The Asymmetric Synthesis of (*R,R*)-Formoterol via Transfer Hydrogenation with Polyethylene Glycol Bound Rh Catalyst in PEG2000 and Water

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ABSTRACT (*R,R*)-formoterol was synthesized in seven steps with 4-hydroxyl-3-nitro-acetophenone as the starting material. The key intermediate, the chiral secondary alcohol **4**, was prepared via Rh-catalyzed asymmetric transfer hydrogenation with (*S,S*)-PEGBsDPEN as the ligand and sodium formate as the hydrogen donor under mild conditions. With a mixture of PEG 2000 and water as the reaction media, the catalyst system could be recycled four times. *Chirality 22:206–211, 2010.*

KEY WORDS: (*R,R*)-formoterol; asthma; asymmetric transfer hydrogenation; PEGBsDPEN; recycle

INTRODUCTION

Formoterol (Scheme 1) is a long-lasting, very potent β_2-adrenoceptor agonist, which is used as a bronchodilator in the therapy of asthma and chronic bronchitis. Because of the two stereocenters in the molecule structure, there are four different stereoisomers that demonstrate different pharmacological potencies, respectively, the order is $(R,R) > (R,S) \gg (S,R) > (S,S)$.[1]

Toxicology studies indicated that the (*S,S*)-isomer is toxic in a manner independent of β_2-adrenoceptor binding and may increase the toxicological burden of the racemic drug.[2] Therefore, the use of (*R,R*)-Formoterol for asthma could eliminate adverse effects of (*S,S*)-Formoterol that arise during therapeutic use. Recently, (*R,R*)-Formoterol has been launched by Sepracor Inc (October 2006). Despite the unique strongpoint of (*R,R*)-Formoterol, there were few reports of the asymmetric synthesis of this useful chiral drug. Murase et al.[1] described a preparation employing a resolution process of two enantiomers. Trofast et al.[3] reported a HPLC-semipreparative separation of diastereomers. Hett et al.[4,5] developed a diastereo- and enantioselective synthesis of Formoterol utilizing borane reduction with *cis*-1-amino-2-indanol as the chiral ligand for the synthesis of the chiral epoxide intermediate. Guerrero and coworkers[6] described a synthetic route to enantiomeric pure (*R,R*)-Formoterol through the enzyme-directed preparation. However, from a practical standpoint, it is highly desirable to develop new methods for preparing the key intermediate, chiral secondary alcohol **4,** with good stereo control. In our previous study, we reported a new chiral ligand PEGBsDPEN, its application to the Ru-catalyzed asymmetric hydrogenation of aromatic ketones,[7] and total synthesis of (*R*)-Salmeterol, which is a selective long-acting β_2-adrenoreceptor agonist.[8] Herein, we report a convenient synthesis of (*R,R*)-Formoterol via catalytic asymmetric hydrogenation using Rh-PEGBsDPEN.

EXPERIMENTAL

General Methods

NMR spectra were recorded with TMS as the internal standard on a Varian 300 MHz spectrometer. Coupling constants were given in Hz. Enantiomeric excess was determined by HPLC on Chiralcel OJ-H columns. Optical rotation was determined on a Perkin Elmer 341 polarimeter. MS spectra were recorded on an Agilent LC-MS 6120 with ESI.

(*S,S*)-TsDPEN and (*R,R*)-TsDPEN were synthesized according to literature methods.[9] PEG2000 and (*R,R*)-tartaric acid were purchased from Sinopharm Chemical Regent Co. Ltd (China). Dichloro(p-cymene)ruthenium(II) dimer and Dichloropentamethylcyclopentadienylrhodium (III) dimer were purchased from Alfa Aesar. All the reactions were monitored by thin layer chromatography on silica gel.

