JOC The Journal of Organic Chemistry

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Stereoselective Synthesis of Norephedrine and Norpseudoephedrine by Using Asymmetric Transfer Hydrogenation Accompanied by Dynamic Kinetic Resolution

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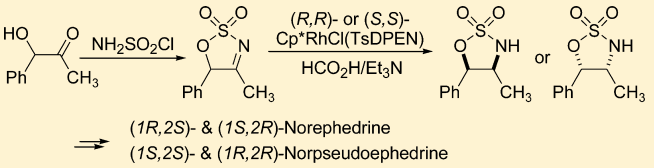
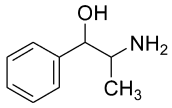
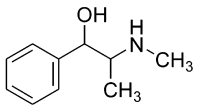
Supporting Information

ABSTRACT: Each of the enantiomers of both norephedrine and norpseudoephedrine were stereoselectively prepared from the common, prochiral cyclic sulfamidate imine of racemic 1-hydroxy-1-phenyl-propan-2-one by employing asymmetric transfer hydrogenation (ATH) catalyzed by the well-defined chiral Rh-complexes, (*S*,*S*)- or (*R*,*R*)-Cp*RhCl(TsDPEN), and HCO_2H/Et_3N as the hydrogen source. The ATH processes are carried out under mild conditions (rt, 15 min) and are accompanied by dynamic kinetic resolution.



β-Amino alcohols are important structural motifs in natural products and pharmacologically active compounds.[1−3] Among this large group of substances, members of the phenethylamine and amphetamine family of *Ephedra* alkaloids, including ephedrine, pseudoephedrine, norephedrine (NE, **1a** and **1b**), and norpseudoephedrine (NPE, **2a** and **2b**) (Figure 1), are





1a:(*1R*,*2S*)-(-)-Norephedrine (*1R*,*2S*)-(-)-Ephedrine
1b:(*1S*,*2R*)-(+)-Norephedrine (*1S*,*2R*)-(+)-Ephedrine
2a:(*1S*,*2S*)-(+)-Norpseudoephedrine (*1S*,*2S*)-(+)-Pseudoephedrine
2b:(*1R*,*2R*)-(-)-Norpseudoephedrine (*1R*,*2R*)-(-)-Pseudoephedrine

Figure 1. Norephedrine (**1a** and **1b**) and norpseudoephedrine (**2a** and **2b**).

known to display sympathomimetic psychoactivities. These alkaloids, which have been used as stimulants, decongestants, and anorectics,[4−7] also serve the function of chiral ligands or chiral auxiliaries in various stereoselective processes.[1,2]

While ephedrine and norephedrine are relatively easily obtained from commercial sources, the availability of norpseudoephedrine[8] is limited by the fact that it is a component of a mixture obtained by extraction of the khat shrub (*Catha edulis*) found in central Asia and eastern Africa. Moreover, only (1*S*,2*S*)-NPE (**2a**) is produced naturally, and its enantiomer (1*R*,2*R*)-NPE (**2b**) is difficult to obtain from natural sources.[4,6] Therefore, development of efficient and stereoselective methods for the synthesis of each enantiomer of norephedrine (NE) and norpseudoephedrine (NPE) is highly desirable.

Previous asymmetric syntheses of NE or NPE have been accomplished to varying degrees of success mainly by using "stoichiometric" amounts of optically active starting materials or enzymatically prepared, optically active intermediates. Most of these procedures are attended by moderate degrees of stereoselectivity and involve long preparative routes that are difficult to scale-up. For example, Krause et al. described an eight-step synthesis of (*S*,*S*)-NPE from a chiral amino alcohol used as an intermediate in an earlier chloroamphenicol synthesis.[9] Lee et al. also developed a synthesis of *N*-*Boc*-(*S*,*S*)-NPE that utilized addition of an organolithium reagent to an enantiomerically pure aziridine-2-carboxaldehyde and required separation of the resulting diastereomeric mixture (91:9) by employing flash chromatography.[10] In the route devised by Claremon et al., a five-step sequence was employed to transform an optically active allylic alcohol, obtained by using Sharpless' kinetic resolution method, to (*R*,*R*)-NPE in 92% ee.[11] Komatsu and his co-workers developed a synthesis of (*R*,*R*)-NPE (86% ee), which relied on the formation and subsequent acid-promoted hydrolysis of an oxazolidine formed from *β*-methylstyrene and benzoyl chloride using a chiral nitridomanganese complex.[12] Recently, Hitchcock et al. described an efficient, stereoselective conversion of *N*-*Boc*-NE to its corresponding diastereomer NPE by using a one-pot, *O*-mesylate formation and intramolecular inversion of configuration at the alcohol chiral center.[6]

A few reports exist describing "catalytic" asymmetric syntheses of NE beginning with achiral starting materials. In one example of this approach, Hamada et al. utilized a chiral nickel-catalyzed asymmetric hydrogenation reaction of 1-phenyl-2-aminopropan-1-one to

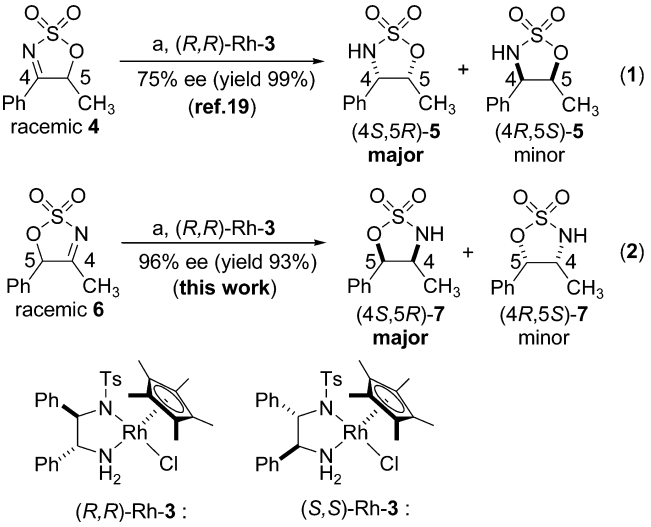
Received: April 30, 2012
Published: May 23, 2012

