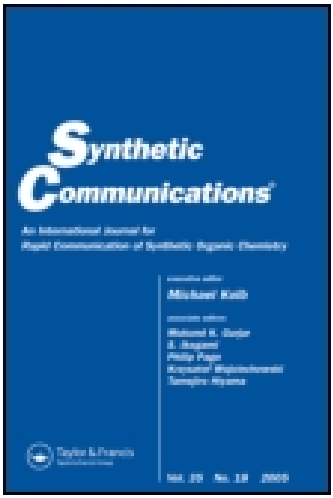

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Enantioselective Synthesis of Phenyl-ethanolamines Through Application of Chiral Sulfoxide

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Enantioselective Synthesis of Phenyl-ethanolamines Through Application of Chiral Sulfoxide

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Abstract: Efficient enantioselective synthesis of (*R*)- and (*S*)-enantiomers of 2-(*tert*-butylamino)-1-(*p*-methoxyphenyl)-ethanol has been achieved in high enantiomeric excess by using asymmetric sulfoxide as a chiral auxiliary. The present synthetic approach was further extended to the asymmetric synthesis of (*R*)-salbutamol.

Keywords: β-Amino-arylethanols, asymmetric sulfoxide, bronchodilator, chiral auxiliary, salbutamol

INTRODUCTION

The 2-amino-arylethanol derivatives form an important class of compounds because of their presence in several natural products[1] and their usefulness as pharmaceuticals, chiral auxiliaries, and chiral building blocks.[2] The enantioselective synthesis of substituted (*R*)-phenylethanolamines such as isoproterenol (**1**), terbutaline (**2a**), salbutamol (**2b**) (Figure 1), and a large number of related 2-amino-arylethanols has received considerable interest as these compounds display β_2-adrenergic receptor agonist activity, resulting in antiasthmatic and bronchodilatory properties. The prominent natural 2-amino-arylethanols include octopamine (**3a**), tembemide (**3b**), and aegeline (**3c**), which display β-adrenergic

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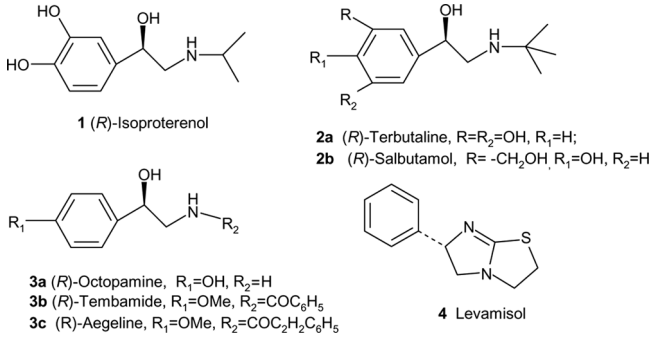


Figure 1. Structural features of salbutamol, terbutaline, isoproterenol, octopmine, tembemide, aegeline, and levamizole.

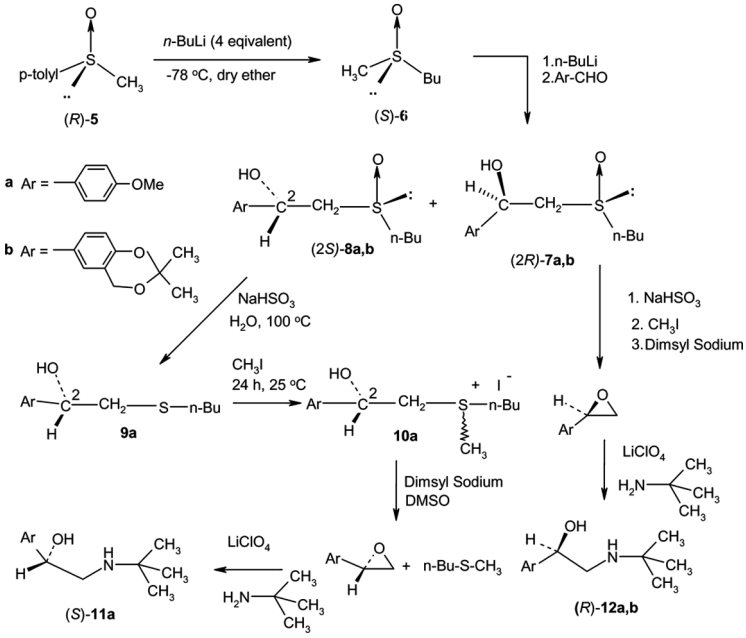
receptor agonist and hypoglycemic properties.[3] Moreover, (*S*)-2-amino-phenylethanol derivatives find utility in the synthesis of (*S*)-levamisole (**4**) analogues.[4]

