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Highly Efficient, Enantioselective Syntheses of (*S*)-(+)- and (*R*)-(−)-Dapoxetine Starting with 3-Phenyl-1-propanol

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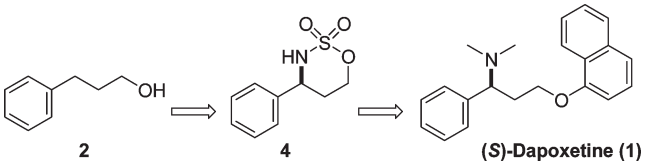

A highly efficient, enantioselective sequence has been developed for the synthesis of (*S*)- and (*R*)-dapoxetine. The pathways involve the intermediacy of the 6-membered-ring sulfamate esters **4**, which were generated by Du Bois asymmetric C−H amination reactions of the prochiral sulfamate **3**, catalyzed by the chiral dirhodium(II) complexes. During the course of our research, the absolute configuration of the enantiomer of 4-pheny[1,2,3]oxathiazinane 2,2-dioxide (**4r**), prepared by the Du Bois asymmetric C−H amination reaction of **3** and the Rh_2(*S*-nap)$_4$ catalyst, is determined to be *R* and not *S* as was originally reported.

Selective serotonin reuptake inhibitors (SSRIs) are a class of compounds typically used for the treatment of depression and anxiety disorder.[1] Among these substances, Fluoxetine (Prozac),[1c,1d] Paroxetine (Paxil),[1e] and Sertraline (Zoloft)[1f] are widely prescribed for depression and other psychiatric disorders, such as bulimia and anxiety (Figure 1). Recently, it has been suggested that premature ejaculation (PE) might be associated with perturbation of serotonergic 5-hydroxytryptamine (5-HT) neurotransmission.[2] Although PE is a non-life-threatening condition, along with erectile dysfunction it is one of the most common male sexual disorders, which could cause elevated levels of anxiety and have a negative impact on the quality of an individual's life and that of their partner. (*S*)-(+)-Dapoxetine hydrochloride (**1**; (*S*)-(+)-*N*,*N*-dimethyl-[3-(naphthalen-1-yloxy)-1-phenylpropyl]amine; Priligy),[3] a potent SSRI with a short half-life, has been developed specifically for the treatment of PE. This substance was first launched in 2009 in Europe where it is used for the oral, on-demand treatment of PE in men between 18 and 64 years of age.

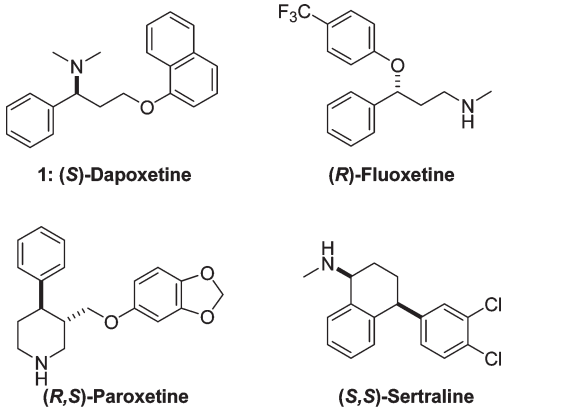

FIGURE 1. Examples of selective serotonin reuptake inhibitors (SSRIs).

In the context of drug development, selective syntheses of individual enantiomers of targets are extremely important since the antipodes usually display different pharmacological and/or physiological properties.[4] For example, (*S*)-dapoxetine is 3.5 times more potent as an SSRI than is (*R*)-dapoxetine.[5] Previously (*S*)-dapoxetine was produced from a racemic mixture of dapoxetine by means of tartaric acid promoted chiral resolution of a racemic mixture. An alternative synthesis of (*S*)-dapoxetine, starting from (*R*)-1-phenyl-1,3-propandiol and selective displacement of the secondary alcohol moiety with dimethylamine, was described.[6] Another route for the preparation of (*S*)-(+)-dapoxetine, beginning with chiral 1,3-amino alcohols that are obtained by enzyme-catalyzed resolution of racemic 1,3-amino alcohols, has also been reported.[7] However, each of the reported methods for the synthesis of (*S*)-(+)-dapoxetine have the intrinsic disadvantage that the undesired (*R*)-enantiomer is discarded or recycled after racemization. Consequently, the development of an efficient and enantioselective synthesis of (*S*)-dapoxetine is highly desirable.