form (1*R*,2*S*)-NE. This process was carried out using a high pressure hydrogen (100 atm) and was attended by only a modest level of enantioselectivity (76% ee).[13] In another approach, Sharpless asymmetric aminohydroxylation of 1-phenylpropene was utilized to form NPE as only a minor regioisomeric product and with a low level of enantioselectivity (73% ee).[14] Recently, highly efficient and stereoselective synthesis of (1*R*,2*R*)-*N*-pivaloyl-norpseudoephedrine (NPE) by using asymmetric hydrogenation (8 atm of H_2, 64 h), in the presence of (*S*)-TolBINAP/(*R*)-DMAPEN-Ru(II) catalyst, accompanied by dynamic kinetic resolution (92%, dr = 96:4, 99% ee), was disclosed by Ohkuma et al.[15]

Strategies that take advantage of enzyme-catalyzed reactions have also been devised to prepare these targets. For example, a hydroxynitrile lyase mediated nitro-aldol reaction of benzaldehyde with nitroethane was observed to form (1*S*,2*R*)-NE through a sequence involving subsequent reduction of nitro group of the product to an amino group (dr 9:1, 95% ee).[16] Microbiological reduction of 2-azido-1-phenyl-1-propanone, employing *Rhodotorula glutinis*, followed by reduction of the resulting azido alcohols in the presence of $(Boc)_2O$, using Pd/C and H_2, was employed to form a 1:1 mixture of *N*-*Boc*-(1*R*,2*S*)-NE and *N*-*Boc*-(1*R*,2*R*)-NPE with excellent degrees of stereoselectivity.[17] Reduction of 1-phenyl-1,2-propanedione-2-oxime by utilizing Baker's yeast, combined with $LiAlH_4$ reduction, has also been used to generate (*R*,*S*)-NE and (*R*,*R*)-NPE in a 4:1 ratio.[18]

Recently, we described an efficient procedure for the asymmetric transfer hydrogenation (ATH) of prochiral cyclic sulfamidate imines that employs HCO_2H/Et_3N as the hydrogen source and well-defined chiral Rh-complexes as catalysts.[19] In this earlier effort, we discovered that ATH of the racemic 4-phenyl-5-methyl cyclic imine **4**, containing a preexisting stereogenic center, is accompanied by dynamic kinetic resolution (DKR), although the level of stereoselectivity was not high (75% ee, Scheme 1, eq 1). In this study, we also demonstrated

Scheme 1[a]



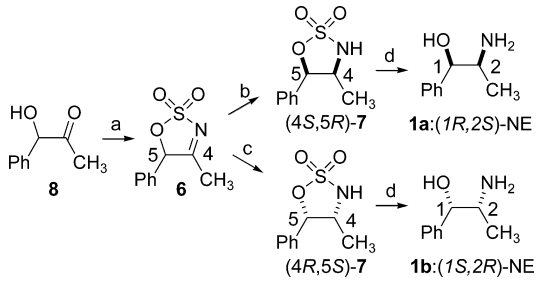
[a](a) HCO_2H/Et_3N, (*R*,*R*)-Rh-**3** catalyst (0.3 mol %), EtOAc, rt, 15 min.

that the C-5 stereogenic center in **4** is configurationally labile, undergoing rapid racemization under the ATH reaction conditions. As a consequence, the absolute stereochemistry of the reduction products is controlled by dynamic kinetic resolution and governed by the chirality of the Rh-catalyst.

In exploring ways to improve the stereochemical performance of ATH-DKR reactions of 4,5-disubstituted cyclic sulfamidate imine **4**, we also observed that introduction of aryl groups in place of alkyl groups at the C-5 stereogenic center leads to drastic improvements of the stereochemical course of the process owing to more rapid racemization at the benzylic position.[20] On the basis of these earlier findings, we envisioned that 4-methyl-5-phenyl cyclic sulfamidate imine **6**, which contains a configurationally labile benzylic C-5 stereogenic center, might react under the ATH-DKR conditions to produce the corresponding 4-methyl-5-phenyl cyclic sulfamidate **7** with a high degree of stereoselectivity. Moreover, we believed that the resulting chiral sulfamidate **7** would serve as a valuable starting material for enantioselective synthesis of both norephedrine (NE) and norpseudoephedrine (NPE). In studies described below aimed at exploring these proposals, we have developed highly stereoselective and efficient syntheses of each enantiomer of NE and NPE from 4-methyl-5-phenyl cyclic sulfamidate **7**, which was prepared using ATH-DKR reaction of **6**.

The requisite cyclic sulfamidate imine **6**, serving as the starting point for the preparative routes, was prepared by reaction of readily available 1-hydroxy-1-phenyl-propan-2-one (**8**) with NH_2SO_2Cl (Scheme 2). Racemic **6** was then subjected

Scheme 2[a]



[a](a) (i) NH_2SO_2Cl, DMA; (ii) cat. PTSA, toluene, 84%; (b) HCO_2H/Et_3N, (*R*,*R*)-Rh-**3** catalyst (0.3 mol %), EtOAc, rt, 15 min, 93%, dr > 25:1, 96% ee (>99% ee after single recrystallization); (c) HCO_2H/Et_3N, (*S*,*S*)-Rh-**3** catalyst (0.3 mol %), EtOAc, rt, 15 min. 99%, dr > 25:1, 96% ee (>99% ee after single recrystallization); (d) $LiAlH_4$, THF, rt, 1 h, 72% for **1a**, 76% for **1b**.