Preparation of 1-(4-(benzyloxy)-3-nitrophenyl) ethanone 2

To a suspension of Na_2CO_3 (8.49 g, 80 mmol) in a mixture of acetone (80 ml) and H_2O (80 ml) was added 1-(4-hydroxy-3-nitrophenyl)ethanone (10.86 g, 60 mmol). The mixture was kept stirring at 65°C until the suspension dissolved completely. Potassium iodide (2.22 g, 13.4 mmol) was added followed by benzyl chloride (8.0 ml, 72 mmol) added drop wise. The mixture was refluxed and

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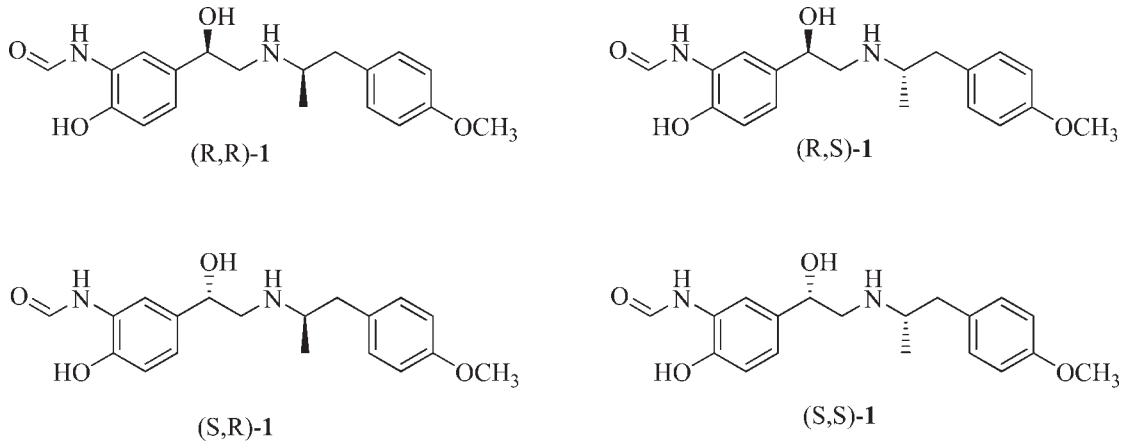


Scheme 1. Four stereoisomers of formoterol.

stirred for 48 h. When the mixture was cooled to room temperature, the precipitate was filtered and washed with water to afford the crude product. Recrystallization of the crude product in acetone gave light yellow crystals (14.77 g, 90.5% yield). Mp. 135–136°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.58 (s, 3H, COCH_3), 5.29 (s, 2H, PhCH_2O), 7.19 (d, J = 8.7 Hz, 1H, Ar—*H*), 7.42–7.32 (m, 5H, Ar—*H*), 8.10 (d, J = 10.8 Hz, 1H, Ar—*H*), 8.40 (s, 1H, Ar—*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.6, 71.6, 114.8, 126.2, 127.1, 128.7, 129.0, 129.9, 134.0,134.9, 139.8, 155.2, 194.8; LC/MS (ESI) *m/z*: 272.1 ($M+H^+$), Calc mass: 271.1.

Preparation of 1-(4-(benzyloxy)-3-nitrophenyl)-2-bromoethanone 3

To a suspension of 1-(4-(benzyloxy)-3-nitrophenyl)ethanone (11.42 g, 42 mmol) in acetic acid (150 ml) was slowly added bromine (8.75 g, 54.6 mmol) at 20°C. The mixture was stirred until the color faded out. Ice water (75 ml) was added to the mixture; the precipitate was filtered and washed with water. Crystallization of the crude solid in ethanol gave the pale yellow crystals (11.76 g, 85% yield). Mp. 137–138°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.36 (s, 2H, COCH_2Br), 5.31 (s, 2H, PhCH_2O), 7.21 (d, J = 8.7 Hz, 1H, Ar—*H*), 7.43–7.35 (m, 5H, Ar—*H*), 8.13 (d, J = 8.1 Hz, 1H, Ar—*H*), 8.44 (s, 1H, Ar—*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.1, 71.9, 115.1, 126.2, 127.0, 127.2, 128.8, 129.1, 134.7, 134.8, 140.0, 155.8, 188.5; LC/MS (ESI *m/z*): 350.0, 352.0 ($M+H^+$), Calc mass: 348.9.