Only a few strategies are currently available for the asymmetric synthesis of (*S*)-(+)-dapoxetine. The first

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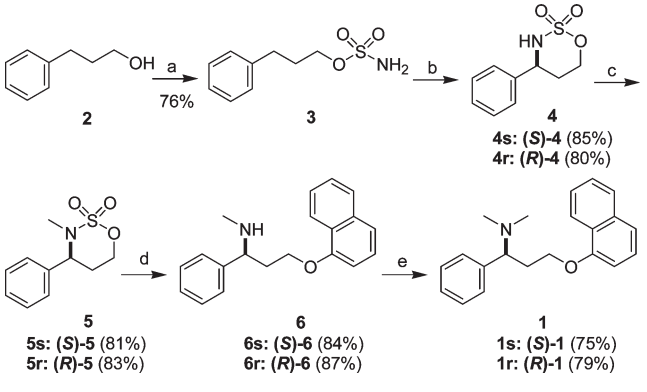
asymmetric synthesis of (*S*)-(+)-dapoxetine hydrochloride and its ^{14}C-isotopomer, beginning with (*R*)-*N*-*Boc*-phenylglycine, was described by a research group at Lilly.[8] Recently, stereoselective syntheses of (*S*)-(+)-dapoxetine from *trans*-methyl cinnamate[9] and cinnamyl alcohol,[10] employing respective Sharpless asymmetric dihydroxylation and epoxidation processes in key steps, were developed. Unfortunately, both of these routes are long (9 to 10 steps) and they require a radical deoxygenation step to remove the undesired hydroxyl group and a non-atom-economic Mitsunobu reaction to introduce the 1-naphthol moiety. A formal synthesis of (*S*)-(+)-dapoxetine from enantiopure 3-hydroxyazetidine-2-one was described in a recent paper.[11] However, this route also required radical deoxygenation and Mitsunobu reaction steps.

As part of ongoing studies aimed at the synthesis of antidepressant SSRIs, we have uncovered a highly efficient and enantioselective syntheses of the (*S*)-(+)- and (*R*)-(−)-enantiomers of dapoxetine starting with the readily available 3-phenyl-1-propanol (**2**). The routes, described below, involve intermediate 6-membered-ring sulfamate esters **4**, which were prepared by chiral dirhodium(II) complex catalyzed Du Bois asymmetric C−H amination reactions of a prochiral sulfamate (**3**).[12a]

Recently, Du Bois and his co-workers described a novel method for the enantioselctive synthesis of the cyclic sulfamate ester **4** by using an asymmetric C−H amination reaction of the prochiral sulfamate ester **3**, catalyzed by a chiral valerolactam-derived, dirhodium(II) complex.[12a] The 6-membered-ring oxathiazinanes **4**, possessing both a chiral carbon that bears an amine moiety and cyclic sulfamidate group, which is reactive with various nucleophiles, are extremely valuable precursors of 1,3-functionalized amine derivatives including 1,3-amino alcohols and dapoxetine derivatives. Consequently, we employed the Du Bois methodology to prepare the requisite sulfamate ester **4** by using the Rh_2(*S*-nap)$_4$-catalyzed C−H amination reaction of **3**. This process produced the alleged (*S*)-sulfamate ester **4r** in a 80% yield and 92.6% ee. However, contrary to the original proposal,[12a] the absolute configuration of **4r** ($[\alpha]^{27}_D$ +6.14 (*c* 1.0, $CHCl_3$)) was shown by us to be *R* (vide infra).

SCHEME 1. Synthetic Process to Dapoxetine (1) from 3-Phenyl-1-propanol (2)[a]



[a]Reagents and conditinos: (a) $ClSO_2NH_2$, DMA, 0 °C to rt; (b) 2 mol % Rh_2(*S*-nap)$_4$ or Rh_2(*R*-nap)$_4$, PhI=O, 4 Å MS, CH_2Cl_2, rt; (c) CH_3I, K_2CO_3, cat. TBAI, DMF, 0 °C to rt; (d) NaH, 1-naphthol, DMF then 5 M HCl, rt; (e) HCO_2H, HCOH, reflux.

