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Stereoselective Amination of Chiral Benzylic Ethers Using Chlorosulfonyl Isocyanate: Total Synthesis of (+)-Sertraline

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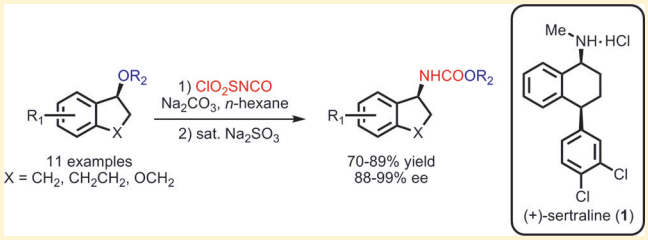
Supporting Information

ABSTRACT: The stereoselective amination of various chiral benzylic ethers using chlorosulfonyl isocyanate is developed, and the application of this method to the total synthesis of a potent antidepressant, (+)-sertraline, from readily available 1-naphthol is also described.



INTRODUCTION

Compounds with amine functionality at the C-1 position of an indane or tetraline framework have received considerable attention as potential medical agents because of their interesting pharmacological properties (Figure 1).[1] For example, (+)-sertraline (Zoloft) has become the most frequently prescribed agent for the treatment of depression due to its selective inhibition of the reuptake of human synaptosomal serotonin.[2] (+)-Indatraline (Lu-19005) has been used as a nonselective monoamine transporter inhibitor to block the reuptake of dopamine, norepinephrine, and serotonin.[3] Rasagiline (Azilect) is a drug for the treatment of Parkinson's disease.[4] Also, indinavir is a component of highly active antiretroviral therapy to treat HIV infections and AIDS,[5] and irindalone exhibits antihypertensive effects via the selective blocking of the 5-HT$_2$ receptor.[6]

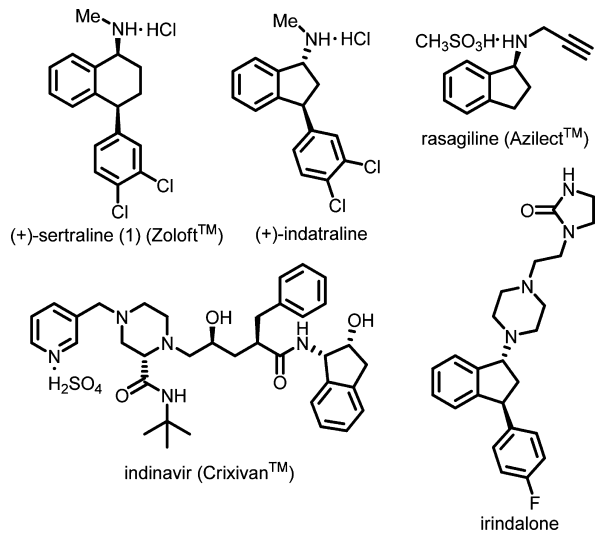


Figure 1. Biologically active compounds containing 1-amino indane or tetraline scaffold.

In particular, (+)-sertraline (**1**), commercialized by Pfizer in 1991, is primarily used to treat major depression in adult outpatients as well as compulsive, panic, and social anxiety disorders. The commercial production of (+)-sertraline relies on the resolution of racemic mixtures prepared from D-mandelic acid.[7] Due to its potent pharmacological activities and unique structural features, several synthetic approaches for (+)-sertraline have been developed. The majority of synthetic strategies are classified into four large categories: asymmetric reduction of ketimines,[8] asymmetric arylation,[9] the construction of functionalized tetraline,[10] and the use of chiral starting material.[11] As part of an ongoing research program aimed at the development of a new methodology using chlorosulfonyl isocyanate (CSI),[12] and its application to the total syntheses of biologically active natural products,[13] we recently reported the regioselective allylic amination of cyclic allylic ethers using chlorosulfonyl isocyanate to give cyclic allylic amine compounds.[14] In connection with our previous work on the regioselective amination of racemic cyclic allylic ethers using CSI, we became interested in developing an efficient synthetic route for the introduction of a chiral amine moiety to the benzylic position of the tetraline ring. Herein, we describe stereoselective amination of a variety of chiral cyclic ethers using CSI and its application to the total synthesis of (+)-sertraline (**1**).

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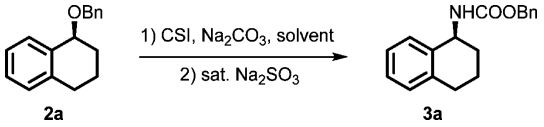
Table 1. Optimization of the Reaction of 2a with CSI[a]



2a 3a

entry	solvent	temp (°C)	yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	0	77	74
2	toluene	0	75	78
3	CCl_4	0	73	81
4	*n*-hexane	0	71	89
5	*n*-hexane	−20	74	94
6	*n*-hexane	−40	78	96

[a]Reaction conditions: **2a** (0.6 mmol), CSI (150 mol %), Na_2CO_3 (300 mol %), solvent (6 mL) for 10 h under N_2. [b]The cited yields are of material isolated by silica gel chromatography. [c]Enantiomeric excess (% ee) was determined by chiral stationary phase HPLC analysis.