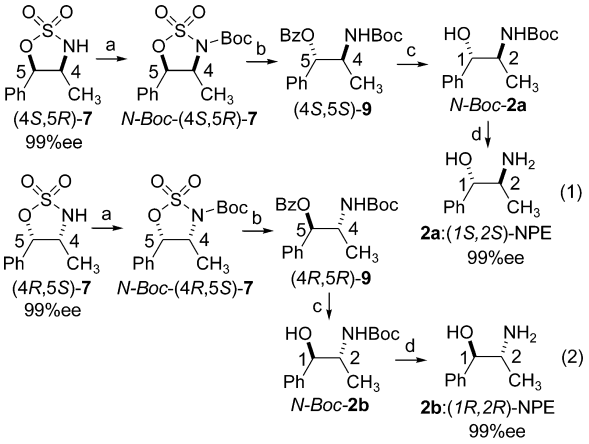
to the ATH-DKR reaction conditions, employing a mixture of HCO_2H/Et_3N as the hydrogen source in the presence of 0.3 mol % of (*R*,*R*)-Rh-**3** catalyst, Cp*RhCl(TsDPEN) (Cp* = pentamethylcyclopentadienyl, TsDPEN = (1*R*,2*R*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine). Significantly, the ensuing reaction takes place with a high level of stereoselectivity (75% ee for **5** to 96% ee for (4*S*,5*R*)-**7**) (Scheme 1, eq 2). None of the 4,5-*trans* sulfamidates are detected in the crude product mixture by using ^1H NMR analysis. Moreover, a single recrystallization of (4*S*,5*R*)-**7** (96% ee) affords enantiomerically pure (4*S*,5*R*)-**7** (>99% ee). The absolute configuration of (4*S*,5*R*)-**7** was confirmed by using X-ray crystallographic analysis[21] (see the Supporting Information). In addition, ATH-DKR reaction of **6** under the same reaction conditions, except employing (*S*,*S*)-Rh-**3** instead of (*R*,*R*)-Rh-**3** as catalyst, was observed to produce the enantiomeric sulfamidate (4*R*,5*S*)-**7** as the major product with a good level of stereoselectivity (96% ee) (Scheme 2). In a similar manner as with (4*S*,5*R*)-**7**, a single recrystallization of (4*R*,5*S*)-**7** (96% ee) affords enantiomerically pure (4*R*,5*S*)-**7** (>99% ee).

dx.doi.org/10.1021/jo300867y | *J. Org. Chem.* 2012, 77, 5454−5460

The cyclic sulfamidate (4*S*,5*R*)-**7** (99% ee) has the same absolute configuration as (1*R*,2*S*)-norephedrine (NE) (**1a**). Consequently, it was treated with $LiAlH_4$ (rt, 1 h) to remove the sulfonyl moiety with retention of stereochemistry at C-4 and C-5 and generate (1*R*,2*S*)-norephedrine (**1a**) (99% ee) (Scheme 2). Under the same reaction conditions, (4*R*,5*S*)-**7** (99% ee) is smoothly converted to (1*S*,2*R*)-norephedrine (**1b**) without deterioration of optical purity (Scheme 2). By using this approach, both enantiomers of norephedrine (**1a** and **1b**) were efficiently (**1a**: 51% overall yield from **8** and **1b**: 57% overall yield from **8**) prepared from the common cyclic imine **6** by using a concise route that takes advantage of highly enantioselective ATH-DKR reactions.

Our attention next turned to the use of this strategy for the synthesis of the norpseudoephedrine enantiomers **2a** and **2b**. It is well-known that cyclic sufamidates, having electron-withdrawing substituents on nitrogen, are highly susceptible to nucleophilic ring-opening at the C-5 carbon.[22,23] Therefore, *N-Boc*-(4*S*,5*R*)-**7** was prepared from the cyclic sulfamidate, (4*S*,5*R*)-**7** (99% ee) (Scheme 3). Subsequent treatment of

Scheme 3[a]



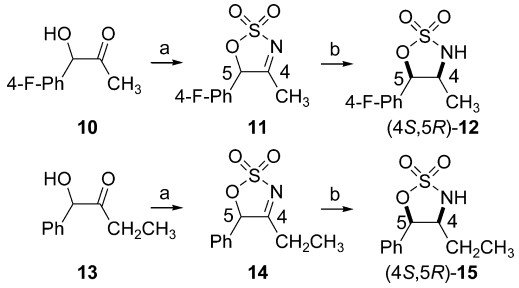
[a](a) $(Boc)_2O$, cat. DMAP, CH_2Cl_2, 96% for *N-Boc*-(4*S*,5*R*)-**7**, 94% for *N-Boc*-(4*R*,5*S*)-**7**; (b) (i) $PhCO_2H$, CsF, DMF, 60 °C, 12 h; (ii) 1 N HCl/CH_2Cl_2, rt, 1 h, 94% for (4*S*,5*S*)-**9**, 91% for (4*R*,5*R*)-**9**; (c) KCN, MeOH, 97% for *N-Boc*-**2a**, 99% for *N-Boc*-**2b**; (d) CF_3CO_2H, CH_2Cl_2, 76% for **2a**, 79% for **2b**.

N-Boc-(4*S*,5*R*)-**7** with benzoic acid[24] in the presence of CsF leads to smooth production (DMF, 60 °C, 12 h, 94%) of *O*-benzoyl-*N-Boc*-(4*S*,5*S*)-**9** with inversion of configuration at C-5. Selective removal of the *O*-benzoyl group in **9** using KCN in MeOH affords *N-Boc*-(1*S*,2*S*)-norpseudoephedrine (*N-Boc*-(1*S*,2*S*)-**2a**). Finally, CF_3CO_2H promoted removal of *N-Boc* group from *N-Boc*-**2a** provides (1*S*,2*S*)-norpseudoephedrine ((1*S*,2*S*)-NPE, **2a**) without deterioration of optical purity (**2a**: 99% ee, 66% overall yield from (4*S*,5*R*)-**7** over 4 steps). Since enantiomerically pure (4*R*,5*S*)-**7** is also readily available (see Scheme 2), enantiomeric (1*R*,2*R*)-norpseudoephedrine ((1*R*,2*R*)-NPE, **2b**) was generated using a nearly identical procedure as that employed to prepare for (1*S*,2*S*)-NPE (**2a**) from (4*S*,5*R*)-**7** (**2b**: 99% ee, 67% overall yield from (4*R*,5*S*)-**7** over 4 steps).