With the cyclic sulfamate ester **4r** in hand, completion of the route to dapoxetine (**1r**) was straightforward (Scheme 1). Methylation of the supposed (*S*)-sulfamate ester **4r** with CH_3I affords the cyclic *N*-methyl-sulfamate ester **5r** (83% yield, 91.1% ee). Subsequent reaction of **5r** with 1-naphthol in the presence of base smoothly produced *N*-methyl-[3-(naphthalen-1-yloxy)-1-phenylpropyl]amine (**6r**) in good yield (87% yield, 92.5% ee). Finally, reductive amination of **6r**, under Eschweiler−Clarke conditions[9] with formaldehyde and formic acid as the hydrogen source, gave dapoxetine (**1r**) in good yield (79%) and a 91.2% ee (determined by using chiral HPLC). ^{1}H and ^{13}C NMR spectroscopic and HRMS data for the synthetic dapoxetine matched those previously reported for this substance. However, surprisingly the sign of the optical rotation of the synthetic dapoxetine ($[\alpha]^{28}_D$ −67.0 (*c* 0.3, $CHCl_3$)) was opposite to the reported value ($[\alpha]^{25}_D$ +64.2 (*c* 0.3, $CHCl_3$),[9] +61.7 (*c* 0.3, $CHCl_3$),[10] +62.5 (*c* 0.3, $CHCl_3$)[7a]). Consequently, we concluded that we had prepared (*R*)-(−)-dapoxetine rather than its (*S*)-(+)-enantiomer. Since it was virtually impossible that the configuration of the chiral carbon atom bearing the amine moiety had changed during the execution of the sequence shown in Scheme 1, we doubted the assignment of absolute configuration to the cyclic sulfamate ester **4r**, which was proposed to have the *S*-configuration when prepared with the Rh_2(*S*-nap)$_4$ Du Bois catalyst.[12a]

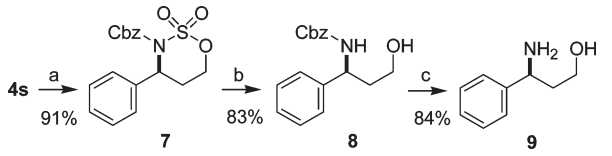
To make the correct absolute configuration assignment to **4r**, we prepared both enantiomers **4s** and **4r** starting with **3** and the enantiomeric Rh_2(*S*-nap)$_4$ and Rh_2(*R*-nap)$_4$ catalysts and employing essentially the same reaction conditions described by Du Bois and his co-workers.[12a] The unknown Rh_2(*R*-nap)$_4$ catalyst was generated by reaction between $Rh_2(OAc)_4$ and (*R*)-3-tosylaminovalerolactam, which was obtained from unnatural D-(−)-ornithine hydrochloride in a manner that is similar to the procedure employed for the preparation of Rh_2(*S*-nap)$_4$ catalyst from L-(+)-ornithine hydrochloride by Du Bois and his co-workers.[12a,15] The synthesized Rh_2(*R*-nap)$_4$ catalyst has essentially the same ^{1}H NMR spectroscopic and optical properties of Rh_2(*S*-nap)$_4$ except for the sign of the optical rotation ($[\alpha]^{29}_D$ −70.5 (*c* 0.2, $CHCl_3$) for Rh_2(*R*-nap)$_4$ and $[\alpha]^{27}_D$ +71.5 (*c* 0.2, $CHCl_3$) for Rh_2(*S*-nap)$_4$). Treatment of the prochiral sulfamate ester **3** with PhI=O and Rh_2(*R*-nap)$_4$ catalyst smoothly afforded the antipodal cyclic sulfamate ester **4s** ($[\alpha]^{27}_D$ −6.0 (*c* 1.0, $CHCl_3$), 85% yield, 91.7% ee). The physical data of **4s**, generated from **3** by using the Rh_2(*R*-nap)$_4$ catalyst, are essentially the same as those of **4r**. However, the sign of the optical rotation and the chiral HPLC column (Chiralcel OD-H, 8% isopropanol/hexane) eluting order of

(8) Wheeler, W. J.; O'Bannon, D. D. *J. Labelled Compd. Radiopharm.* **1992**, *XXXI*, 305.
(9) Siddiqui, S. A.; Srinivasan, K. V. *Tetrahedron: Asymmetry* **2007**, *18*, 2099.
(10) Venkatesan, K.; Srinivasan, K. V. *ARKIVOC* **2008**, *xvi*, 302.
(11) Chincholkar, P. M.; Kale, A. S.; Gumaste, V. K.; Deshmukh, A. R. A. S. *Tetrahedron* **2009**, *65*, 2605.
(12) (a) Zalatan, D. N.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 9220. (b) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935.
(13) (*S*)-3-Amino-3-phenylpropan-1-ol (98% ee, 95%) was purchased from Acros Organics (http://www.acros.com), Catalog No. 36217.
(14) Tse, M. K.; Bhor, S.; Klawonn, M.; Anilkumar, G.; Jiao, H.; Dobler, C.; Spannenberg, A.; Magerlein, W.; Hugl, H.; Beller, M. *Chem.—Eur. J.* **2006**, *12*, 1855.
(15) Maguire, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 948.

the **4s** and **4r** are opposite each other. Therefore, **4s** and **4r** prepared from **3** by using the respective $Rh_2(R\text{-nap})_4$ and $Rh_2(S\text{-nap})_4$ catalysts are enantiomers.