RESULTS AND DISCUSSION

The initial study focused on the reaction of (*S*)-1-benzyloxy-1,2,3,4-tetrahydronaphthalene (**2a**) with CSI to optimize the chemical yield and the enantioselectivity, as shown in Table 1. The coupling of **2a** and CSI in methylene chloride at 0 °C furnished the corresponding carbamate **3a** in 77% yield and moderate enantioselectivity (74% ee) (Table 1, entry 1). Solvent screening showed that the highest enantioselectivity (89% ee) could be obtained with *n*-hexane solvent, providing the desired product **3a** in 71% yield (Table 1, entry 4), whereas the use of other solvents such as toluene and CCl_4 was relatively ineffective. In particular, the reaction between **2a** and CSI in *n*-hexane at −40 °C afforded the desired product **3a** in 78% yield with excellent enantioselectivity (96% ee), as shown in entry 6. These results reveal that the stereochemistry is retained more so in nonpolar solvents and at low temperature.

To explore the substrate scope and limitations of this process, the established reaction conditions were applied to benzylic ethers **2b** and **2c** and bicyclic benzylic ethers **2d**−**2k**, as shown in Table 2. Treatment of benzylic ethers **2b** and **2c** with CSI afforded the corresponding carbamates **3b** and **3c** in good yields with high enantioselectivities (Table 2, entries 2 and 3). A variety of bicyclic benzyl ethers **2d**−**2i** were well converted to the corresponding products **3d**−**3i** in high yields (75−89%) with high enantioselectivities (88−98% ee), respectively (Table 2, entries 4−9). However, (*S*)-1-(benzyloxy)-5-methyl-2,3-dihydro-1*H*-indene (**2f**) gave decreased enantioselectivity (88% ee) presumably due to the increased carbocation stability by the *para*-methyl group in the transition state (Table 2, entry 6). In addition, 1,2-*anti*-dibenzyloxy indane **2j** and tetraline **2k** led to the formation of the C-1 adducts **3j** and **3k** with excellent regioselectivity and diastereoselectivity (>99% de) (Table 2, entries 10 and 11).

A plausible reaction mechanism is outlined in Scheme 1. The initial attack by the oxygen of benzyl ether to CSI delivers an oxonium ion **I**, which can be converted to a major compound **3a** by S_Ni mechanism through a four-centered transition structure **IIa**. This observation is consistent with the formation of a tight ion pair in nonpolar *n*-hexane solvent, compared to relatively polar dichloromethane solvent. Another plausible S_N1 mechanism can be in competition with the S_Ni mechanism. However, S_N1 mechanism may partially proceed due to the incomplete orbital overlap between p orbital of the benzene ring and p orbital of benzylic sp^2 carbocation in the reaction intermediate **IIb**.

On the basis of the above results, the total synthesis of (+)-sertraline (**1**) was achieved from commercially available 1-naphthol (**4**), as shown in Scheme 2. The condensation of 1-naphthol (**4**) with an excess of 1,2-dichlorobenzene at 100 °C using anhydrous $AlCl_3$ afforded the ketone **5** in 82% yield,[15] which was diastereoselectively converted to the chiral alcohol **7** in 48% yield with excellent enantioselectivity (99% ee) by use of (*R*)-(+)-2-methyl-CBS-oxazaborolidine catalyst **6** and *N*,*N*-diethylaniline borane as reducing agent.[16] Benzylation of the alcohol **7** under standard conditions (benzyl bromide and NaH in anhydrous THF and DMF) proceeded cleanly to afford the compound **8** in 82% yield. Treatment of the compound **8** with chlorosulfonyl isocyanate and sodium carbonate in anhydrous *n*-hexane at −40 °C for 40 h, followed by reduction of the *N*-chlorosulfonyl group with an aqueous sodium sulfite solution furnished the desired carbamate **9** in 80% yield with excellent diastereoselectivity (>99% de).

In order to obtain the target compound **1**, we first tried to reduce the carbamate **9** under $LiAlH_4$ or $LiAlH(OMe)_3$. However, the direct reduction of the carbamate **9** proved to be problematic since $LiAlH_4$ and $LiAlH(OMe)_3$ partially reduced the aromatic chloride to give a mixture of the desired product **1** and byproducts. In view of these unsuccessful results, we turned our attention to the methylation of the carbamate **9** and subsequent deprotection of the Cbz group. Treatment of **9** with methyl iodide and sodium hydride in anhydrous THF and DMF furnished the compound **10** in 99% yield. Finally, removal of the Cbz group by Raney Ni-catalyzed hydrogenolysis afforded (+)-sertraline (**1**) as a HCl salt form. The spectroscopic data and specific rotation of **1** were identical to those reported in the literature.[2b,10,17]

CONCLUSION

In conclusion, we have described a regioselective and stereoselective introduction of an NHCbz group into chiral benzylic ethers using chlorosulfonyl isocyanate (CSI) in the ring system. Furthermore, we have demonstrated the application of this methodology to the total synthesis of (+)-sertraline, which was achieved in six steps (19% overall yield) from 1-naphthol. We believe that this synthetic protocol will be useful for the preparation of various biologically active natural products and drugs containing amino indane, amino tetraline, and cyclic amine moieties.