The results of this effort show that all of the enantiomers of norephedrine (**1a** and **1b**) and norpseudoephedrine (**2a** and **2b**) can be obtained in an enantioselective manner (99% ee) from the common, readily available cyclic imine **6** by using the ATH-DKR procedure with (*S*,*S*)- or (*R*,*R*)-Rh-**3** as catalysts and concise synthetic routes (2 steps for NE and 5 steps for NPE from the common cyclic imine **6**).

In an extension of this study, (4*S*,5*R*)-4-methyl-5-(4-fluorophenyl) cyclic sulfamidate **12** and (4*S*,5*R*)-4-ethyl-5-phenyl cyclic sulfamidate **15** were efficiently prepared from the corresponding cyclic imines **11** and **14** with high levels of enantioselectivity using the ATH-DKR procedure described below (Scheme 4). These substances can be used as intermediates in

Scheme 4[a]



[a](a) (i) NH_2SO_2Cl, DMA; (ii) cat. PTSA, toluene, 81% for **11**, 84% for **14**; (b) HCO_2H/Et_3N, (*R*,*R*)-Rh-**3** catalyst (0.3 mol %), EtOAc, rt, 15 min, for **12**: 84% (dr > 25:1, 93% ee), for **15**: 79% (dr > 25:1, 93% ee).

routes for the stereoselective preparation of analogues of norephedrine and norpseudoephedrine that are not observed in nature.

In summary, the investigation described above has led to the development of an efficient, stereoselective procedure for the synthesis of all of the stereoisomers of norephedrine and norpseudoephedrine from readily available, racemic 1-hydroxy-1-phenyl-propan-2-one (**8**). The concise synthetic pathways employed for these purposes take advantage of asymmetric transfer hydrogenation (ATH)[25] reactions of the common prochiral cyclic sulfamidate imine **6**, occurring with dynamic kinetic resolution (DKR)[25] and promoted by using HCO_2H/Et_3N as the hydrogen source and the well-defined chiral Rh-complexes, (*S*,*S*)- or (*R*,*R*)-Cp*RhCl(TsDPEN).

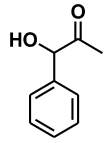
EXPERIMENTAL SECTION

General Methods. Dichloromethane, ether, and THF were dried and purified using a solvent purification system. The formic acid/triethylamine (molar ratio = 5/2) azeotrope is commercially available or can be prepared by the distillation of the formic acid/triethylamine mixture according to the literature procedure.[26] (*S*,*S*)- and (*R*,*R*)-Cp*RhCl(TsDPEN) [(*S*,*S*)- and (*R*,*R*)-Rh-**3**] were prepared from the reaction of $[RhCl_2(pentamethyl\text{-}cyclopentadienyl)]_2$ and (1*S*,2*S*)- or (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine, respectively, in CH_2Cl_2 in the presence of triethylamine, according to the literature procedure.[27] HRMS were measured with electron impact (EI) ionization and double focusing mass analyzer (magnetic and electric fields).

*Representative Experimental Procedure for the Synthesis of 1-Hydroxy-1-phenyl-propan-2-one (**8**).* To a solution of CH_3MgI (55.0 mmol, 3.0 M in ether) in 80 mL ether was added dropwise a solution of 2-phenyl-2-trimethylsilyloxyacetonitrile[28] (5.64 g, 27.5 mmol). The reaction mixture was stirred under reflux for 4 h. After cooling to room temperature, the reaction mixture was poured to 120 g of ice, containing 5 mL of concentrated H_2SO_4. After it was stirred for 8 h, the layers were separated, and the water layer was extracted with ether (40 mL × 2). Combined ether layer was washed with brine and dried with anhydrous $MgSO_4$, and the solvent was evaporated.

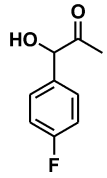
dx.doi.org/10.1021/jo300867y | J. Org. Chem. 2012, 77, 5454−5460

The residue was purified by column chromatography to afford the desired hydroxy ketone **8** (2.9 g, 70%).[29]



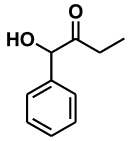
Colorless oil, yield: 70% (2.9 g); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.39 (m, 5H), 5.09 (d, 1H, J = 2.19 Hz), 4.30 (d, 1H, J = 3.3 Hz), 2.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2, 138.1, 129.1, 128.9, 127.5, 80.3, 25.4; HRMS (EI) m/z calcd for $C_9H_{10}O_2$ 150.0681, found 150.0683.

*1-Hydroxy-1-(4-fluoro-phenyl)-propan-2-one (**10**).*



Colorless oil, yield: 84.1% (3.9 g); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26−7.32 (m, 2H), 7.04−7.10 (m, 2H), 5.07 (d, 1H, J = 4.05 Hz), 4.30 (d, 1H, J = 4.11 Hz), 2.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.9, 164.7, 161.4, 133.93, 133.89, 129.3, 129.2, 116.3, 116.0, 79.5, 25.3; HRMS (EI) m/z calcd for $C_9H_9FO_2$ 168.0587, found 168.0586.

*1-Hydroxy-1-phenyl-butan-2-one (**13**).*[30]

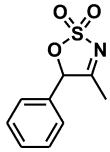


Colorless oil, yield: 84.0%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.29 (m, 5H), 5.09 (d, 1H, J = 4.26 Hz), 4.35 (d, 1H, J = 4.35 Hz), 2.43−2.28 (q, 2H, J = 7.8 Hz), 1.00 (t, 3H, J = 7.32 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.07, 138.26, 128.88, 128.56, 127.27, 79.40, 31.09, 7.55.

Synthesis of Sulfamoyl Chloride (NH_2SO_2Cl). Anhydrous formic acid (40.0 mmol, 1.5 mL) was added dropwise to neat chlorosulfonyl isocyanate (40.0 mmol, 3.5 mL) at 0 °C with rapid stirring. Vigorous gas evolution was observed during the addition process. The resulting viscous suspension was stirred at room temperature until gas evolution ceased (1−2 h). The resulting white solid was stored in a refrigerator and stable for more than 3 months at −15 °C.