In pharmaceuticals, selective interactions are profoundly important because one of the enantiomers of a compound has beneficial effect, whereas the second enantiomer may have disastrous results. (*R*)-Isoproterenol (**1**) possesses the desired bronchodilatory activity, whereas the (*S*)-isomer is approximately 90 times less potent.[5] The stereo-controlled induction of chirality into organic molecules remains an important challenge to synthetic organic chemists. Some of the known methods of obtaining optically active phenylethanolamines include resolution of racemic mixture,[6] asymmetric reduction of α-halo-, α-azido-, or α-amino-acetophenones,[7] and reduction of chiral cyanohydrins.[8] In addition, the enzymatic conversions,[9] Sharpless dihydroxylation,[3] asymmetric dihydroxylation,[4] and asymmetric Henry reaction[10] have also been utilized for obtaining nonracemic β-amino-phenylethanol derivatives.

In recent years, the sulfoximines[11] and sulfoxides[12] have been used as highly dependable chiral auxiliary in synthetic organic chemistry. We report herein the use of asymmetric sulfoxide in the enantioselective synthesis of 2-amino-1-arylethanols.

RESULTS AND DISCUSSION

The condensation of (+)-(*S*)-*n*-butyl methyl sulfoxide (**6**) with *p*-anisaldehyde in the presence of n-BuLi at −78°C yielded a diastereomeric mixture of *n*-butyl (2-hydroxy-2-p-methoxyphenyl)-ethyl sulfoxides (2*R*-**7a**) and (2*S*-**8a**) (Scheme 1). These diastereomers were separated in pure form



Scheme 1. Synthesis of (*R*)- and (*S*)-enantiomes of 1-*p*-methoxyphenyl-2-*tert*-butylamino-ethanol and (*R*)-salbutamol using asymmetric sulfoxide as a chiral auxiliary.

by fractional crystallization, and the diastereomeric excess (*de*) of separated diastereomers was evaluated by chiral high-performance liquid chromatography (HPLC; Chiracel OD analytical column) with hexane–propan-2-ol (ratio 85:15) as the mobile phase. The isomers (2*R*)-**7a** and (2*S*)-**8a** were obtained in a 1:4 ratio. Similarly, the condensation of (+)-(*S*)-*n*-butyl methyl sulfoxide (**6**) with 2,2-dimethyl-4H-benzo[3,4-*e*]1,3-dioxin-6-carboxaldehyde in the presence of n-BuLi at −78°C yielded a diastereomeric mixture of (2*R*)-(**7b**) and (2*S*)-**8b** n-butyl (2,2-dimethyl-4H-benzo[3,4-e]1,3-dioxin-6-yl)-ethyl sulfoxides. These diastereomers were separated in pure form by fractional crystallization and the diastereomeric excess (*de*) of separated diastereomers was evaluated by chiral HPLC (Chiracel OD analytical column) with hexane–propan-2-ol (ratio 85:15) as the mobile phase. The isomers (2*R*)-**7b** and (2*S*)-**8b** were obtained in a 1:5 ratio.