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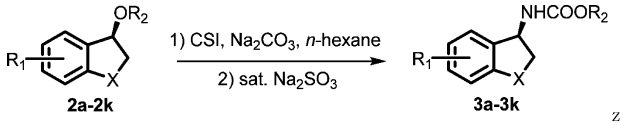
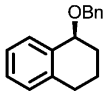
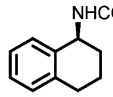
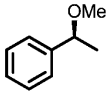
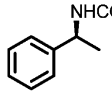
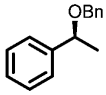
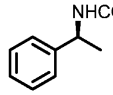
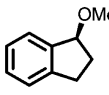
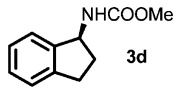
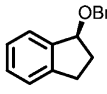
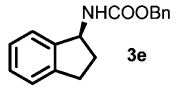
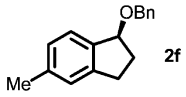
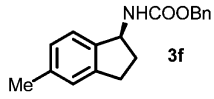
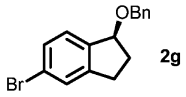
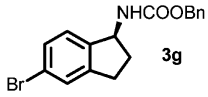
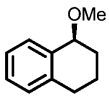
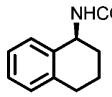
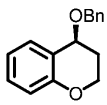
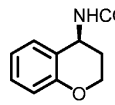
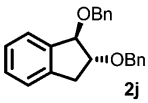
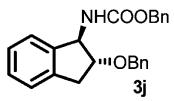
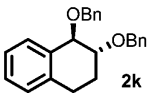
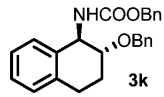
Table 2. Reaction of Chiral Benzylic Ethers with CSI[a]



entry	substrate	product	yield (%)[b]	ee (%)[c]
1	 2a	 3a	78	96
2	 2b	 3b	70	99
3	 2c	 3c	70	96
4	 2d	 3d	86	96
5	 2e	 3e	89	97
6	 2f	 3f	80	88
7	 2g	 3g	80	94
8	 2h	 3h	83	97
9	 2i	 3i	75	98
10	 2j	 3j	75	> 99[d]
11	 2k	 3k	85	> 99[d]

[a]Reaction conditions: **2a**−**2k** (0.6 mmol), CSI (150 mol %), Na_2CO_3 (300 mol %), *n*-hexane (6 mL) at −40 °C for 10 h under N_2. Chiral ethers **2a**−**2k** above 99% ee were used, except for **2f** (97% ee), **2g** (98% ee), and **2i** (98% ee). Absolute configurations of substrates and products were confirmed by comparison with literature data. [b]The cited yields are of material isolated by silica gel chromatography. [c]Enantiomeric excess (% ee) was determined by chiral stationary phase HPLC analysis. [d]Diastereomeric excess (% de) was determined by chiral stationary phase HPLC and ^{1}H NMR analysis.

EXPERIMENTAL SECTION

General Information. All chemicals and solvents were of laboratory grade from commercial suppliers and were used without further purification. All reactions were performed under an inert atmosphere of nitrogen. Silica gel chromatography was performed with silica gel 60 (particle size 40−63 μm). Nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded either on 300 or 500 MHz spectrometers for $CDCl_3$ solutions and chemical shifts are reported as parts per million (ppm) relative to, respectively, residual TMS δ_H (0.00 ppm) and $CDCl_3$ δ_C (77.0 ppm) as internal standards. Resonance patterns are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In addition, the notation br is used to indicate a broad signal. Coupling constants (*J*) are reported in hertz (Hz). IR spectra were recorded on Infrared spectrophotometer and are reported as cm^{-1}. Liquid chromatography mass spectral analyses (LC/MS) were measured using ESI ionization. High-resolution mass spectral analyses (HRMS) were measured using EI, CI, or FAB ionization. High-performance liquid chromatography (HPLC) analyses were performed on chiral columns. Optical rotations were measured in the solvent indicated.