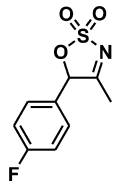
Representative Experimental Procedure for the Synthesis of Cyclic Sulfamidate Imine from Hydroxyl-Ketone. Sulfamoyl chloride (924 mg, 8.0 mmol) was added portionwise to a solution of 1-hydroxy-1-phenyl-propan-2-one (**8**) (600 mg, 4.0 mmol) in DMA (10 mL) with stirring. After stirring at room temperature for 1 h, the reaction mixture was diluted with EtOAc (50 mL) and washed with brine. The solvent was removed, the residue was dissolved in toluene, and *p*-toluenesulfonic acid (0.1 equiv) was added. The reaction mixture was heated to reflux temperature for 0.5 h with azeotropic removal of water (this step can be carried out in the open air without Dean−Stark apparatus). After cooling to room temperature, the reaction mixture was diluted with EtOAc (50 mL) and washed with saturated $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$ and evaporated, and then the residue was purified by column chromatography on silica gel to give the desired imine **6** (710 mg, 84.1%).

*4-Methyl-5-phenyl-5H-[1,2,3]oxathiazole 2,2-dioxide (**6**).*



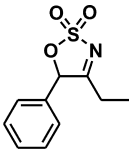
White solid, yield: 84.1% (710 mg); mp 61−65 °C; ATR-FTIR, ν (cm^{-1}) 1625, 1363, 1355, 1191; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.52 (m, 3H), 7.37−7.39 (m, 2H), 6.03 (s, 1H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.4, 131.2, 131.0, 129.9, 127.5, 91.7, 17.5; HRMS (EI) m/z calcd for $C_9H_9NO_3S$ 211.0303, found 211.0308.

*5-(4-Fluoro-phenyl)-4-methyl-5H-[1,2,3]oxathiazole 2,2-dioxide (**11**).*



White solid, yield: 80.7% (740 mg); mp 106−107 °C; ATR-FTIR, ν (cm^{-1}) 1512, 1366, 1355, 1191, 1159; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.40 (m, 2H), 7.18−7.22 (m, 2H), 6.05 (s, 1H), 2.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.0, 165.0, 163.0, 129.6, 129.6, 127.05, 127.02, 117.1, 116.9, 90.7, 17.4; HRMS (EI) m/z calcd for $C_9H_8FNO_3S$ 229.0209, found 229.0217.

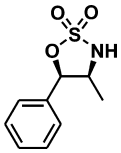
*4-Ethyl-5-phenyl-5H-[1,2,3]oxathiazole 2,2-dioxide (**14**).*



Colorless oil, yield: 84% (756 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.48 (m, 3H), 7.34−7.36 (m, 2H), 6.04 (s, 1H), 2.30−2.52 (m, 2H), 1.21 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.7, 131.5, 130.9, 129.8, 127.5, 91.2, 24.8, 9.4; HRMS (EI) m/z calcd for $C_{10}H_{11}NO_3S$ 225.0460, found 225.0458.

Representative Experimental Procedure for Asymmetric Transfer Hydrogenation of Cyclic Imines. To the cyclic imine **6** (410.2 mg, 1.94 mmol) in EtOAc (20 mL) was added (*R*,*R*)-Cp*RhCl(TsDPEN) ((*R*,*R*)-Rh-**3**) (3.7 mg, 0.3 mol %), and then an azeotropic mixture of HCO_2H/Et_3N (molar ratio = 5:2, 2 mL) was added via a syringe. After stirring at room temperature for 15 min, the reaction mixture was diluted with EtOAc (20 mL) and washed with water (3 × 30 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated, and then the residue was purified by column chromatography on silica gel to give the desired cyclic sulfamidate (4*S*,5*R*)-**7** (386 mg, 93.2%).

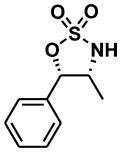
*(4S,5R)-4-Methyl-5-phenyl-[1,2,3]oxathiazolidine 2,2-dioxide, (**4S,5R**)-**7**.*



White soild, yield: 93.2% (386 mg); mp 101−104 °C; 96.1% ee (Chiralcel AD-H, 10% isopropanol/hexanes, 1.5 mL/min, 254 nm, t_R(minor) = 9.1 min, t_R(major) = 10.6 min); $[\alpha]_D^{21}$ = −30.9 (c 0.3, CH_3OH); ATR-FTIR, ν (cm^{-1}) 3212, 1337, 1177, 1139; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.49 (m, 3H), 7.36−7.38 (m, 2H), 5.84 (d, 1H, J = 5.8 Hz), 4.33−4.41 (m, 2H), 1.02 (d, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.1, 129.5, 129.1, 126.1, 88.3, 56.3, 15.7; HRMS (EI) m/z calcd for $C_9H_{11}NO_3S$ 213.0460, found 213.0464.

A single recrystallization (EtOAc/*n*-hexane) of (4*S*,5*R*)-**7** (96.1% ee) afforded the optically pure (84%, >99% ee) product.

*(4R,5S)-4-Methyl-5-phenyl-[1,2,3]oxathiazolidine 2,2-dioxide, (**4R,5S**)-**7**.*



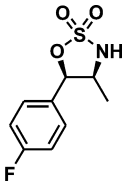
White soild, yield: 99.6% (412 mg); mp 102−104 °C; 96.4% ee (Chiralcel AD-H, 10% isopropanol/hexanes, 1.5 mL/min, 254 nm,

dx.doi.org/10.1021/jo300867y | *J. Org. Chem.* 2012, 77, 5454−5460

t_R(major) = 9.1 min, t_R(minor) = 10.6 min); $[\alpha]_D^{22}$ = +33.0 (*c* 0.3, CH_3OH); ATR-FTIR, ν (cm^{-1}) 3212, 1336, 1176, 1139; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44−7.48 (m, 3H), 7.36−7.40 (m, 2H), 5.84 (d, 1H, *J* = 5.7 Hz), 4.32−4.40 (m, 2H), 1.02 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.1, 129.5, 129.1, 126.1, 88.2, 56.2, 15.7; HRMS (EI) *m*/*z* calcd for $C_9H_{11}NO_3S$ 213.0460, found 213.0463.