Preparation of (R)-1-(4-(benzyloxy)-3-nitrophenyl)-2-bromoethanol 4

To a suspension of η5-pentamethylcyclopentadienylrhodium dimer ($[RhCl_2(Cp^*)]_2$) (43.2 mg, 0.072 mmol) and (*S,S*)-PEGBsDPEN (192 mg, 0.144 mmol) in H_2O (25 ml) was added PEG-2000 (25.0 g, 12.5 mmol). The mixture was purged with argon and stirred at 40°C for 1 h to afford the catalyst in situ. HCOONa (4.89 g, 72 mmol) and 1-(4-(benzyloxy)-3-nitrophenyl) −2-bromoethanone (5.04 g, 14.4 mmol) were added to the preformed catalyst solution. The mixture was stirred at room temperature for 1 h until the reaction completed. Diethyl ether was added to the reaction system, and the organic phase was extracted under argon. The aqueous solution containing PEG 2000 and the catalyst remained for the next cycle. The combined organic phases were washed with brine (100 ml) and dried over anhydrous sodium sulfate. After the filtration, the organic solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel to give **4** as white solid (4.76 g, 94% yield). The enantiomeric excess was determined by chiral HPLC on a Chiracel OJ-H column. (Hex/IPA = 65/35, 254 nm, 0.8 ml/min) Retention time: 27.01 min (major), 31.81 min; 94% ee; Mp. 69–70°C; $[\alpha]_D^{20}$ = −17.9 (c = 1.07, EtOH)[5]; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.52 (d, J = 9.0 Hz, 1H, CH_2Br), 3.63 (d, J = 10.5 Hz, 1H, CH_2Br), 4.90 (m, 1H, Ar—C*H*OH), 5.23 (s, 2H, PhCH_2O), 7.12 (d, J = 8.4 Hz, 1H, Ar—*H*), 7.42–7.31 (m, 5H, Ar—*H*), 7.52 (d, J = 8.7 Hz, 1H, Ar—*H*), 7.88 (s, 1H, Ar—*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 39.8, 71.6, 72.5, 123.6, 127.2, 128.5, 128.9, 131.8, 133.3, 135.5, 140.1, 151.9, 115.5; LC/MS (ESI) *m/z*: 352.2, 354.2 ($M+H^+$), Calc mass: 351.0.

Recycling of the Catalyst

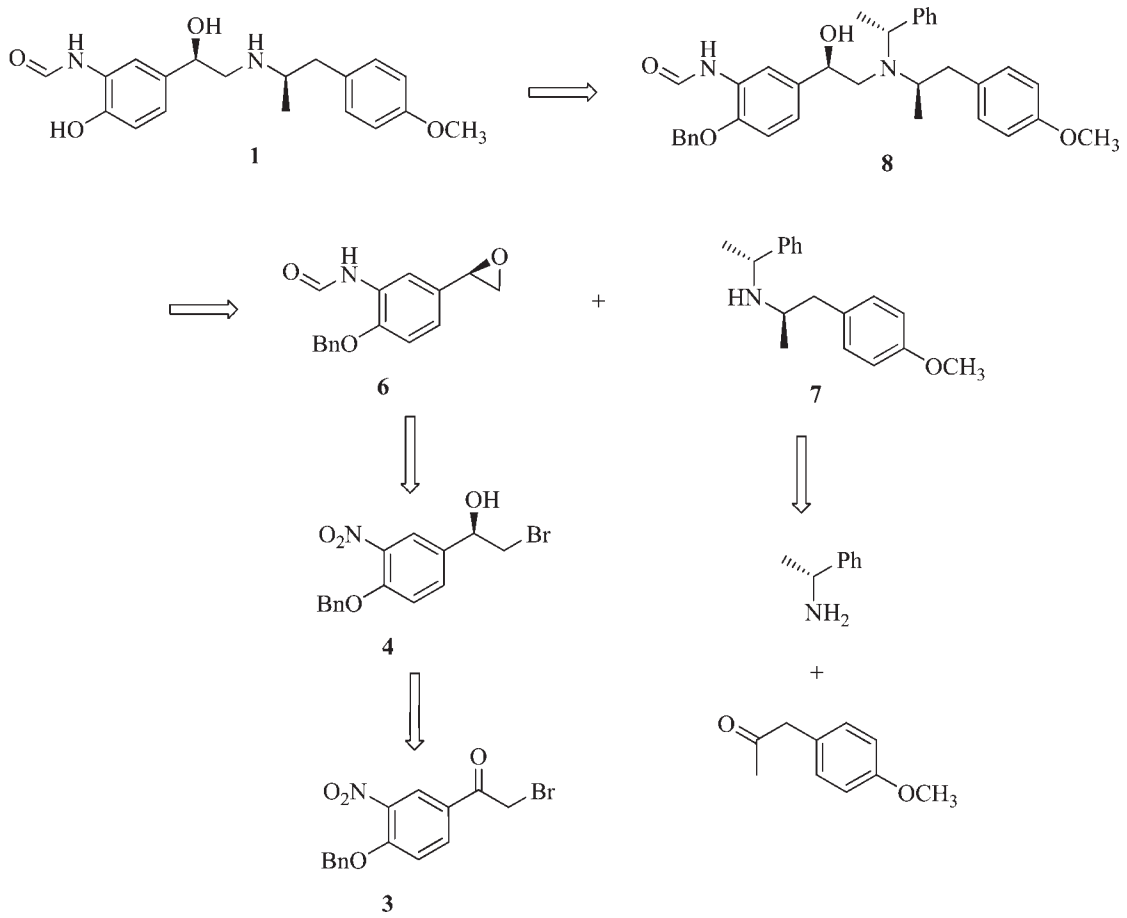
Under an argon atmosphere, to the aqueous solution containing PEG 2000 and the catalyst from the asymmetric hydrogenation above, was added HCO_2H (0.29 mL, 14.4 mmol) and 1-(4-(benzyloxy)-3-nitrophenyl)-2-bromo-ethanone (5.04 g, 14.4 mmol). The resulting solution was allowed to react at 40°C for 1–12 h and worked up as the first ATH reaction.