The absolute configuration of the enantiomer of **4s** synthesized with $Rh_2(R\text{-nap})_4$ was determined by converting it to commercially available (*S*)-3-amino-3-phenylpropan-1-ol (**9**)[13] by the route shown in Scheme 2.

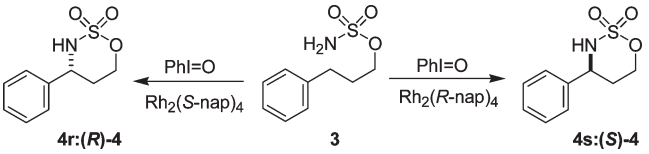
SCHEME 2. Conversion of 4s to the Known 1,3-Amino Alcohol 9[a]



[a]Reagents and conditions: (a) NaO^{t}Bu, Cbz-Cl, DME; (b) CH_3CN/H_2O, 75 °C then 1 N HCl, rt; (c) H_2/Pd−C, EtOAc.

As expected, the optical and spectroscopic properties of **9** ($[\alpha]^{28}_D$ −20.4 (*c* 0.44, $CHCl_3$), 93% ee), generated from this enantiomer of **4s**, are essentially identical with those of commercial (*S*)-**9**[13] ($[\alpha]^{27}_D$ −22.0 (*c* 0.40, $CHCl_3$), 98% ee) as well as those reported originally[14] for the latter substance ($[\alpha]^{27}_D$ −22.5 (*c* 0.5, CH_2Cl_2), 100% ee). These findings enable us to assign the *S* configuration to the major enantiomer of **4s** produced by C−H amination catalyzed by $Rh_2(R\text{-nap})_4$ and the *R* configuration to the antipode **4r** produced by using the $Rh_2(S\text{-nap})_4$ catalyst (Scheme 3).

SCHEME 3. (*R*)-4 and (*S*)-4 from Du Bois Asymmetric C−H Amination Reaction of 3 with Respective $Rh_2(S\text{-nap})_4$ and $Rh_2(R\text{-nap})_4$ Catalysts



The absolute configuration of 4-phenyl[1,2,3]oxathiazinane 2,2-dioxide (**4r**) was confirmed to be *R* by X-ray crystallographic analysis[16] (see the Supporting Information).

These findings demonstrate that the cyclic (*S*)-sulfamate ester **4s** was required for an (*S*)-(+)-dapoxetine synthesis following the plan described in Scheme 1. With the (*S*)-sulfamate ester **4s**, which was obtained from the prochiral sulfamate ester **3** with PhI=O and $Rh_2(R\text{-nap})_4$ catalyst, the route to (*S*)-dapoxetine (**1s**) was straightforward. Methylation of **4s** with CH_3I afforded the *N*-methyl cyclic sulfamate ester **5s** (81% yield, 92.0% ee) and subsequent reaction with 1-naphthol in the presence of NaH in DMF smoothly generated *N*-methyl-[3-(naphthalen-1-yloxy)-1-phenylpropyl]amine (**6s**) (84% yield, 91.2% ee). Finally, reductive amination of **6s** under Eschweiler−Clarke conditions gave (*S*)-dapoxetine **1s** (75% yield, 91.8% ee). Reductive amination of **6s** with $Na(CN)BH_3$ and formaldehyde also led to efficient production of **1s**. ^1H and ^{13}C NMR spectroscopic data of synthetic **1s**, including the magnitude and sign of the optical rotation ($[\alpha]^{28}_D$ +63.2 (*c* 0.3, $CHCl_3$), lit. $[\alpha]^{25}_D$ +64.2 (*c* 0.3, $CHCl_3$),[9] +61.7 (*c* 0.3, $CHCl_3$),[10] +62.5 (*c* 0.3, $CHCl_3$)[7a]), were in perfect agreement with those previously reported for this substance. The overall sequence for the synthesis of (*S*)-(+)-dapoxetine (**1s**) is highly efficient taking place in a greater than 33% overall yield over five synthetic steps beginning with readily available 3-phenyl-1-propanol (**2**).

