:1 hexane/EtOAc); IR (neat) ν: 2954, 1651, 1606, 1508, 1240, 1065, 1008, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.61 (q, *J* = 8.2 Hz, 6H, CH_3CH_2Si), 0.93 (t, *J* = 8.2 Hz, 9H, CH_3CH_2Si), 1.73 (d, *J* = 6.9 Hz, 3H, CH_3CH=C), 5.06 (s, 2H, $PhCH_2O$), 5.10 (q, *J* = 6.9 Hz, 1H, CH_3CH=C), 6.88–6.92 (m, 2H, *ortho* proton of 4-benzyloxyphenyl group), 7.31–7.45 (m, 7H, *Ar*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 5.34 (CH_2), 6.70 (CH_3), 11.47 (CH_3), 69.95 (CH_2), 103.73 (CH), 114.18 (CH), 126.62 (CH), 127.50 (CH), 127.92 (CH), 128.53 (CH), 132.68 (C), 136.96 (C), 149.96 (C), 158.17 (C); HRMS (EI) $C_{22}H_{30}O_2Si$ (M^+) 354.2015, found 354.2027.

(*S*)-1-(4-Benzyloxyphenyl)-2-[(2-nitrophenylsulfonyl)amino]-1-propanone (5e). [*N*-(2-nitrophenylsulfonyl)imino]phenyliodinane (**4**) (806.4 mg, 2.0 mmol, 1.05 equiv) was added in one portion to a solution of **3e** (673.6 mg, 1.90 mmol, *Z*/*E* = >99:1) and Rh_2(*S*-TFPTTL)$_4$·2EtOAc (**2a**) (90.4 mg, 0.057 mmol, 3 mol %) in CH_2Cl_2 (15 mL) at –60 °C. After stirring at this temperature for 36 h, the reaction mixture was treated with 90% aqueous TFA (*ca*. 0.5 mL) followed by stirring for 0.5 h at rt. The mixture was partitioned between EtOAc (50 mL) and pH 7.0 phosphate buffer (15 mL). The separated organic layer was washed with water (2 × 20 mL) and brine (2 × 20 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation furnished the crude product, which was purified by column chromatography (silica gel, 3:1 hexane/EtOAc). Rh_2(*S*-TFPTTL)$_4$ (**2a**) {75.0 mg, 83%, R_f = 0.71 (2:1 hexane/EtOAc)} was eluted first through the column. The fractions containing the product were collected and concentrated to provide **5e** (786.1 mg, 94% yield) as a colorless viscous oil; R_f = 0.23 (2:1 hexane/EtOAc); $[\alpha]_D^{23}$ +5.33° (*c* 1.51, $CHCl_3$) for 91% ee; IR (neat) *ν*: 3330, 1679, 1544, 1378, 1359, 1222, 1174, 972 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.49 (d, *J* = 7.2 Hz, 3H, CH_3CHN), 5.13 (s, 2H, $PhCH_2O$), 5.17 (dq, *J* = 8.2, 7.2 Hz, 1H, CH_3CHN), 6.65 (d, *J* = 8.2 Hz, 1H, N*H*), 6.98–7.02 (m, 2H, *Ar*), 7.33–7.43 (m, 5H, *Ar*), 7.56 (dt, *J* = 1.4, 7.7 Hz, 1H, *Ar*), 7.64 (dt, *J* = 1.4, 7.7 Hz, 1H, *Ar*), 7.79–7.83 (m, 2H, *Ar*), 7.86 (dd, *J* = 1.4, 7.7 Hz, 1H, Ar), 7.99 (dd, *J* = 1.4, 7.7 Hz, 1H, *Ar*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.16 (CH_3), 54.12 (CH), 70.19 (CH_2), 114.95 (CH), 125.49 (CH), 126.28 (C), 127.43 (CH), 128.32 (CH), 128.68 (CH), 130.01 (CH), 130.91 (CH), 132.71 (CH), 133.49 (CH), 134.33 (C), 135.75 (C), 147.56 (C), 163.41 (C), 195.63 (C=O); HRMS (FAB) calcd for $C_{22}H_{21}N_2O_6S$ ($M+H^+$) 441.1120, found 441.1126. The enantiomeric excess of **5e** was determined to be 91% by HPLC with a Daicel Chiralpak IA column (3:1 hexane/*i*-PrOH, 1.0 mL/min): t_R (major) = 30.5 min for (*S*)-enantiomer; t_R (minor) = 33.9 min for (*R*)-enantiomer.