Preparation of Formic-Acetic Anhydride

To acetic anhydride (21.4 ml, 215 mmol) was added 96% formic acid solution (16.2 ml, 431 mmol) at room temperature over 30 min. The solution was stirred for 30 min at 20–30°C and used without further purification.

Preparation of N-(2-(benzyloxy)-5-((R)-2-bromo-1-hydroxyethyl)phenyl) formamide 5

To a solution of (*R*)-1-(4-(benzyloxy)-3-nitrophenyl)-2-bromoethanol (12.15 g, 34.5 mmol) in THF (30 ml) was added dimethyl sulfide (7.71 mg, 0.174 mmol) and 5%Pt/C (1.21 g). The mixture was stirred under hydrogen (50 psi) at 40°C for 4 h, and the catalyst was filtered off. The above



Scheme 2. Retro synthetic analysis of (*R,R*)-formoterol 1.

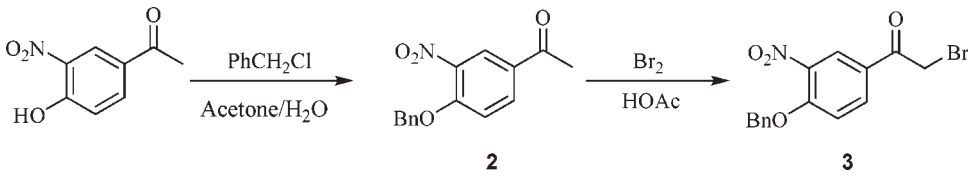
solution of formic-acetic anhydride was added to the THF solution of aniline derivative over 30 min at 10°C. The solution was brought to room temperature and stirred for another 30 min, and the solvent then removed under reduced pressure. The residue was diluted with water and extracted with toluene (80 ml). The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude product. Crystallization of the crude product with a mixture of heptanes and toluene (1:1) gave the desired product **5** (10.08 g, 83% yield). Mp. 130–131°C; $[\alpha]_D^{20} = -25.2$ (c = 1.1, $CHCl_3$)[5]; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.46 (m, 2H, CHOHCH_2Br), 4.76 (m, 1H, Ar—C*H*OH), 5.00 (S, 2H, PhCH_2O), 6.88 (m, 1H, Ar—*H*), 7.04 (m, 1H, Ar—*H*), 7.29 (m, 5H, Ar—*H*), 7.84 (m, 1H, Ar—*H*), 8.28 (d, 1H, J = 11.7 Hz, *H*CONH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 40.0, 71.0, 73.4, 111.5, 118.4, 121.9, 127.0, 127.7, 128.0, 128.6, 128.8, 133.7, 135.9, 147.0, 159.2; LC/MS (ESI m/z): 350.2, 352.2 ($M+H^+$), Calc mass: 349.0.