In conclusion, a highly efficient (33% and 34% overall yields and 5 steps) and enantioselective strategy has been developed for the synthesis of (*S*)-(+)- and (*R*)-(−)-dapoxetine starting from 3-phenyl-1-propanol (**2**). The routes proceeded through the intermediacy of 6-membered-ring sulfamate esters **4s** and **4r**, which were prepared by Du Bois asymmetric C−H amination reactions of prochiral sulfamate **3** catalyzed by the respective chiral valerolactam-derived dirhodium(II) complexes, $Rh_2(R\text{-nap})_4$ or $Rh_2(S\text{-nap})_4$. Subsequent *N*-methylation reactions of **4s** and **4r**, followed by nucleophilic substitution reactions of the resulting cyclic sulfamate esters **5** with 1-naphthol and final *N*-methylations of **6**, smoothly afforded (*S*)-(+)- or (*R*)-(−)-dapoxetine, respectively.

During the course of our research, the absolute configuration of the enantiomer of 4-pheny[1,2,3]oxathiazinane 2,2-dioxide (**4r**), prepared by Du Bois asymmetric C−H amination reaction of the sulfamate ester **3** and the $Rh_2(S\text{-nap})_4$ catalyst, was determined to be *R* and not *S* as was originally reported. The correct absolute configuration assignment was made by comparing the optical properties of 3-amino-3-phenylpropan-1-ol (**9**), prepared from **4s**, with those of the commercially available substance. In addition, the absolute configuration of **4r** was determined by using X-ray crystallographic analysis.

Experimental Section

(*S*)-4-Phenyl[1,2,3]oxathiazinane 2,2-Dioxide: (*S*)-4. A mixture of sulfamate **3** (200 mg, 0.9 mmol), $Rh_2(R\text{-nap})_4$ (24 mg, 0.02 mmol), and powdered 4 Å molecular sieves (500 mg) was suspended in dry dichloromethane (2.0 mL). A single portion of PhI=O (240 mg, 1.1 mmol) was then added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was loaded directly onto silica gel and purified by flash chromatography (*n*-hexane:ethyl acetate = 4:1) to afford the desired product (168 mg, 85%) as a white crystal: 91.7% ee (Chiralcel OD-H, 8% isopropanol/hexanes, 1.0 mL/min, 210 nm, t_r(major) = 27.9 min, t_r(minor) = 33.9 min); $[\alpha]^{36}_D$ −6.0 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.44 (m, 5H), 4.82−4.90 (m, 2H), 4.62−4.68 (m, 1H), 4.40 (br d, 1H, *J* = 9.2 Hz), 2.18−2.33 (m, 1H), 1.98−2.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 129.2, 128.9, 126.3, 71.9, 59.0, 30.2; HRMS (EI) *m*/*z* calcd for $C_9H_{11}NO_3S$ 213.0460, found 213.0462.

(*S*)-3-Methyl-4-phenyl[1,2,3]oxathiazinane 2,2-Dioxide: (*S*)-5. To a solution of (*S*)-**4** (154 mg, 0.72 mmol) in DMF (3 mL) were added CH_3I (93 μL, 1.5 mmol), K_2CO_3 (122 mg, 0.88 mmol), and a catalytic amount of *n*-Bu_4NI at 0 °C and the mixture was stirred at rt for 6 h. The reaction mixture was diluted with ethyl acetate (30 mL) and H_2O (15 mL). The biphasic solution was extracted with ethyl acetate (3 times). The combined organic layer was washed successively with water and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give a residue that was subjected to flash chromatography on silica gel (*n*-hexane:ethyl acetate = 10:1) to afford the desired product (81%) as a white crystal: 92.0% ee (Chiralcel OD-H, 10% isopropanol/hexanes, 1.2 mL/min, 210 nm, t_r(major) = 18.5 min, t_r(minor) = 15.6 min); $[\alpha]^{28}_D$ −3.0 (*c* 0.3, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.41 (m, 5H), 4.76−4.85 (m, 2H), 4.55−4.58 (m, 1H), 2.46−2.55 (m, 1H), 2.49 (s, 3H), 1.88−1.91 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$)

(16) (a) Thompson, A. L.; Watkin, D. J. *Tetrahedron: Asymmetry* **2009**, *20*, 712. (b) Flack, H. D.; Bernardinelli, G. *Chirality* **2008**, *20*, 681.