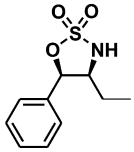
A single recrystallization (EtOAc/*n*-hexane) of (4*R*,5*S*)-7 (96.4% ee) afforded the optically pure (90%, >99% ee) product.

(4S,5R)-5-(4-Fluoro-phenyl)-4-methyl-[1,2,3]oxathiazolidine 2,2-dioxide, ***(4S,5R)-12****.*



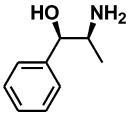
White soild, yield: 83.8% (376 mg); mp 112−114 °C; 92.8% ee (Chiralcel AD-H, 10% isopropanol/hexanes, 1.5 mL/min, 254 nm, t_R(minor) = 9.3 min, t_R(major) = 12.1 min); $[\alpha]_D^{22}$ = −18.0 (*c* 0.3, CH_3OH); ATR-FTIR, ν (cm^{-1}) 3223, 1340, 1179, 1168, 1137; ^1H NMR (500 MHz, CD_3OD) δ 7.41−7.46 (m, 2H), 7.13−7.19 (m, 2H), 5.83 (d, 1H, *J* = 6.2 Hz), 4.24−4.28 (m, 1H), 0.91 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 166.2, 162.9, 131.90, 131.86, 130.0, 129.9, 116.7, 116.4, 89.0, 57.0, 15.4; HRMS (EI) *m*/*z* calcd for $C_9H_{10}FNO_3S$ 231.0365, found 231.0372.

(4S,5R)-4-Ethyl-5-phenyl-[1,2,3]oxathiazolidine 2,2-dioxide, ***(4S,5R)-15****.*



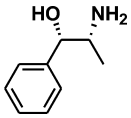
White soild, yield: 79.0% (327 mg); mp 115−116 °C; 93.4% ee (Chiralcel AD-H, 10% isopropanol/hexanes, 1.0 mL/min, 254 nm, t_R(minor) = 12.0 min, t_R(major) = 13.8 min); $[\alpha]_D^{22}$ = −31.9 (*c* 0.3, CH_3OH); ATR-FTIR, ν (cm^{-1}) 3221, 1339, 1179, 1139, 1123; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.46 (m, 5H), 5.85 (d, 1H, *J* = 6.0 Hz), 4.56 (br, d, 1H, *J* = 8.7 Hz), 4.09−4.13 (m, 1H), 1.16−1.31 (m, 2H), 0.95 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.3, 129.5, 129.0, 126.3, 88.3, 62.4, 23.3, 11.1; HRMS (EI) *m*/*z* calcd for $C_{10}H_{13}NO_3S$ 227.0616, found 227.0624.

Synthesis of Norephedrine. *(1R,2S)-2-Amino-1-phenyl-propan-1-ol,* ***(1R,2S)-1a****, [(1R,2S)-(−)-Norephedrine].* To a suspension of $LiAlH_4$ (2 M solution in THF, 630 μL, 3 equiv) in THF (1.5 mL), (4*S*,5*R*)-7 (90.0 mg, 0.42 mmol, >99% ee) in THF (3 mL) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 1 h, and then 1 N HCl was added. The mixture was stirred at 60 °C for 1 h and then cooled to room temperature. 1 N NaOH was added, and aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (CH_2Cl_2/MeOH = 1:1) to give the product as white solid (42 mg, 71.5%).



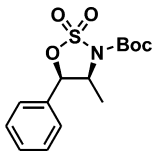
White solid, yield: 71.5% (42 mg); mp 51−53 °C; >99% ee (Chiralcel AD-H, 10% isopropanol/hexanes, 1.0 mL/min, 254 nm, t_R(minor) = 8.3 min, t_R(major) = 16.4 min); $[\alpha]_D^{22}$ = −15.1 (*c* 0.3, CH_3OH), lit.[31] $[\alpha]_D^{26}$ = −14.5 (*c* 1.2, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ 7.29−7.40 (m, 5H), 4.57 (d, 1H, *J* = 4.8 Hz), 3.22−3.26 (m, 1H), 1.00 (d, 3H, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 128.2, 127.5, 126.5, 77.5, 51.9, 18.2; HRMS (EI) *m*/*z* calcd for $C_9H_{13}NO$ 151.0997, found 151.0994.

(1S,2R)-2-Amino-1-phenyl-propan-1-ol, ***(1S,2R)-1b****, [(1S,2R)-(+)-Norephedrine].*



From >99% ee of (4*R*,5*S*)-7. White solid, yield: 75.6% (48 mg); mp 50−53 °C; >99% ee (Chiralcel AD-H, 10% isopropanol/hexanes, 1.0 mL/min, 254 nm, t_R(major) = 8.3 min, t_R(minor) = 16.4 min); $[\alpha]_D^{22}$ = +16.9 (*c* 0.6, CH_3OH), lit.[31] $[\alpha]_D^{26}$ = +14.0 (*c* 1.2, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.27−7.35 (m, 5H), 4.52 (d, 1H, *J* = 4.8 Hz), 3.15−3.23 (m, 1H), 1.78(br, s, 3H), 0.96 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.6, 128.3, 127.6, 126.7, 77.7, 52.0, 18.4; HRMS (EI) *m*/*z* calcd for $C_9H_{13}NO$ 151.0997, found 151.0995.