General Procedure for the Synthesis of Chiral Benzylic Alcohols (i–vi).[16] To a stirred mixture of (*R*)-(+)-2-methyl-CBS-oxazaborolidine catalyst (0.35 mmol) in anhydrous toluene (9.5 mL) was added *N*,*N*-diethylaniline borane (11.66 mmol) at 25 °C. Ketone (5.83 mmol) in anhydrous toluene (9.5 mL) was slowly added with the aid

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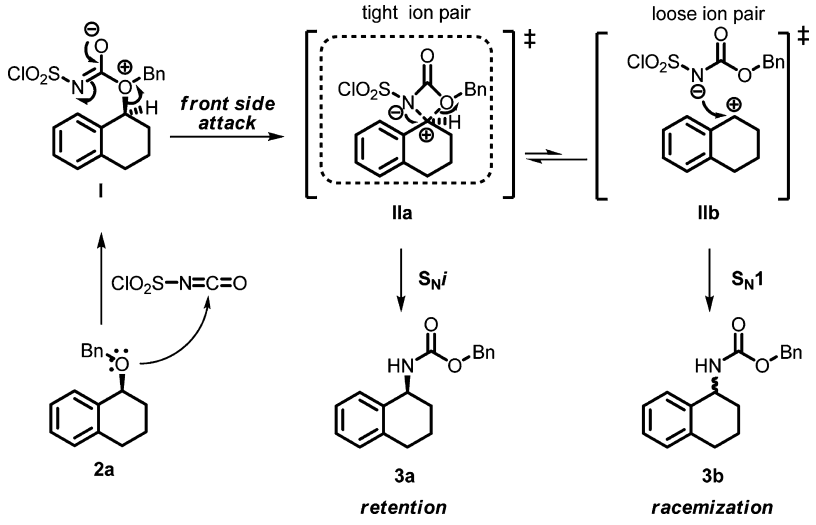
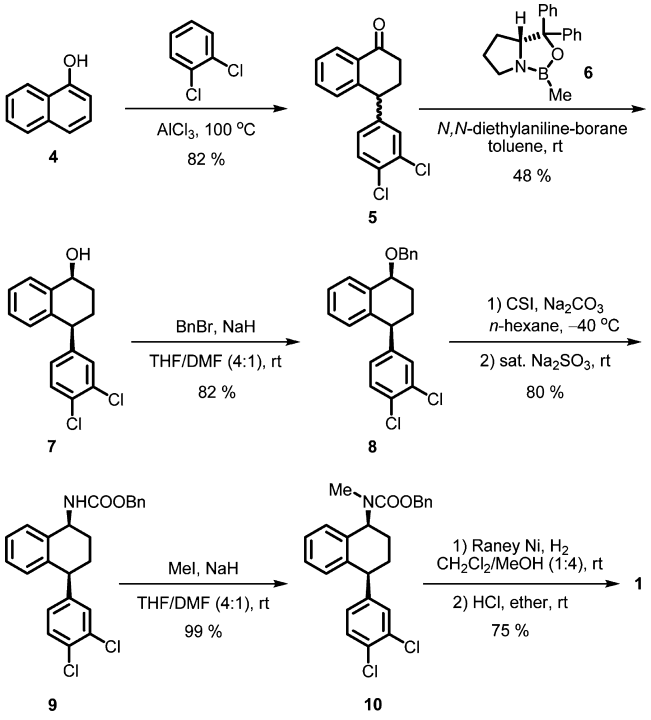
Scheme 1. Proposed Reaction Mechanism (S_Ni vs S_N1)



Scheme 2. Total Synthesis of (+)-Sertraline (1)



of a syringe pump over 3 h, and the resulting mixture was stirred at 25 °C for 1 h under N_2. The reaction mixture was carefully quenched with MeOH (1 mL) and 1 N HCl (1 mL) and then extracted with EtOAc (2 × 30 mL). The organic layer washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc) to afford chiral benzylic alcohol.

(S)-1,2,3,4-Tetrahydronaphthalen-1-ol (i): white solid; yield = 80%; R_f = 0.31 (*n*-hexane/EtOAc = 6/1); $[\alpha]^{26}_D$ +34.0 (*c* 1.0, $CHCl_3$), lit.[18] $[\alpha]^{27}_D$ +33.9 (*c* 1.13, $CHCl_3$); mp 38–40 °C; IR (neat) υ 3345, 2936, 2865, 1454, 1204, 1068, 739 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.65 (d, *J* = 6.9 Hz, 1H), 1.74–1.84 (m, 1H), 1.88–2.04 (m, 3H), 2.68–2.89 (m, 2H), 4.79 (t, *J* = 4.53 Hz, 1H), 7.09–7.13 (m, 1H), 7.18–7.24 (m, 2H), 7.42–7.45 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.8, 29.2, 32.3, 68.2, 126.2, 127.6, 128.7, 129.0, 137.1, 138.9; LC/MS (ESI) *m*/*z* 171.23 $(M + Na)^+$; HPLC (Chiralcel OD-RH column, $CH_3CN:H_2O$ = 10:90 to 100:0, 1.0 mL/min, 265 nm) R_t (major) = 12.49 min, R_t (minor) = 12.83 min; ee = 99%.

(S)-1-Phenylethanol (ii): colorless oil; yield = 80%; R_f = 0.16 (*n*-hexane/EtOAc = 5/1); $[\alpha]^{25}_D$ −50.0 (*c* 1.0, $CHCl_3$); lit.[19] $[\alpha]^{20}_D$ −39.2 (*c* 2.54, $CHCl_3$); IR (neat) υ 3359, 2974, 2927, 1495, 1452, 1369, 1078, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (d, *J* = 6.5 Hz, 3H), 1.82 (br s, 1H), 4.90 (q, *J* = 6.5 Hz, 1H), 7.27–7.40 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.0, 70.0, 125.3, 127.2, 128.3, 145.7; LC/MS (ESI) *m*/*z* 123.08 $(M + H)^+$; HPLC (Chiralcel OD column, *n*-hexane:*i*-PrOH = 95:5, 0.6 mL/min, 257 nm) R_t (minor) = 13.37 min, R_t (major) = 16.36 min; ee = 99%.