δ 137.5, 129.3, 129.0, 127.6, 71.7, 64.3, 32.6, 28.1; HRMS (EI) *m*/*z* calcd for $C_{10}H_{13}NO_3S$ 227.0616, found 227.0611.

(*S*)-Methyl[3-(naphthalen-1-yloxy)-1-phenylpropyl]amine: (*S*)-6. The mixture of 1-naphtol (140 mg, 0.97 mmol) and NaH (42 mg, 0.97 mmol) in DMF (1 mL) was stirred at rt for 10 min. A solution of (*S*)-**5** (111 mg, 0.49 mmol) in DMF (1 mL) was added to a reaction mixture and stirred at rt for 1 h. HCl (1 M, 1.5 mL, 5 equiv) was added and the mixture was stirred at rt for 2 h, then basified with 2 M NaOH. The reaction mixture was diluted with ethyl acetate (10 mL) and H_2O (5 mL). The biphasic solution was extracted with ethyl acetate (3 times). The combined organic layer was washed successively with water and brine, and dried over anhydrous $MgSO_4$, and concentrated in vacuo to give a residue that was subjected to flash chromatography on silica gel (dichloromethane:methanol = 10:1) to afford the desired product (120 mg, 84%) as an orange oil: 91.2% ee (Chiralcel OD-H, 2% isopropanol/hexanes, 1.2 mL/min, 210 nm, t_r(major) = 12.6 min, t_r(minor) = 10.0 min); $[\alpha]^{28}_D$ +60.3 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24−8.26 (m, 1H), 7.78−7.80 (m, 1H), 7.46−7.51 (m, 2H), 7.39−7.41 (m, 1H), 7.25−7.34 (m, 7H), 6.70 (d, 1H, *J* = 7.5 Hz), 4.13−4.17 (m, 1H), 3.97−4.02 (m, 1H), 3.90−3.92 (m, 1H), 2.41−2.47 (m, 1H), 2.33 (s, 3H), 2.17−2.2 3 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 134.6, 128.8, 127.59, 127.55, 127.5, 126.5, 126.1, 126.0, 125.8, 125.3, 122.1, 120.3, 104.7, 65.5, 62.8, 37.2, 34.4; HRMS (EI) *m*/*z* calcd for $C_{20}H_{21}NO$ 291.1623, found 291.1622.

(*S*)-Dimethyl[3-(naphthalen-1-yloxy)-1-phenylpropyl]amine: (*S*)-1. To a solution of (*S*)-**6** (54 mg, 0.19 mmol) in formic acid (38 μL, 1.0 mmol) was added a 30% aqueous solution of formaldehyde (100 μL, 1.0 mmol) and the reaction mixture was refluxed for 8 h. After this time the solution was acidified with concd HCl until pH 1 and basified with 4 N NaOH. The reaction mixture was diluted with ethyl acetate and washed with aqueous $NaHCO_3$ solution. The organic phase was separated and dried over $MgSO_4$. After evaporation of solvent the crude residue was purified by flash chromatography (*n*-hexane:ethyl acetate = 1:3) to afford the desired product (42.5 mg, 75%) as a colorless oil: 91.8% ee (Chiralcel OD-H, 2% isopropanol/hexanes, 0.7 mL/min, 210 nm, t_r(major) = 10.1 min, t_r(minor) = 8.9 min); $[\alpha]^{28}_D$ +63.2 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26−8.28 (m, 1H), 7.79−7.81 (m, 1H), 7.28−7.52 (m,10H), 6.67 (d, 1H, *J* = 7.5 Hz), 4.07−4.12 (m, 1H), 3.91−3.95 (m, 1H), 3.62−3.65 (m, 1H), 2.63−2.70 (m, 1H), 2.26−2.34 (m, 1H), 2.28 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 139.7, 134.7, 128.8, 128.4, 127.6, 127.5, 126.5, 126.1, 125.9, 125.3, 122.2, 120.2, 104.8, 67.9 (1C, C_3), 65.8 (1C, C_1), 43.0 (2C, $C_4 + C_{4'}$), 33.2 (1C, C_2); HRMS (EI) *m*/*z* calcd for $C_{21}H_{23}NO$ 305.1780, found 305.1765.

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Supporting Information Available: Characterization data for all new compounds including copies of ^{1}H, ^{13}C NMR spectra and chromatograms for the determination of enantiomeric excess of all chiral compounds on chiral HPLC, and X-ray crystallography data of **4r** with a cif file. This material is available free of charge via the Internet at http://pubs.acs.org.