(1*R*,2*S*)-1-(4-Benzyloxyphenyl)-2-[(2-nitrophenylsulfonyl)amino]-1-propanol (8). $Zn(BH_4)_2$[36] (0.64 M in THF, 3.2 mL, 2.06 mmol) was added to a solution of **5e** (603.9 mg, 1.37 mmol) in THF (15 mL) at

0 °C. After stirring at 0 °C for 0.5 h, the reaction was quenched with 10% aqueous HCl (5 mL) and the whole was extracted with EtOAc (40 mL). The organic layer was washed with water (2 × 10 mL) and brine (2 × 10 mL), and dried over anhydrous Na_2SO_4. Filtration and concentration *in vacuo* furnished the crude product, which was purified by column chromatography (silica gel, 2:1 hexane/EtOAc) to give **8** (576 mg, 95%) as colorless needles; R_f = 0.53 (1:1 hexane/EtOAc); mp 54.0–56.0 °C (2:1 hexane/EtOAc); $[\alpha]_D^{23}$ –57.6° (*c* 1.14, MeOH) for 91% ee; IR (KBr) ν: 3528, 3321, 1540, 1356, 1332, 1227, 1054 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.01 (d, *J* = 6.9 Hz, 3H, C*H*$_3$CHN), 2.16 (br-s, 1H, O*H*), 3.78 (ddq, *J* = 3.9, 8.3, 6.9 Hz, 1 H, CH$_3$C*H*N), 4.73 (d, *J* = 3.9 Hz, 1 H, C*H*OH), 5.04 (s, 2H, PhC*H*$_2$O), 5.51 (d, *J* = 8.3 Hz, 1H, N*H*), 6.88–6.91 (m, 2H, *Ar*), 7.16–7.19 (m, 2H, *Ar*), 7.34 (m, 1H, *Ar*), 7.38–7.44 (m, 4H, *Ar*), 7.70 (dt, *J* = 1.7, 7.4 Hz, 1H, *Ar*), 7.73 (dt, *J* = 1.7, 7.4 Hz, 1H, *Ar*), 7.84 (m, 1H, *Ar*), 8.14 (m, 1H, *Ar*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.61 (CH_3), 55.98 (CH), 69.97 (CH_2), 75.65 (CH), 114.71 (CH), 125.41 (CH), 127.32 (CH), 127.45 (CH), 128.04 (CH), 128.60 (CH), 130.63 (CH), 132.15 (C), 132.89 (CH), 133.36 (CH), 134.80 (C), 136.75 (C), 147.61 (C), 158.47 (C); HRMS (FAB) $C_{22}H_{22}N_2O_6SNa$ $(M+Na)^+$ 465.1096, found 465.1091.