Preparation of (R)-N-(2-(benzyloxy)-5-(oxiran-2-yl)phenyl)formamide 6

To a solution of *N*-(2-(benzyloxy)-5-((*R*)-2-bromo-1-hydroxyethyl)phenyl)formamide **5** (8.78 g, 25 mmol) in a mixture of THF (25 ml) and MeOH (25 ml) was added potassium carbonate (10.35 g, 75 mmol). The mixture was stirred vigorously at room temperature for 2 h and then concentrated to remove the solvent. Toluene (80 ml) and water (80 ml) were added to the residue. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product. The crude product was dissolved in a mixture of heptanes and toluene (100 mL, 1:1) at 110°C. The resulting mixture was cooled slowly to ambient temperature, and the precipitate was collected by filtration, washed with hexane, and dried in vacuo to give the desired product **6** (6.59 g, 98% yield) of as an off-white solid. Mp. 66–67°C; $[\alpha]_D^{20} = +3.75$ (c = 0.9, EtOH)[5]; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.72 (m, 1H, CH—CH_2), 3.00 (m, 1H, CH—CH_2), 3.73 (m, 1H, Ar—C*H*), 5.00 (s, 2H, PhCH_2O), 7.00–6.86 (m, 2H, Ar—*H*), 7.32–7.29 (m, 5H, Ar—*H*), 7.79 (m, 1H, Ar—*H*), 8.29 (d, 1H, J = 11.7 Hz, *H*CONH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 49.9, 51.2, 70.0, 110.6, 117.3, 120.0, 121.4, 126.1, 126.7, 126.9, 127.6, 127.8, 129.6, 134.9, 145.9, 157.9; LC/MS (ESI) m/z: 270.1 ($M+H^+$), Calc mass: 269.1.

Preparation (R)-1-(4-methoxyphenyl)-N-((R)-1-phenylethyl)propan-2-amine 7

To a solution of 1-(4-methoxyphenyl)propan-2-one (8.22 g, 50 mmol) and (*R*)-1-phenylethanamine (6.11 g, 50.4



Scheme 3. Synthetic route for prochiral α-bromoketone 3.

mmol) in methanol was added 5% Pt/C (0.83 g). The mixture was stirred and hydrogenated at 60°C for 24 h. Removal of the catalyst by filtration and evaporation of the solvent gave the (*R,R*)-amine product **7**. To this amine **7** was added (*R,R*)-tartaric acid (7.45 g, 50 mmol) in hot ethanol (50 ml). Crystallization from ethanol (100 ml) gave the crystalline product, Mp. 90–94°C; $[\alpha]_D^{20}$ = +50.2 (*c* = 1.02, EtOH); ^{1}H NMR (300 MHz, D_2O) δ: 1.05 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 1.54 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 2.54 (dd, *J* = 12.6 Hz, *J*′ = 9.3 Hz, 1H, CH$_2$C*H*NH), 3.09 (m, 2H, ArC*H*$_2$CH), 3.68 (s, 3H, OC*H*$_3$), 4.39 (s, 2H, HOC*H*$_2$-COOH), 4.45 (dd, *J* = 13.5 Hz, *J*′ = 6.9 Hz, 1H, ArC*H*NH), 6.79–6.77 (d, *J* = 8.4 Hz, 2H, Ar—*H*), 6.97–6.94 (d, *J* = 8.4 Hz, 2H, Ar—*H*), 7.41–7.34 (m, 5H, Ar—*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.2, 19.1, 36.8, 53.3, 55.6, 55.2, 72.8, 127.2, 127.3, 128.5, 129.5, 129.6, 130.4, 135.7, 157.8, 176.2. Ethyl acetate and ammonia were added to the crystals and worked up to give 10.76 g of the pure (*R,R*)-amine **7** as oil. (dr 96:4, 80% yield). $[\alpha]_D^{20}$ = +29.7 (*c* = 1.24, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.89 (d, *J* = 6.2 Hz, 3H, CHC*H*$_3$), 1.29 (d, *J* = 6.4 Hz, 3H, CHC*H*$_3$), 2.44 (dd, *J* = 12.6 Hz, *J*′ = 6.9 Hz, 1H, CH$_2$C*H*NH), 2.76 (m, 2H, ArC*H*$_2$CH), 3.76 (s, 2.88H, OC*H*$_3$), 3.79 (s, 0.12H, OC*H*$_3$), 3.90 (dd, *J* = 13.2 Hz, *J*′ = 6.9 Hz, 1H, ArC*H*NH), 6.79–6.77 (m, 2H, Ar—*H*), 6.99–6.96 (m, 2H, Ar—*H*), 7.31–7.21 (m, 5H, Ar—*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.6, 25.0, 42.1, 52.4, 55.5, 55.7, 113.9, 126.5, 126.8, 127.0, 128.5, 128.6, 130.4, 130.5, 131.8, 146.5, 158.1; LC/MS (ESI) *m/z*: 270.2 ($M+H^+$), Calc mass: 269.2.