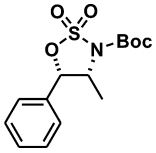
Synthesis of Norpseudoephedine. *(4S,5R)-4-Methyl-2,2-dioxo-5-phenyl-2*λ^6*-[1,2,3]oxathiazolidine-3-carboxylic Acid tert-Butyl Ester,* ***N-Boc-(4S,5R)-7****.*



(4*S*,5*R*)-7 (50.3 mg, 0.24 mmol, >99% ee) was dissolved in dry CH_2Cl_2. Boc_2O (103 mg, 0.48 mmol) and DMAP (3 mg, 0.02 mmol) were added, and the mixture was stirred at room temperature for 10 min. After removal of the solvent, the residue was purified by column chromatography (*n*-hexane/EA = 10:1) to give the product as white solid (72.4 mg, 96.3%).

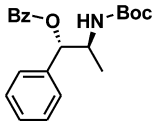
White soild, yield: 96.3% (72.4 mg); mp 102−105 °C; >99% ee (Chiralcel AD-H, 30% isopropanol/hexanes, 1.0 mL/min, 254 nm, t_R(major) = 4.6 min, t_R(minor) = 7.3 min); $[\alpha]_D^{24}$ = −53.0 (*c* 0.3, CH_3OH); ATR-FTIR, ν (cm^{-1}) 2989, 1730, 1364, 1327, 1185; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44−7.48 (m, 3H), 7.34−7.35 (m, 2H), 5.99 (d, 1H, *J* = 5.2 Hz), 4.59−4.61 (m, 1H), 1.61 (s, 9H), 1.11 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 131.5, 129.5, 129.1, 125.5, 85.6, 82.4, 58.7, 28.1, 14.4; HRMS (EI) *m*/*z* calcd for $C_{14}H_{19}NO_5S$ 313.0984, found 313.0950.

(4R,5S)-4-Methyl-2,2-dioxo-5-phenyl-2λ^6*-[1,2,3]oxathiazolidine-3-carboxylic Acid tert-Butyl Ester,* ***N-Boc-(4R,5S)-7****.*



White soild, yield: 94.0% (71 mg); mp 101−104 °C; >99% ee (Chiralcel AD-H, 30% isopropanol/hexanes, 1.0 mL/min, 254 nm, t_R(minor) = 4.6 min, t_R(major) = 7.3 min); $[\alpha]_D^{22}$ = +51.2 (*c* 0.3, CH_3OH); ATR-FTIR, ν (cm^{-1}) 2991, 1730, 1364, 1327, 1185; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.46 (m, 3H), 7.30−7.33 (m, 2H), 5.96 (d, 1H, *J* = 5.2 Hz), 4.56−4.59 (m, 1H), 1.58 (s, 9H), 1.08 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 131.5, 129.5, 129.1, 125.5, 85.6, 82.4, 58.7, 28.1, 14.4; HRMS (EI) *m*/*z* calcd for $C_{14}H_{19}NO_5S$ 313.0984, found 313.0980.

(4S,5S)-2-(tert-Butoxycarbonyl-amino)-1-(benzoyl-oxy)-1-phenyl-propane, ***(4S,5S)-9****.*



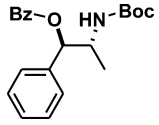
The mixture of ***N-Boc-*****(4*S*,5*R*)-7** (30 mg, 0.10 mmol), CsF (22 mg, 0.14 mmol) and benzoic acid (18 mg, 0.14 mmol) in DMF (1 mL) was stirred at 60 °C for 12 h. After evaporating of the solvent, the residue was dissolved in the mixture of 1 N HCl (3 mL) and CH_2Cl_2 (3 mL). The resulting solution was stirred at room temperature for 1 h. The reaction mixture was basified by addition of saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 three times and then

dx.doi.org/10.1021/jo300867y | J. Org. Chem. 2012, 77, 5454−5460

washed with brine. The combined organic layers were dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (*n*-hexane/EA = 5:1) to give the product as white solid (32 mg, 93.7%).

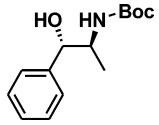
Yield: 93.7% (32 mg); mp 77−80 °C; >99% ee (Chiralcel AD-H, 40% isopropanol/hexanes, 1.0 mL/min, 254 nm, t_R(major) = 6.8 min, t_R(minor) = 15.6 min); $[\alpha]_D^{23}$ = −14.7 (*c* 0.3, CH_3OH); ATR-FTIR, ν (cm^{-1}) 3378, 2977, 1719, 1683, 1521, 1272; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, 2H, *J* = 7.3 Hz), 7.32−7.60 (m, 8H), 5.86−5.87 (m, 1H), 4.56−4.60 (m, 1H), 4.34−4.33 (m, 1H), 1.34 (s, 9H), 1.14 (d, 3H, *J* = 5.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 155.3, 137.8, 133.1, 130.0, 129.9, 128.5, 128.4, 127.2, 79.4, 79.2, 50.2, 28.3, 17.7; HRMS (EI) *m*/*z* calcd for $C_{21}H_{25}NO_4$ 355.1784, found 355.1775.

(4R,5R)-2-(tert-Butoxycarbonyl-amino)-1-(benzoyl-oxy)-1-phenyl-propane, ***(4R,5R)-9****.*



Yield: 91.0% (129 mg); mp 77−80 °C; >99% ee (Chiralcel AD-H, 40% isopropanol/hexanes, 1.0 mL/min, 254 nm, t_R(minor) = 6.8 min, t_R(major) = 15.6 min); $[\alpha]_D^{24}$ = +15.2 (*c* 0.3, CH_3OH); ATR-FTIR, ν (cm^{-1}) 3366, 2976, 1702, 1683, 1508, 1268; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09−8.12 (m, 2 Hz), 7.30−7.56 (m, 8H), 5.82−5.85 (m, 1H), 4.54 (m, 1H), 4.28−4.31 (m, 1H), 1.32 (s, 9H), 1.12 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 155.4, 137.9, 133.2, 130.1, 130.0, 128.6, 128.5, 127.3, 79.5, 79.3, 50.3, 28.4, 17.9; HRMS (EI) *m*/*z* calcd for $C_{21}H_{25}NO_4$ 355.1784, found 355.1786.