(4*S*,5*R*)-5-(4-Benzyloxyphenyl)-4-methyl-3-(2-nitrophenylsulfonyl)-1,3-oxazolidin-2-one (9). Triphosgene (42.1 mg, 0.14 mmol) was added at 0 °C to a solution of **8** (62.8 mg, 0.14 mmol, 91% ee) and Et_3N (71.8 mg, 0.71 mmol) in CH_2Cl_2 (3 mL). After stirring at 0 °C for 0.5 h, the reaction was quenched with crushed ice. The mixture was partitioned between EtOAc (20 mL) and water (3 mL). The organic layer was washed with brine (2 × 3 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude product, which was purified by column chromatography (silica gel, 2:1 hexane/EtOAc) to provide **9** (60.5 mg, 92%) as colorless needles; R_f = 0.34 (2:1 hexane/EtOAc); mp 107.0–108.5 °C; $[\alpha]_D^{23}$ +235.1° (*c* 1.14, $CHCl_3$); IR (KBr) ν: 2924, 1779, 1543, 1516, 1373, 1348, 1253, 1178, 969 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.16 (d, *J* = 6.9 Hz, 3H, C4-C*H*$_3$), 4.82 (dq, *J* = 6.9, 7.4 Hz, 1H, C4-*H*), 5.08 (s, 2H, PhC*H*$_2$O), 5.82 (d, *J* = 7.4 Hz, 1H, C5-*H*), 7.03 (d, *J* = 8.6 Hz, 2H, *Ar*), 7.25 (d, *J* = 8.6 Hz, 2H, *Ar*), 7.33–7.44 (m, 5H, *Ar*), 7.80–7.86 (m, 3H, *Ar*), 8.48 (m, 1H, *Ar*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.36 (CH_3), 58.77 (CH), 70.08 (CH_2), 80.39 (CH), 115.10 (CH), 124.59 (CH), 124.66 (C), 127.28 (CH), 127.49 (CH), 128.12 (CH), 128.63 (CH), 130.67 (CH), 132.25 (CH), 134.80 (C), 135.40 (C), 136.49 (C), 147.94 (C), 151.18 (C), 159.33 (C=O); HRMS (EI) $C_{23}H_{20}N_2O_7S$ (M^+) 468.0991, found 468.1002.

(1*R*,2*S*)-1-(4-Benzyloxyphenyl)-2-[(2-nitrophenylsulfonyl)amino]-1-propyl acetate (10). Acetic anhydride (195 mg, 1.91 mmol) was added to a solution of **8** (564.5 mg, 1.28 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (15.9 mg, 0.13 mmol) in pyridine (2 mL) at 0 °C. After stirring at rt for

0.5 h, the reaction was quenched with crushed ice. The mixture was partitioned between EtOAc (25 mL) and H_2O (5 mL). The organic layer was washed with 1 N HCl (2 × 5 mL) and brine (2 × 5 mL), and dried over anhydrous Na_2SO_4. Filtration and concentration *in vacuo* furnished the crude product, which was purified by column chromatography (silica gel, 3:1 hexane/EtOAc) to give **10** (576.7 mg, 93%) as a white solid; R_f = 0.38 (3:2 hexane/EtOAc); mp 51.0–55.0 °C; $[\alpha]_D^{23}$ –35.9° (*c* 1.06, $CHCl_3$) for 91% ee; IR (KBr) *ν*: 3290, 2979, 1719, 1540, 1365, 1336, 1251, 1163, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.10 (d, *J* = 6.9 Hz, 3H, C*H*$_3$CHN), 2.02 (s, 3H, C*H*$_3$CO), 3.97 (ddq, *J* = 4.6, 8.6, 6.9 Hz, 1H, CH_3C*H*N), 5.01 (s, 2H, PhC*H*$_2$O), 5.40 (d, *J* = 8.6 Hz, 1H, N*H*), 5.54 (d, *J* = 4.6 Hz, 1H, C*H*OAc), 6.87 (d, *J* = 8.6 Hz, 2H, *Ar*), 7.13 (d, *J* = 8.6 Hz, 2H, *Ar*), 7.32–7.42 (m, 5H, *Ar*), 7.70 (m, 2H, *Ar*), 7.82 (dd, *J* = 1.1, 7.4 Hz, 1H, *Ar*), 8.10 (dd, *J* = 1.1, 7.4 Hz, 1H, *Ar*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.22 (CH_3), 20.87 (CH_3), 53.86 (CH), 69.89 (CH_2), 76.43 (CH), 114.73 (CH), 125.43 (CH), 127.40 (CH), 127.89 (CH), 127.95 (C), 128.02 (CH), 128.57 (CH), 130.37 (CH), 132.99 (CH), 133.40 (CH), 134.76 (C), 136.61 (C), 147.48 (C), 158.72 (C), 169.82 (C=O); HRMS (EI) $C_{24}H_{24}N_2O_7S$ (M^+) 484.1304, found 484.1299; Anal. Calcd for $C_{24}H_{24}N_2O_7S$: C, 59.49; H, 4.99; N, 5.78; S, 6.62. Found: C, 59.31; H, 4.95; N, 5.72; S, 6.60.