The β-hydroxy sulfoxide (2*S*)-**8a** was further subjected to the reduction with sodium hydrogen sulfite to obtain the β-hydroxy sulfide **9a**. The sulfide **9a** was converted into sulfonium iodide **10a** by treatment with methyl iodide.[13] The sulfonium iodide **10a** was crystallized from the

reaction mixture. The treatment of the sulfonium iodide **10a** with dimsyl sodium in dimethylsulfoxide (DMSO) yielded the (*S*)-*p*-methoxystyrene oxide,[14] which on addition of *t*-butylamine in the presence of $LiClO_4$[15] gave (*S*)-1-*p*-methoxyphenyl-2-*tert*-butylamino-ethanol (**11a**, *ee* 96%). The (*R*)-1-*p*-methoxyphenyl-2-*tert*-butylamino-ethanol (**12a**, *ee* 95%) and (*R*)-2-(N-*tert*-butylamino)-1-(2,2-dimethyl-4H-benzo[3,4-*e*]1,3-dioxin-6-yl}-ethanol (**12b**, *ee* 96%**)** were similarly synthesized starting from (2*R*)-β-hydroxy sulfoxides **7a** and **7b** respectively. The compound **12b** has been converted to (*R*)-salbutamol acetate by the treatment with aqueous acetic acid.[16]

EXPERIMENTAL

General Procedures

All solvents were purified by standard procedures. Infrared (IR) spectra were recorded on a Perkin-Elmer model 681 spectrometer. ^{1}H NMR spectra were recorded on Varian (400 and 500 MHz) spectrometers in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are reported in parts per million (ppm) of the applied field, and coupling constants are expressed in hertz (Hz). Optical rotations were measured on a Jasco DIP-370 digital polarimeter. The enantiomeric excess (*ee* %) of phenylethanol amine derivatives was determined by chiral HPLC (Chiracel OD-H analytical column) with hexane–propan-2-ol (85:15) as the mobile phase and ultraviolet (UV) detection at 230 nm. Microanalyses were performed in a Carlo Erba Model 1106 elemental analyzer. Melting points are uncorrected. The silica gel (100–200 mesh) for column chromatography was activated by heating at 120°C for 4 h.

Preparation of (+)-(*S*)-N-Butyl Methyl Sulfoxide (6)

A solution of n-butyl lithium (8.2 g, 55 ml, 0.128 mol) in hexane was added to a solution of (*R*)-methyl-*p*-tolyl sulfoxide **5** (5.0 g, 0.032 mol) in ethyl ether (200 ml) at −78°C under nitrogen to give a precipitate, which rapidly dissolved to produce a clear tan-colored solution. The reaction mixture was quenched after ½ h by addition of saturated ammonium chloride solution and was extracted two times with chloroform. The chloroform extract was washed with brine and dried over anhydrous sodium sulfate, and the solvent was removed in vacuum. The chromatography of the residue on silica gel with ether/acetone as eluents gave (*S*)-*n*-butyl methyl sulfoxide (**6**); yield 3.3 g (86%).

White solid; mp 53–54°C; lit.[12b] mp 52–53°C; $[\alpha]_D^{20}$ +112° (*c* 1.00, acetone); lit.[12b] $[\alpha]_D^{20}$ +108° (*c* 1.00, acetone); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.98 (t, $J = 7$ Hz, 3H), 1.44–1.56 (m, 2H), 1.69–1.80 (m, 2H), 2.57 (s, 3H), 2.61–2.80 (m, 2H). IR (KBr): 3230, 2934, 1341, 1163 cm^{-1}. Anal. calcd. for $C_5H_{12}OS$: C, 49.9; H, 10.1; S, 26.6. Found: C, 49.6; H, 9.8; S, 26.4%.

Synthesis of N-Butyl (2-Hydroxy-2-p-methoxyphenyl)-ethyl Sulfoxides (7a and 8a)

n-Butyl lithium (3.5 ml, 15% in hexane, 1.1 equiv.) was added to a cooled (−78°C) solution of (+)-(*S*)-*n*-butyl methyl sulfoxide (**6**) (0.9 g, 7.5 mmol) {$[\alpha]_D^{20}$ +112 (*c* 1.0, acetone)} in dry ether (distilled from sodium, 50 ml) under nitrogen. The mixture was stirred for 10 min at −78°C, and a solution of *p*-anisaldehyde (0.83 mmol, 1.1 equiv.) in ether (10 ml) was added all at once. The mixture was allowed to warm up to 0°C for 5 min, and it was poured into an ammonium chloride solution. The ether layer was separated, and the aqueous layer was extracted well with ether. The organic extracts were combined, washed with brine, dried over sodium sulfate, and evaporated to give a viscous residue, which was crystallized from ether–hexane (ca. 50:50) at 25°C to obtain a white crystalline solid, (2*R*)-**7a** (17%). The mother liquors were concentrated and redissolved in hexane with the addition of only a small amount of ether. Upon cooling to 0°C, the diastereomer (2*S*)-**8a** (68%) was crystallized.