Preparation of (R,R)-Formoterol 1

A mixture of the chiral epoxide **6** (5.38 g, 20 mmol) and the chiral amine **7** (5.38 g, 20 mmol) was heated to 120°C and stirred for 24 h to give the protected amine **8**. To a solution of the amine **8** in methanol (40 ml) was added 5% Pd/C (0.54 g). The mixture was stirred under an atmosphere of hydrogen (45 psi) for 12 h. The Pd/C catalyst was filtered off through a pad of Celite. Evaporation of the solvent under reduced pressure gave the crude product as a slurry, which was further purified by flash chromatography on silica gel (chloroform/methanol = 10/1) to give (*R,R*)-Formoterol as the white solid (5.57 g, 81% yield). Mp. 73–75°C; $[\alpha]_D^{20}$ = −41.0 (*c* = 1.05,$CHCl_3$) [6]; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.23 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 2.80–2.40 (m, 5H, ArC*H*C*H*$_2$, C*H*$_2$NH), 3.65 (s, 3H, OC*H*$_3$), 4.44 (m,1H, ArC*H*OH), 6.74–6.67 (m, 3H, Ar—*H*), 6.92 (m, 1H, Ar—*H*), 7.17 (m,1H, Ar—*H*), 7.39 (m, 1H, Ar—*H*), 8.02 (d, *J* = 11.7 Hz, 1H, Ar—*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.2, 43.1, 55.0, 56.3, 72.1, 112.9, 113.1, 119.3, 127.8, 129.2, 129.9, 131.4, 134.7, 149.5, 161.6, 166.7,; LC/MS (ESI) *m/z*: 345.2 ($M+H^+$), Calc mass: 344.2.

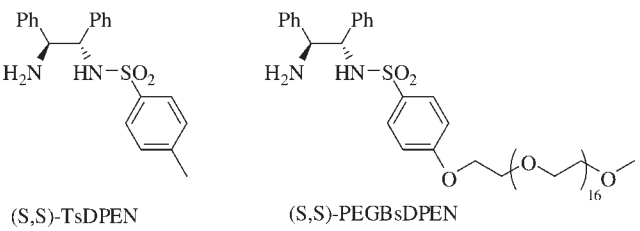
RESULTS AND DISCUSSIONS

As shown in the retrosynthetic analysis (Scheme 2), epoxide **6** and amine **7** are two important chiral intermediates for the synthesis of (*R,R*)-Formoterol. The reaction of chiral epoxide **6** with amine **7** gave the intermediate **8**. Removal of protective groups afforded the desired product (*R,R*)-Formoterol **1**.

The chiral amine **7** could be obtained by one-pot Pt/C catalyzed hydrogenation of chiral 1-phenylethanamine and 1-(4-methoxyphenyl)propane-2-one. In the synthesis of chiral epoxide **6,** α-bromoketone **3** is a very important intermediate. In the presence of potassium carbohydrate, 4-hydroxyl-3-nitro-acetophenone reacted with benzyl chloride to give acetophenone derivative **2**. The bromination of compound **2** in acetic acid then provided the prochiral α-bromoketone **3** (Scheme 3).