(S)-2,3-Dihydro-1H-inden-1-ol (iii): white solid; yield = 71%; R_f = 0.28 (*n*-hexane/EtOAc = 4/1); $[\alpha]^{25}_D$ +30.6 (*c* 1.0, $CHCl_3$), lit.[20] $[\alpha]^{22}_D$ +29.3 (*c* 0.97, $CHCl_3$); mp 69–72 °C; IR (neat) υ 3344, 2941, 1614, 1490, 1255, 1035, 894 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.72 (d, *J* = 6.9 Hz, 1H), 1.90–2.00 (m, 1H), 2.44–2.55 (m, 1H), 2.77–2.88 (m, 1H), 3.02–3.11 (m, 1H), 5.25 (q, *J* = 6.9 Hz, 1H), 7.23–7.26 (m, 3H), 7.41–7.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.8, 36.0, 76.5, 124.2, 124.9, 126.7, 128.3, 143.1, 145.0; LC/MS (ESI) *m*/*z* 157.00 $(M + Na)^+$; HPLC (Chiralcel OD-RH column, $CH_3CN:H_2O$ = 10:90 to 100:0, 1.0 mL/min, 265 nm) R_t (major) = 10.97 min, R_t (minor) = 11.18 min; ee = 99%.

(S)-5-Methyl-2,3-dihydro-1H-inden-1-ol (iv): white solid; yield = 90%; R_f = 0.26 (*n*-hexane/EtOAc = 4/1); $[\alpha]^{25}_D$ +31.2 (*c* 1.0, $CHCl_3$); mp 75–78 °C; IR (neat) υ 3218, 2912, 2847, 1470, 1446, 1408, 1063, 818 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.79 (br s, 1H), 1.88–1.99 (m, 1H), 2.35 (s, 3H), 2.40–2.52 (m, 1H), 2.72–2.82 (m, 1H), 2.97–3.07 (m, 1H), 5.20 (t, *J* = 6.6 Hz, 1H), 7.05 (d, *J* = 2.7 Hz, 1H), 7.07 (s, 1H), 7.29 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 29.6, 36.1, 76.2, 123.9, 125.5, 127.5, 138.2, 142.2, 143.6; LC/MS (ESI) *m*/*z* 171.09 $(M + Na)^+$; HRMS (CI) calcd for $C_{10}H_{11}O$ $(M - H)^+$ 147.0810, found 147.0809; HPLC (Chiralcel OD-RH column, $CH_3CN:H_2O$ = 20:80, 1.0 mL/min, 270 nm) R_t (major) = 19.96 min, R_t (minor) = 22.17 min; ee = 97%.

(S)-5-Bromo-2,3-dihydro-1H-inden-1-ol (v): white solid; yield = 89%; R_f = 0.24 (*n*-hexane/EtOAc = 4/1); $[\alpha]^{25}_D$ +75.1 (*c* 0.33, $CHCl_3$); mp 108–110 °C; IR (neat) υ 3310, 2964, 2920, 2846, 1340, 1309, 1053, 811 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.88–1.99 (m, 2H), 2.42–2.53 (m, 1H), 2.74–2.85 (m, 1H), 2.97–3.07 (m, 1H), 5.18 (t, *J* = 6.6 Hz, 1H), 7.26 (d, *J* = 2.7 Hz, 1H), 7.34 (s, 1H), 7.37 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.6, 36.0, 75.8, 122.2, 125.7, 128.0, 129.8, 143.9, 145.6; LC/MS (ESI) *m*/*z* 235.17 $(M + Na)^+$; HRMS (CI) calcd for $C_9H_{10}BrO$ $(M + H)^+$ 212.9915, found 212.9916; HPLC (Chiralcel OD-RH column, $CH_3CN:H_2O$ = 35:65, 1.0 mL/min, 265 nm) R_t (major) = 7.35 min, R_t (minor) = 8.28 min; ee = 98%.