10 (419.0 mg, 91% ee) was dissolved in 4.5 mL of boiling MeOH and stored at rt overnight. Colorless needles of **10** (47.0 mg, 11%, 3% ee){mp 130.5–131.5 °C, $[\alpha]_D^{23}$ –1.46° (*c* 1.12, $CHCl_3$)} were removed by filtration, and the filtrate was concentrated *in vacuo* to afford **10** (350 mg, 84%, >99% ee) as colorless needles; mp 50.0–51.0 °C; $[\alpha]_D^{23}$ –41.2° (*c* 1.05, $CHCl_3$).

The homochirality of **10** was established by comparison of retention time in HPLC (Chiralpak, AD-H, 1:1 hexane/*i*-PrOH, 1.0 mL/min) with a racemic sample: t_R (minor) = 8.45 min for *ent*-**10**, t_R (major) = 10.53 min for **10**.

(1*R*,2*S*)-1-(4-Benzyloxyphenyl)-2-[*N*-[2-(4-benzyloxyphenyl)ethyl]-*N*-(2-nitrophenylsulfonyl)amino]-1-propyl acetate (11). Diethyl azodicarboxylate (2.2 M in toluene, 0.75 mL, 1.65 mmol) was added to a solution of **10** (400 mg, 0.826 mmol, >99% ee), 2-(4-benzyloxyphenyl)ethan-1-ol[32] (377.1 mg, 1.65 mmol), and triphenylphosphine (433.3 mg, 1.65 mmol) in THF (4 mL) at rt, and the mixture was stirred for 3 h. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel, 9:1 toluene/Et_2O) to afford **11** (468.4 mg, 82%) as a colorless viscous oil; R_f = 0.36 (2:1 hexane/EtOAc); $[\alpha]_D^{23}$ –30.4° (*c* 1.07, $CHCl_3$); IR ($CHCl_3$) *ν*: 3031, 2942, 1744, 1544, 1372, 1349, 1233, 1175, 1024 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35 (d, *J* = 6.9 Hz, 3H, C*H*$_3$CHN), 2.07 (s, 3H, C*H*$_3$CO), 2.79 (dt, *J* = 5.4, 11.5 Hz, 1H, ArC*H*$_2$CH$_2$N), 2.91 (dt, *J* = 5.4, 11.8 Hz, 1H, ArC*H*$_2$CH$_2$N), 3.44 (ddd, *J* = 5.4, 11.5, 15.1 Hz, 1H, ArCH$_2$C*H*$_2$N), 3.50 (ddd, *J* = 5.4, 11.8, 15.1 Hz, 1H, ArCH$_2$C*H*$_2$N), 4.33 (dq, *J* = 5.7, 6.9 Hz, 1 H, CH$_3$C*H*N), 5.01 (s, 2H, PhC*H*$_2$O), 5.05 (s, 2H, PhC*H*$_2$O), 5.83 (d, *J* = 5.7 Hz, 1H, ArC*H*OAc), 6.80-6.83 (m, 2H, *Ar*), 6.91-6.94 (m, 2H, *Ar*), 7.08-7.11 (m, 2H, *Ar*), 7.13-7.16 (m, 2H, *Ar*),