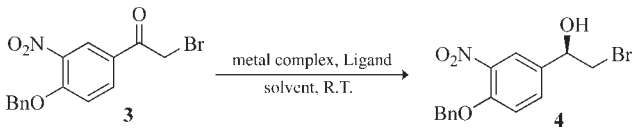
Chiral secondary alcohol **4** is the key intermediate for preparation of epoxide **6**. It could be synthesized by several methods including biotransformation and asymmetric reduction.[3–6] To the best of our knowledge, there are few reports involving asymmetric hydrogenation[10,11] to prepare this key intermediate. On the basis of this background, we chose this useful method to prepare the key intermediates of (*R,R*)-Formoterol, because of operational simplicity and the readily availability of the reductants.

As the solubility of α-bromoketone **3** in water is poor, we firstly chose the HCOOH-Et_3N azeotropic mixture as the hydrogen donor and Ru- or Rh-TsDPEN (Scheme 4) as the catalyst. (Table 1) However, only trace products were obtained when the reaction was carried out at room temperature for 24 h with 5:2 HCOOH-NEt_3 azeotropic mixture as the hydrogen donor (entry 1–2). The yield increased to 37% with 62% ee at a lower HCOOH/NEt_3 ratio (1:1).[12] On the other hand, when sodium formate in water was selected as the hydrogen donor,



Scheme 4. Chiral ligand for asymmetric transfer hydrogenation.

TABLE 1. Various conditions for asymmetric transfer hydrogenation of α-bromoketone[a]

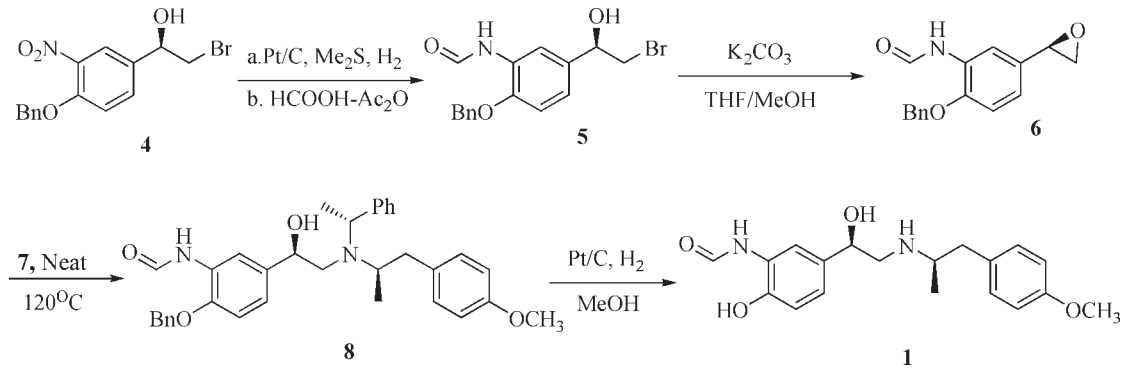


Entry	Catalyst	Hydrogen donor	Yield (%)[b]	ee (%)[c]
1	Ru/(*S,S*)-TsDPEN	HCOOH-Et_3N(5:2)	Trace	–
2	Rh/(*S,S*)-TsDPEN	HCOOH-Et_3N(5:2)	Trace	–
3	Ru/(*S,S*)-TsDPEN	HCOOH-Et_3N(1:1)	37	62(*R*)
4	Ru/(*S,S*)-TsDPEN	HCOONa/H_2O	81	86(*R*)
5	Rh/(*S,S*)-TsDPEN	HCOONa/H_2O	82	92(*R*)
6	Ru/(*S,S*)-PEGBsDPEN	HCOONa/H_2O	82	87(*R*)
7	Rh/(*S,S*)-PEGBsDPEN	HCOONa/H_2O	85	94(*R*)
8	Rh/(*S,S*)-TsDPEN	HCOONa/PEG2000-H_2O[d]	92	93(*R*)
9	Rh/(*R,R*)-TsDPEN	HCOONa/PEG2000-H_2O	90	92(*S*)
10	Rh/(*S,S*)-PEGBsDPEN	HCOONa/PEG2000-H_2O	94	94(*R*)

[a]The reaction was carried out at room temperature for 1 h (S/C: substrate to catalyst) = 100/1).
[b]Isolated yields were obtained by flash chromatography.
[c]The enantiomeric excess was determined by HPLC on a chiralcel OJ-H column; the absolute configuration was assigned on the basis of signs of optical rotation.
[d]PEG2000/H_2O = 1/1(m/m).