(S)-Chroman-4-ol (vi): white solid; yield = 83%; R_f = 0.18 (*n*-hexane/EtOAc = 4/1); $[\alpha]^{25}_D$ −66.9 (*c* 1.0, $CHCl_3$), lit.[18] $[\alpha]^{22}_D$ −62.0 (*c* 1.8, $CHCl_3$); mp 73–76 °C ; IR (neat) υ 3383, 2954, 2928,

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2882, 1611, 1585, 1252, 1063, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.97−2.11 (m, 3H), 4.22 (d, J = 3.9 Hz, 1H), 4.23 (dd, J = 3.0, 1.2 Hz, 1H), 4.76 (q, J = 5.1 Hz, 1H), 6.83 (d, J = 8.1 Hz, 1H), 6.90 (dt, J = 6.6, 0.9 Hz, 1H), 7.20 (dt, J = 9.0, 1.5 Hz, 1H), 7.29 (dd, J = 7.5, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.8, 61.9, 63.2, 117.0, 120.5, 124.3, 129.7, 129.7, 154.5; LC/MS (ESI) m/z 173.27 $(M + Na)^+$; HRMS (CI) calcd for $C_9H_{11}O_2$ $(M + H)^+$ 151.0759, found 151.0760; HPLC (Chiralcel OD-RH column, CH_3CN:H_2O = 10:90, 1.0 mL/min, 225 nm) R_t (major) = 21.74 min, R_t (minor) = 26.67 min; ee = 98%.

*General Procedure for the Synthesis of Chiral Benzylic Ethers (**2a**−**k**).* To a stirred mixture of chiral benzylic alcohol (1.42 mmol) in anhydrous THF (6 mL) and DMF (1.5 mL) was added NaH (2.13 mmol, 60% in mineral oil) at 0 °C. After stirring for 30 min, CH_3I or BnBr (4.26 mmol) was added at 0 °C under N_2. The reaction mixture was stirred at room temperature for 12 h under N_2. The reaction mixture was carefully quenched with H_2O (10 mL), then extracted with EtOAc (2 × 30 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc) to afford chiral benzylic ether.

*(S)-1-(Benzyloxy)-1,2,3,4-tetrahydronaphthalene (**2a**):* colorless oil; yield = 85%; R_f = 0.27 (*n*-hexane/EtOAc = 20/1); $[\alpha]^{26}_D$ +1.5 (*c* 1.0, $CHCl_3$); IR (neat) υ 2937, 2864, 1492, 1347, 1058, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70−1.80 (m, 1H), 1.92−2.12 (m, 3H), 2.67−2.90 (m, 2H), 4.54 (dd, J = 8.7, 4.2 Hz, 1H), 4.60 (d, J = 11.8 Hz, 1H), 4.70 (d, J = 11.8 Hz, 1H), 7.08−7.21 (m, 3H), 7.28−7.43 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.9, 27.9, 29.1, 70.2, 74.6, 125.7, 127.4, 127.8, 128.3, 129.0, 129.3, 136.7, 137.6, 138.9; LC/MS (ESI) m/z 261.24 $(M + Na)^+$; HRMS (CI) calcd for $C_{17}H_{17}O$ $(M - H)^+$ 237.1279, found 237.1276; HPLC (Chiralcel OD column, *n*-hexane:*i*-PrOH = 98:2, 0.5 mL/min, 267 nm) R_t (major) = 9.45 min, R_t (minor) = 10.65 min; ee = 99%.

*(S)-1-Methoxy-1-phenylethane (**2b**):* colorless oil; yield = 87%; R_f = 0.38 (*n*-hexane/EtOAc = 15/1); $[\alpha]^{26}_D$ −107.6 (*c* 1.0, $CHCl_3$), lit.[21] $[\alpha]^{22}_D$ −117.3 (*c* 0.8, CH_3CN); IR (neat) υ 2978, 2931, 2821, 1451, 1219, 1116, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (d, J = 6.5 Hz, 3H), 3.22 (s, 3H), 4.29 (q, J = 6.5 Hz, 1H), 7.24−7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.9, 56.4, 79.6, 126.2, 127.4, 128.4, 143.5; LC/MS (ESI) m/z 137.29 $(M + H)^+$; HRMS (CI) calcd for $C_9H_{11}O$ $(M - H)^+$ 135.0810, found 135.0811; HPLC (Chiralcel OD column, *n*-hexane:*i*-PrOH = 99:1, 0.5 mL/min, 260 nm) R_t (major) = 7.14 min, R_t (minor) = 8.37 min; ee = 99%.

*(S)-1-Benzyloxy-1-phenylethane (**2c**):* colorless oil; yield = 85%; R_f = 0.43 (*n*-hexane/EtOAc = 15/1); $[\alpha]^{26}_D$ −87.0 (*c* 1.0, $CHCl_3$), lit.[22] $[\alpha]^{22}_D$ −100.6 (*c* 0.5, $CHCl_3$); IR (MeOH) υ 3030, 2976, 2863, 1452, 1097, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, J = 6.5 Hz, 3H), 4.30 (d, J = 11.8 Hz, 1H), 4.47 (d, J = 11.8 Hz, 1H), 4.53 (q, J = 6.5 Hz, 1H), 7.24−7.37 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.2, 70.2, 77.2, 126.3, 127.4, 127.5, 127.6, 128.3, 128.4, 138.6, 143.7; LC/MS (ESI) m/z 213.39 $(M + H)^+$; HRMS (CI) calcd for $C_{15}H_{17}O$ $(M + H)^+$ 213.1279, found 213.1277; HPLC (Chiralcel OD column, *n*-hexane:*i*-PrOH = 99.5:0.5, 0.5 mL/min, 260 nm) R_t (major) = 16.65 min, R_t (minor) = 17.29 min; ee = 99%.