Compound (2*R*)-**7a**

White solid; mp 64–65°C; $[\alpha]_D^{20}$ +36.26° (*c* 1.00, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.97 (t, 3H), 1.74–1.43 (m, 4H), 3.07–2.71 (m, 4H), 3.81 (s, 3H), 4.22 (s, 1H), 5.34 (d, $J = 9$ Hz, 1H), 6.90 (d, $J = 8.5$ Hz, 2H), 7.34 (d, $J = 8.5$ Hz, 2H). IR (KBr): 3243, 2953, 2927, 1518, 1466, 1077, 1038, 992, 827 cm^{-1}. Anal. calcd. for $C_{13}H_{20}O_3S$: C, 60.9; H, 7.8; S, 12.5. Found: C, 60.6; H, 7.4; S, 12.3%.

Compound (2*S*)-**8a**

White solid; mp 112–113°C; $[\alpha]_D^{20}$ −38.99° (*c* 1.00, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.96 (t, 3H), 1.76–1.44 (m, 4H), 3.06–2.67 (m, 4H), 3.80 (s, 3H), 3.93 (d, $J = 4$ Hz, 1H), 5.32 (d, $J = 10.5$ Hz, 1H), 6.90 (d, $J = 8.5$ Hz, 2H), 7.33 (d, $J = 8.5$ Hz, 2H); IR (KBr): 3256, 2960,

2927, 1518, 1466, 1255, 1018, 834, 683 cm^{-1}. Anal. calcd. for $C_{13}H_{20}O_3S$: C, 60.9; H, 7.8; S, 12.5. Found: C, 60.7; H, 7.7; S, 12.7%.

Synthesis of N-butyl {2-hydroxy-2-(2,2-dimethyl-4H-benzo[3,4-e]1,3-dioxin-6-yl}-ethyl Sulfoxides (7b and 8b)

This procedure was repeated by substitution of *p*-anisaldehyde with 2,2-dimethyl-4H-benzo[3,4-*e*]1,3-dioxin-6-carboxaldehyde to yield diastereomers of sulfoxides, (2*R*)-**7b** (18%) and (2*S*)-**8b** (70%).

Compound (2*R*)-**7b**

White solid; mp 57–58°C; $[\alpha]_D^{20}$ +13° (*c* 1.00, acetone); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.98–0.95 (t, 3H), 1.54 (s, 6H), 1.77–1.43 (m, 4H), 2.90–2.70 (m, 4H), 4.84 (s, 2H), 4.86 (s, 2H), 5.31 (d, $J = 10$ Hz, 1H), 6.81 (d, $J = 8.5$ Hz, 1H), 7.06 (d, $J = 1.8$ Hz, 1H), 7.16 (dd, $J = 8.5$, 1.8 Hz, 1H); IR (KBr): 3203, 2966, 2927, 1618, 1503, 1120, 1019, 906, 861 cm^{-1}. Anal. calcd. for $C_{16}H_{24}O_4S$: C, 61.5; H, 7.7; S, 10.2 Found: C, 61.3; H, 7.6; S, 10.4%.

Compound (2*S*)-**8b**

White solid; mp 104–106°C; $[\alpha]_D^{20}$ −11.11° (*c* 1.00, acetone); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.98–0.96 (t, 3H), 1.53 (s, 6H), 1.75–1.40 (m, 4H), 3.03–2.72 (m, 4H), 4.84 (s, 2H), 4.96–4.88 (bs, 1H), 5.31 (d, $J = 10$ Hz, 1H), 6.81 (d, $J = 8.5$ Hz, 1H), 7.06 (d, $J = 1.8$ Hz, 1H), 7.17 (d, $J = 8.5$, 1.8 Hz, 1H); IR (KBr): 3203, 2927, 2874, 1637, 1499, 1268, 1150, 1123, 1012, 913, 867 cm^{-1}. Anal. calcd. for $C_{16}H_{24}O_4S$: C, 61.5; H, 7.7; S, 10.2. Found: C, 61.2; H, 7.8; S, 10.5%.