Ru- and Rh-catalysts gave 86% ee and 92% ee, respectively, with good yield (entry 4, 5). Under the same condition, the yield and enantioselectivity were slightly improved using Ru- and Rh-(*S,S*)-PEGBsDPEN as catalysts (entry 6, 7). As polyethylene glycol (PEG) was widely used as the solvent and new means for catalyst recycling in various reactions, we added PEG in the reaction to study the possibility of improving the yield and catalyst recycling. When PEG 2000 and water were used as the reaction solvent, both catalyst systems (Rh-TsDPEN and Rh-PEGBsDPEN) provided improved chemical yields with essentially identical ee values (Entries 8 and 10, 92% and 94% yields; 93% and 94% ee, respectively).

Importance has been attached to the recycling of catalysts for the asymmetric hydrogen transfer to control the use of expensive noble metal and chiral ligands. A great number of approaches to catalyst recycling have been reported in recent years, which included both immobilization by anchoring the catalyst on to insoluble and soluble polymers,[13–16] inorganic materials[17,18] and dendrimers,[19–22] and unmodified ruthenium catalyst in liquid biphasic systems[23,24] and aqueous micelles and vesicles.[25] Recently, Fan and coworkers[26] applied mixture of polyethylene glycol and water as media for asymmetric hydrogenation of aromatic ketones and successfully recycled the catalyst for several times. However, when Ru- or Rh-TsDPEN was used as the catalyst, we failed to recycle the catalyst with α-bromoketone **3** as the substrate in PEG because the chiral secondary alcohol **4** cannot be extracted into hexane. Ether was a good solvent for the secondary alcohol **4,** but the catalyst was also very soluble. Therefore, it was difficult to recycle the catalyst with TsDPEN as the ligand for this specific substrate. As PEG2000 precipitated at zero degree, we tried Rh-PEGBsDPEN as the catalyst and PEG2000-H_2O as the reac-



Scheme 5. Synthesis of (*R,R*)-formoterol.

TABLE 2. Catalyst recycling of asymmetric transfer hydrogenation of α-bromoketone 3[a]

Entry	Time (h)	Yield (%)[b]	ee (%)[c]
1	1	94	94
2	1	93	94
3	6	93	94
4	6	89	93
5	12	78	93

[a]The reactions were carried out with Rh/(*S,S*)-PEGBsDPEN as catalyst (S/C = 100/1) and 5.0 equiv. of HCOONa as the hydrogen donor at room temperature in PEG2000-H_2O (1:1,m/m). After each batch, 1 equiv. of HCOOH was added to regenerate HCOONa.
[b]Isolated yields were obtained by flash chromatography.
[c]The enantiomeric excess was determined by HPLC on a Chiralcel OJ-H column.

tion medium. We were pleased to find out that attaching a hydrophilic PEG chain onto the sulfonyl moiety made the catalyst very soluble in PEG2000. At 0°C, the catalyst-PEG2000 system could be readily separated from the secondary alcohol **4**. The product could be successfully extracted with ether, with the catalyst left in the reaction system. ICP analysis showed that less than 0.12 mol % of rhodium was lost in the catalyst after the fifth run. The results of catalyst recycling are listed in Table 2, which indicates that good chemical yields were obtained even on the fourth runs, and the enantioselectivity was quite consistent in all of the five runs (Table 2).

In the presence of 5% Pt/C, the nitro group of secondary alcohol **4** was reduced by hydrogenation, and then reacted with HCOOH—Ac_2O to afford the intermediate **5**. Intermediate **5** could be transformed into epoxide **6** nearly quantitatively in the presence of potassium carbonate with a mixture of THF and MeOH as the solvent at room temperature. Heating the mixture of epoxide **6** and amine **7** to 120°C under neat conditions for 24 h gave the ring opening product **8**. Removal of the protective group by Pd/C catalyzed hydrogenolysis to afforded (*R,R*)-Formoterol in 47.6% overall yield (Scheme 5).

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