7.32–7.36 (m, 2H, *Ar*), 7.38-7.44 (m, 8H, *Ar*), 7.54 (dd, *J* = 1.1, 7.4 Hz, 1H, *Ar*), 7.56 (dd, *J* = 1.1, 7.4 Hz, 1H, *Ar*), 7.62 (dt, *J* = 1.1, 7.4 Hz, 1H, *Ar*), 7.85 (dd, *J* = 1.1, 7.4 Hz, 1H, *Ar*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.53 (CH_3), 21.20 (CH_3), 36.82 (CH_2), 46.78 (CH_2), 57.68 (CH), 69.88 (CH_2), 69.96 (CH_2), 77.64 (CH), 114.59 (CH), 115.00 (CH), 124.23 (CH), 127.41 (CH), 127.43 (CH), 127.81 (CH), 127.92 (CH), 128.03 (CH), 128.54 (C), 128.58 (CH), 128.59 (CH), 129.95 (C), 130.66 (C), 130.86 (CH), 131.58 (CH), 133.46 (CH), 133.58 (C), 136.73 (C), 136.94 (C), 147.95 (C), 157.53 (C), 169.56 (C=O); HRMS (FAB) $C_{24}H_{24}N_2O_7S$ $(M+Na)^+$ 717.2247, found 717.2245.

(1*R*,2*S*)-1-(4-Benzyloxyphenyl)-2-[2-(4-benzyloxyphenyl)ethyl]amino-1-propanol (12). Cs_2CO_3 (628.0 mg, 1.93 mmol) was added to a solution of sulfonamide **11** (447.1 mg, 0.643 mmol) and PhSH (132 μL, 1.29 mmol) in DMF (0.3 mL) at rt. After stirring for 1 h, the mixture was poured into 10% aqueous NaOH (3 mL) and the whole was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with H_2O (2 × 4 mL) and brine (2 × 4 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude product, which was dissolved in MeOH (0.5 mL). K_2CO_3 (444.3 mg, 3.22 mmol) was added to the mixture at rt. After stirring for 2 h, the mixture was partitioned between EtOAc (5 mL) and H_2O (5 mL). The whole was extracted with EtOAc (2 × 15 mL) and the organic layer was washed with brine (2 × 7 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude product, which was purified by column chromatography (silica gel, 19:1 $CHCl_3$/MeOH) to afford **12** (249.6 mg, 83% for 2 steps) as a colorless solid; R_f = 0.32 (9:1 $CHCl_3$/MeOH); mp 52.0–53.0 °C; $[\alpha]_D^{23}$ –8.1° (*c* 1.16, MeOH); IR (KBr) *ν*: 3401, 3304, 3104, 1611, 1511, 1455, 1382, 1241, 1170, 1014 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.3 Hz, 3H, C*H*$_3$CHN), 2.34 (br-s, 1H, O*H*), 2.68–2,81 (m, 2H), 2.85–2.99 (m, 3H), 4.68 (d, *J* = 3.6 Hz, 1 H, ArC*H*OH), 5.04 (s, 2H, PhC*H*$_2$O), 5.05 (s, 2H, PhC*H*$_2$O), 6.91 (d, *J* = 8.6 Hz, 2H, *Ar*), 6.93 (d, *J* = 8.6 Hz, 2H, *Ar*), 7.11 (d, *J* = 8.6 Hz, 2H, *Ar*), 7.21 (d, *J* = 8.6 Hz, 2H, *Ar*), 7.30–7.44 (m, 10H, *Ar*); ^{13}C NMR (100 MHz, CD_3OD) δ 16.37 (CH_3), 35.98 (CH_2), 49.74 (CH_2), 50.65 (CH_2), 60.59 (CH), 71.73 (CH_2), 77.85 (CH), 116.61 (CH), 116.79 (CH), 129.36 (CH), 129.40 (CH), 129.58 (C), 129.60 (C), 130.25 (CH), 130.27 (CH), 131.31 (CH), 131.34 (CH), 133.29 (CH), 136.34 (C), 139.38 (C), 139.49 (C), 159.50 (C), 160.53 (C); HRMS (FAB) $C_{31}H_{34}NO_3$ $(M+H)^+$ 468.2539, found 468.2530.