*(S)-1-Methoxy-2,3-dihydro-1H-indene (**2d**):* colorless oil; yield = 77%; R_f = 0.25 (*n*-hexane/EtOAc = 20/1); $[\alpha]^{26}_D$ +19.3 (*c* 1.0, $CHCl_3$); IR (neat) υ 2946, 2833, 1653, 1454, 1033, 674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.03−2.14 (m, 1H), 2.27−2.39 (m, 1H), 2.77−2.86 (m, 1H), 3.00−3.13 (m, 1H), 3.41 (s, 3H), 4.81 (dd, J = 6.5, 4.2 Hz, 1H), 7.18−7.27 (m, 3H), 7.39−7.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.1, 31.9, 56.1, 84.5, 124.9, 125.0, 126.2, 128.4, 142.5, 144.0; LC/MS (ESI) m/z 149.12 $(M + H)^+$; HRMS (CI) calcd for $C_{10}H_{11}O$ $(M - H)^+$ 147.0810, found 147.0806; HPLC (Chiralcel OD column, *n*-hexane:*i*-PrOH = 99.5:0.5, 0.5 mL/min, 266 nm) R_t (major) = 23.63 min, R_t (minor) = 27.98 min; ee = 99%.

*(S)-1-(Benzyloxy)-2,3-dihydro-1H-indene (**2e**):* colorless oil; yield = 84%; R_f = 0.41 (*n*-hexane/EtOAc = 20/1); $[\alpha]^{26}_D$ −2.5 (*c* 1.0, $CHCl_3$); IR (neat) υ 3020, 2935, 2864, 1720, 1603, 1347, 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.08−2.18 (m, 1H), 2.28−2.39 (m, 1H), 2.74−2.84 (m, 1H), 3.04−3.14 (m, 1H), 4.59 (d, J = 12.2 Hz, 1H), 4.64 (d, J = 12.2 Hz, 1H), 5.01 (dd, J = 6.5, 4.6 Hz, 1H), 7.17−7.42 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.2, 32.4, 70.4, 82.6, 124.9, 125.1, 126.3, 127.5, 127.7, 128.3, 130.3, 138.8, 142.8, 144.0; LC/MS (ESI) m/z 247.38 $(M + Na)^+$; HRMS (CI) calcd for $C_{16}H_{15}O$ $(M - H)^+$ 223.1123, found 223.1119; HPLC (Chiralcel OD column, *n*-hexane:*i*-PrOH = 98:2, 0.5 mL/min, 254 nm) R_t (major) = 9.82 min, R_t (minor) = 11.19 min; ee = 99%.

*(S)-1-(Benzyloxy)-5-methyl-2,3-dihydro-1H-indene (**2f**):* colorless oil; yield = 91%; R_f = 0.43 (*n*-hexane/EtOAc = 20/1); $[\alpha]^{27}_D$ −9.1 (*c* 0.5, $CHCl_3$); IR (neat) υ 2929, 2858, 1495, 1454, 1342, 1089, 808 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.08−2.18 (m, 1H), 2.28−2.39 (m, 1H), 2.34 (s, 3H), 2.74−2.84 (m, 1H), 3.03−3.14 (m, 1H), 4.58 (d, J = 11.8 Hz, 1H), 4.63 (d, J = 11.8 Hz, 1H), 5.00 (dd, J = 6.5, 4.2 Hz, 1H), 7.17−7.43 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 30.1, 32.6, 70.2, 82.4, 124.8, 125.5, 127.1, 127.3, 127.6, 128.3, 138.1, 138.9, 139.9, 144.3; LC/MS (ESI) m/z 239.45 $(M + H)^+$; HRMS (CI) calcd for $C_{17}H_{17}O$ $(M - H)^+$ 237.1279, found 237.1281; HPLC (Chiralcel OD column, *n*-hexane:*i*-PrOH = 100:0, 0.5 mL/min, 225 nm) R_t (major) = 49.97 min, R_t (minor) = 54.50 min; ee = 97%.

*(S)-1-(Benzyloxy)-5-bromo-2,3-dihydro-1H-indene (**2g**):* colorless oil; yield = 89%; R_f = 0.40 (*n*-hexane/EtOAc = 40/1); $[\alpha]^{26}_D$ −16.7 (*c* 1.0, $CHCl_3$); IR (MeOH) υ 3030, 2933, 2856, 1599, 1471, 1453, 1089, 1069, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.10−2.20 (m, 1H), 2.31−2.43 (m, 1H), 2.76−2.86 (m, 1H), 3.03−3.14 (m, 1H), 4.59 (d, J = 11.8 Hz, 1H), 4.64 (d, J = 11.8 Hz, 1H), 4.96 (dd, J = 6.5, 4.2 Hz, 1H), 7.07−7.16 (m, 1H), 7.26−7.40 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.9, 32.4, 70.5, 81.8, 122.2, 126.4, 127.5, 127.6, 127.9, 128.3, 129.3, 138.4, 141.8, 146.2; LC/MS (ESI) m/z 303.08 $(M + H)^+$; HRMS (CI) calcd for $C_{16}H_{16}BrO$ $(M + H)^+$ 303.0385, found 303.0378; HPLC (Chiralcel OD column, *n*-hexane:*i*-PrOH = 98:2, 0.5 mL/min, 270 nm) R_t (minor) = 12.92 min, R_t (major) = 13.16 min; ee = 98%.