Synthesis of (−)-(*S*)-2-(n-Butylthio)-1-(*p*-methoxyphenyl)-ethanol (9a)

A mixture of sulfoxide (2*S*)-**8a** (0.5 g, 1.95 mmol), saturated aqueous sodium bisulfite solution (50 ml), and methanol (5 ml) was refluxed for 4 h and then extracted with several portions of hexane. The organic solution was dried over sodium sulfate and evaporated under reduced pressure to yield sulfide **9a** (0.44 g, 94%).

Colourless liquid; $[\alpha]_D^{20}$ −25.6° (*c* 1.00, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93–0.90 (t, 3H), 1.61–1.40 (m, 4H), 2.91–2.52 (m, 4H), 2.97 (bs, 1H), 3.80 (s, 3H), 4.69 (d, $J = 9$ Hz, 1H), 7.11 (d, $J = 8.5$ Hz, 2H),

7.30 (d, $J = 8.5$ Hz, 2H). IR (KBr): 3461, 2929, 2864, 1611, 1507, 1462, 1254, 1047, 839, 605 cm^{-1}. Anal. calcd. for $C_{13}H_{20}O_2S$: C, 64.9; H, 8.3; S, 13.3. Found: C, 64.6; H, 8.0; S, 13.5%.

Synthesis of (2*S*)-n-Butyl [2-Hydroxy-2-(*p*-methoxyphenyl)-ethyl)-sulfonium Iodide (10a)

The sulfide **9a** (0.4 g, 1.66 mmol) was dissolved in methyl iodide (4 ml), and the mixture was allowed to stand at 25°C for 24 h. The reaction mixture was diluted with diethyl ether (75 ml) and cooled to 0°C overnight. A white solid was crystallized out, which was filtered, washed with cold ether, and dried to obtain compound **10a** (0.585 g, 91%).

White solid; mp 91–92°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.98–0.91 (t, 3H), 1.61–1.40 (m, 4H), 2.91–2.53 (m, 4H), 2.05 (s, 1H), 3.80 (s, 3H), 3.82 & 3.77 (2s, 3H), 4.70 (d, $J = 9$ Hz, 1H), 6.89 (d, $J = 9$ Hz, 2H), 7.03 (d, $J = 8.5$ Hz, 2H); IR (KBr): 3441, 2929, 2844, 1611, 1527, 1254, 1469, 1183, 1047, 845, 768 cm^{-1}. Anal. calcd. for $C_{14}H_{23}IO_2S$: C, 43.9; H, 6.0; S, 8.3. Found: C, 44.2; H, 6.2; S, 8.5%.

Synthesis of (+)-(*S*)-2-(*tert*-butylamino)-1-(4-methoxyphenyl)-ethanol (11a)

A solution of the sulfonium iodide **10a** (0.55 g, 1.516 mmol) in dry dimethyl sulfoxide (2 ml) (distilled from CaH) and dry THF (4 ml) (distilled from sodium) was cooled to −10°C under nitrogen. Then, freshly prepared 1 M sodium methylsulfinylmethide (dimsyl sodium) solution (2 ml) was added over 1 min. The mixture was allowed to warm up to 20°C over 1 h after an additional 20 min at 20–25°C, the mixture was poured into water, and the solution was extracted well with ether. The ether solution was washed twice with water and dried over sodium carbonate. The solvent was removed, and the residue was dried in vacuo.