(1*R*,2*S*)-1-(4-Hydroxyphenyl)-2-[*N*-[2-(4-hydroxyphenyl)ethyl]amino]-1-propanol [(–)-ritodrine] (1g). A solution of benzyl ether **12** (111.0 mg, 0.238 mmol) in EtOH (2 mL) was vigorously stirred with 10% Pd/C (20 mg) under 1 atm of hydrogen at rt for 3 h. The catalyst was removed by filtration through a Celite® pad, and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel, 3:1 $CHCl_3$/MeOH) to afford **1g** (65.7 mg, 96%) as a colorless viscous oil; R_f

= 0.28 (3:1 $CHCl_3$/MeOH); $[\alpha]_D^{21}$ –5.33° (*c* 1.43, EtOH); IR (neat) *ν*: 3282, 3022, 2927, 1614, 1596, 1516, 1451, 1238 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 0.85 (d, *J* = 6.3 Hz, 3H, CH_3CHN), 2.64-2.67 (m, 2H), 2.79–2.90 (m, 3H), 4.65 (d, *J* = 2.9 Hz, 1 H, C*H*OHAr), 6.68 (d, *J* = 8.6 Hz, 2H, *Ar*), 6.71 (d, *J* = 8.6 Hz, 2H, *Ar*), 6.98 (d, *J* = 8.6 Hz, 2H, *Ar*), 7.10 (d, *J* = 8.6 Hz, 2H, *Ar*); ^{13}C NMR (125 MHz, DMSO-d_6) δ 12.91 (CH_3), 33.82 (CH_2), 47.78 (CH_2), 58.39 (CH), 72.27 (CH), 114.67 (CH), 115.16 (CH), 127.20 (CH), 129.32 (C), 129.44 (CH), 132.98 (C), 155.71 (C), 156.21 (C); HRMS (FAB) $C_{31}H_{34}NO_3$ $(M+H)^+$ 288.1600, found 288.1610.

(–)-Ritdorine·hydrochloride (1g·HCl).[13,14] Saturated HCl in EtOH (0.5 mL) was added to a solution of **1g** (50.7 mg) in EtOH (0.5 mL). The solvent was evaporated under reduced pressure to afford (–)-**1g**·HCl (48.8 mg, 89%) as a colorless gum; $[\alpha]_D^{23}$–13.6° (*c* 0.30, EtOH) {lit.,[13] $[\alpha]_D^{20}$ –13.2° (*c* 0.24, EtOH)}; IR (neat) *ν*: 3250, 3019, 2977, 1614, 1596, 1516, 1446, 1223 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.94 (d, *J* = 6.9 Hz, 3H, CH_3CHN), 2.82-2.96 (m, 2H), 3.13 (brs, 2H), 3.34 (1H, m), 5.03 (s, 1 H, ArO*H*), 5.96 (d, *J* = 4.0 Hz, 1H, C*H*OHAr), 6.73 (d, *J* = 8.6 Hz, 2H, *Ar*), 6.75 (d, *J* = 8.6 Hz, 2H, *Ar*), 7.06 (d, *J* = 8.6 Hz, 2H, *Ar*), 7.16 (d, *J* = 8.6 Hz, 2H, *Ar*); ^{13}C NMR (125 MHz, DMSO-d_6) δ 9.37 (CH_3), 30.85 (CH_2), 46.13 (CH_2), 58.43 (CH), 69.29 (CH), 114.89 (CH), 115.39 (CH), 126.91 (CH), 127.57 (C), 129.60 (CH), 131.19 (C), 156.21 (C), 156.58 (C).

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