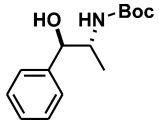
(1S,2S)-2-(tert-Butoxycarbonyl-amino)-1-phenyl-propan-1-ol, ***N-Boc-(1S,2S)-2a****.*



KCN (15.4 mg, 0.24 mmol) was added to a stirred solution of (**4*S*,5*S*)-9** (168.0 mg, 0.47 mmol) in MeOH (5 mL). The resulting mixture was stirred at 65 °C for 4 h. After removal of the solvent, the residue was dissolved in CH_2Cl_2 and then washed with water. The combined organic layers were dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (*n*-hexane/EA = 3:1) to give the product as colorless oil (114.3 mg, 96.8%).

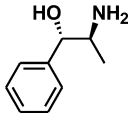
Yield: 96.8% (114.3 mg), >99% ee (Chiralcel AD-H, 30% isopropanol/hexanes, 1.0 mL/min, 254 nm, t_R(major) = 4.5 min, t_R(minor) = 6.2 min); $[\alpha]_D^{21}$ = +37.8 (*c* 0.5, $CHCl_3$), lit.[32] $[\alpha]_D^{21}$ = +34.1 (*c* 0.05, $CHCl_3$); ATR-FTIR, ν (cm^{-1}) 3394, 2975, 1677, 1508, 1247, 1162; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27−7.35 (m, 5H), 4.66 (br, s, 1H), 4.54−4.57 (m, 1H), 3.83−3.90 (m, 1H), 3.20 (br, s, 1H), 1.41 (s, 9H), 1.07 (s, 3H, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 141.8, 128.4, 127.9, 126.7, 79.9, 78.2, 52.6, 28.5, 17.7; HRMS (EI) *m*/*z* calcd for $C_{14}H_{21}NO_3$ 251.1521, found 251.1547.

(1R,2R)-2-(tert-Butoxycarbonyl-amino)-1-phenyl-propan-1-ol, ***N-Boc-(1R,2R)-2b****.*



Yield: 98.8% (117 mg), >99% ee (Chiralcel AD-H, 30% isopropanol/hexanes, 1.0 mL/min, 254 nm, t_R(minor) = 4.5 min, t_R(major) = 6.2 min); $[\alpha]_D^{24}$ = −40.7 (*c* 0.5, $CHCl_3$); ATR-FTIR, ν (cm^{-1}) 3398, 2975, 1685, 1498, 1247, 1165; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28−7.35 (m, 5H), 4.65 (br, s, 1H), 4.54−4.57 (m, 1H), 3.83−3.90 (m, 1H), 3.15 (br, s, 1H), 1.41 (s, 9H), 1.08 (s, 3H, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 141.7, 128.3, 127.7, 126.6, 79.7, 78.0, 52.5, 28.3, 17.6; HRMS (EI) *m*/*z* calcd for $C_{14}H_{21}NO_3$ 251.1521, found 251.1533.

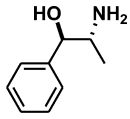
(1S,2S)-2-Amino-1-phenyl-propan-1-ol, ***(1S,2S)-2a****, [(1S,2S)-(+)-Norpseudoephedrine].*



To a solution of ***N*-Boc-(1*S*,2*S*)-2a** (143.2 mg, 0.59 mmol) in CH_2Cl_2 (6 mL), trifluoroacetic acid (230 μL, 2.99 mmol) was added dropwise at room temperature. The reaction mixture was stirred at room temperature overnight. The reaction mixture was basified with 1 N NaOH, and aqueous layer was extracted with CH_2Cl_2 five times. The combined organic layers were dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (CH_2Cl_2/MeOH = 1:1) to give the product as white solid (65.7 mg, 76.2%).

White solid, yield: 76.2% (65.7 mg); mp 70−72 °C; >99% ee (Chiralcel AD-H, 0.1/5/95 Et_3N/isopropanol/hexanes (v/v/v), 1.2 mL/min, 254 nm, t_R(major) = 12.5 min, t_R(minor) = 13.9 min); $[\alpha]_D^{22}$ = +33.4 (*c* 0.3, EtOH), lit.[33] $[\alpha]_D^{22}$ = +34.0 (*c* 3.5, EtOH), lit.[34] $[\alpha]_D^{22}$ = +31.8 (*c* 3.49, EtOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.26−7.35 (m, 5H), 4.20 (d, 1H, *J* = 6.6 Hz), 2.96−3.00 (m, 1H), 2.27 (br, s, 3H), 0.97 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 128.4, 127.6, 126.7, 78.8, 53.0, 20.4; HRMS (EI) *m*/*z* calcd for $C_9H_{13}NO$ 151.0997, found 151.0990.

(1R,2R)-2-Amino-1-phenyl-propan-1-ol, ***(1R,2R)-2b****, [(1R,2R)-(−)-Norpseudoephedrine].*



White solid, yield: 79.4% (71 mg); mp 69−71 °C; >99% ee (Chiralcel AD-H, 0.1/5/95 Et_3N/isopropanol/hexanes (v/v/v), 1.2 mL/min, 254 nm, t_R(minor) = 12.5 min, t_R(major) = 13.9 min); $[\alpha]_D^{24}$ = −31.3 (*c* 0.3, EtOH), lit.[33] $[\alpha]_D^{22}$ = −34.0 (*c* 3.5, EtOH), lit.[34] $[\alpha]_D^{22}$ = −31.4 (*c* 3.49, EtOH); ^1H NMR (500 MHz, $CDCl_3$) δ 7.29−7.36 (m, 5H), 4.25 (d, 1H, *J* = 6.6 Hz), 3.01−3.06 (m, 1H), 2.23 (br, s, 3H), 1.04 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 128.4, 127.7, 126.7, 78.8, 53.1, 20.6; HRMS (EI) *m*/*z* calcd for $C_9H_{13}NO$ 151.0997, found 151.0996.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds and X-ray crystallography data for (4*S*,5*R*)-7. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This investigation was supported by grants from the Expansion of Original Compound Library and System Management (TS113-02) by the Ministry of Knowledge Economy (MKE) of Korea and the Korea Research Institute of Chemical Technology.

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