The crude mixture of (*S*)-*p*-methoxy-styrene oxide and *n*-butylmethyl sulfide (0.3 g) was dissolved in acetonitrile (10 ml), and anhydrous lithium perchlorate (1.5 equiv.) was added with stirring. The resulting solution was treated under stirring at room temperature with *tert*-butyl amine (2 equiv.), and the reaction mixture was stirred for 8 h at room temperature. The solvent was removed in vacuo, and the residue was diluted with water and extracted with ether. The crude mixture was chromatographed over alumina. Elution with 50:50 of methanol–ethyl acetate gave (+)-(*S*)-1-(*p*-methoxyphenyl)-2-(*tert*-butylamino)-ethanol (**11a**), 176 mg [58%; *ee* 96%; HPLC t_R (*R*)-**12a** 11.05 min; t_R (*S*)-**11a** 13.25 min].

Compound **11a**

White solid; mp 110–112°C, $[\alpha]_D^{20}$ +57° (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$ & one drop of D_2O): δ 1.24 (s, 9H), 2.96 (dd, $J = 12$ Hz, 9.2 Hz, 1H), 3.13 (d, $J = 12$ Hz, 1H), 3.77 (s, 3H), 5.28 (d, $J = .9.2$ Hz, 1H), 6.82 (d, $J = 8.8$ Hz, 2H), 7.33 (d, $J = 8.8$ Hz, 2H); IR (KBr): 3423, 2999, 2890, 1963, 1614, 1494, 1250, 1036 cm^{-1}. Anal. calcd. for $C_{13}H_{21}NO_2$: C, 69.9; H, 9.5; N, 6.2. Found: C, 69.7; H, 9.2; N, 6.1%.

Syntheses of (−)-(*R*)-2-(*tert*-butylamino)-1-(*p*-methoxyphenyl)-ethanol (12a) and (−)-(*R*)-2-(*tert*-Butylamino)-1-(2,2-dimethyl-4H-benzo[3,4-e]1,3-dioxin-6-yl)-ethanol (12b)

The compounds (−)-(*R*)-**12a** (*ee* 95%) and (−)-(*R*)-**12b** (*ee* 96%) were prepared similarly from sulfoxide **7a** and **7b** respectively.

Compound **12a**

Mp 112–113°C, $[\alpha]_D^{20}$ −55° (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (s, 9H), 2.56 (dd, $J = 11.5$ Hz, 8.2 Hz, 1H), 2.87 (dd, $J = 11.5$, 4.1 Hz, 1H), 3.77 (s, 3H), 4.48 (dd, $J = .4.1$, 8.2 Hz, 1H), 6.83 (d, $J = 8.8$ Hz, 2H), 7.34 (d, $J = 8.8$ Hz, 2H); IR (KBr): 3423, 2999, 2890, 1963, 1614, 1494, 1250, 1036 cm^{-1}. Anal. calcd. for $C_{13}H_{21}NO_2$: C, 69.9; H, 9.5; N, 6.2. Found: C, 69.8; H, 9.5; N, 6.0%.

Compound **12b**

Mp 103–104°C; lit.[16] mp 102–103°C; $[\alpha]_D^{20}$ −18.7° (*c* 1.0, MeOH); lit.[16] $[\alpha]_D^{20}$ −18.9° (*c* 1.5, MeOH); ^1H NMR (500 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.53 (s, 3H), 1.54 (s, 3H), 2.55 (dd, $J = 11.7$, 9.2 1H), 2.86 (dd, $J = 11.7$,3.5 Hz), 4.50 (dd, $J = 9.2$, 3.5 Hz, 1H), 4.85 (s, 2H), 6.79 (d, $J = 8.5$ Hz, 1H), 7.06 (d, $J = 1.6$ Hz, 1H), 7.14 (d, $J = 8.5$, 1.6 Hz, 1H); IR (KBr): 3203, 2966, 2927, 1618, 1503, 1120, 1019, 906, 861 cm^{-1}. Anal. calcd. for $C_{16}H_{25}NO_3$: C, 68.8; H, 9.0; N, 5.0. Found: C, 68.6; H, 9.2; N, 5.2%.

CONCLUSIONS

Efficient enantioselective syntheses of (*S*)- and (*R*)-1-*p*-methoxyphenyl-2-*tert*-butylamino-ethanols and (*R*)-salbutamol were achieved through the application of chiral sulfoxide.

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