*(S)-1-Methoxy-1,2,3,4-tetrahydronaphthalene (**2h**):* colorless oil; yield = 81%; R_f = 0.20 (*n*-hexane/EtOAc= 20/1); $[\alpha]^{26}_D$ −2.6 (*c* 1.0, $CHCl_3$), lit.[23] $[\alpha]^{12}_D$ −3.5 (*c* 1.0, $CHCl_3$); IR (neat) υ 2938, 1685, 1454, 1054, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.72−1.80 (m, 1H), 1.83−1.93 (m, 1H), 1.95−2.07 (m, 2H), 2.66−2.87 (m, 2H), 3.44 (s, 3H), 4.31 (t, J = 4.2 Hz, 1H), 7.05−7.15 (m, 1H), 7.17−7.22 (m, 2H), 7.32−7.37 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.7, 27.4, 29.1, 56.1, 76.8, 125.6, 127.5, 128.9, 129.3, 136.6, 137.5; LC/MS (ESI) m/z 163.29 $(M + H)^+$; HRMS (CI) calcd for $C_{10}H_{11}$ $(M - CH_3O)^+$ 131.0861, found 131.0862; HPLC (Chiralcel OD column, *n*-hexane:*i*-PrOH = 98:2, 0.5 mL/min, 225 nm) R_t (major) = 10.24 min, R_t (minor) = 11.36 min; ee = 99%.

*(S)-4-(Benzyloxy)chroman (**2i**):* white solid; yield = 85%; R_f = 0.27 (*n*-hexane/EtOAc = 20/1); $[\alpha]^{25}_D$ −74.5 (*c* 1.0, $CHCl_3$); mp 79−80 °C; IR (neat) υ 2984, 2912, 2879, 1610, 1584, 1268, 1119, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.98−2.09 (m, 1H), 2.13−2.21 (m, 1H), 4.20−4.27 (m, 1H), 4.35 (dt, J = 11.1, 2.7 Hz, 1H), 4.47 (t, J = 3.8 Hz, 1H), 4.61 (d, J = 11.8 Hz, 1H), 4.66 (d, J = 11.8 Hz, 1H), 6.85 (t, J = 8.0 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 7.16−7.22 (m, 2H), 7.24−7.40 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.6, 62.1, 69.5, 69.9, 116.9, 119.9, 121.7, 127.6, 127.7, 128.4, 129.6, 130.6, 138.5, 154.9; LC/MS (ESI) m/z 263.33 $(M + Na)^+$; HRMS (EI) calcd for $C_{16}H_{16}O_2$ $(M)^+$ 240.1150, found 240.1154; HPLC (Chiralcel OD column, *n*-hexane:*i*-PrOH = 98:2, 0.5 mL/min, 277 nm) R_t (major) = 13.25 min, R_t (minor) = 16.16 min; ee = 98%.

*(1R,2R)-1,2-Bis(benzyloxy)-2,3-dihydro-1H-indene (**2j**):* colorless oil; yield = 90%; R_f = 0.29 (*n*-hexane/EtOAc = 25/1); $[\alpha]^{25}_D$ −35.5 (*c* 1.0, $CHCl_3$); IR (MeOH) υ 3064, 3030, 2864, 1455, 1353, 1095, 746, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.86 (dd, J = 15.6, 5.7 Hz, 1H), 3.32 (dd, J = 15.6, 6.9 Hz, 1H), 4.36−4.42 (m, 1H), 4.60 (d, J = 11.8 Hz, 1H), 4.67 (d, J = 11.8 Hz, 1H), 4.76 (d, J = 11.8 Hz, 1H), 4.82 (d, J = 11.8 Hz, 1H), 5.06 (d, J = 4.6 Hz, 1H), 7.17−7.42 (m, 14H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.2, 71.3, 71.5, 85.7, 86.4, 124.8, 124.8, 126.7, 127.3, 127.4, 127.5, 127.6, 128.2, 128.2, 128.3, 138.0, 138.4, 139.6, 140.3; LC/MS (ESI) m/z 353.22 $(M + Na)^+$; HRMS (CI) calcd for $C_{23}H_{21}O_2$ $(M - H)^+$ 329.1542, found 329.1540; HPLC (Chiralcel OD column, *n*-hexane:*i*-PrOH = 98:2, 0.5 mL/min, 254 nm) R_t (major) = 15.82 min; ee = 99%.

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*(1R,2R)-1,2-Bis(benzyloxy)-1,2,3,4-tetrahydronaphthalene (**2k**):* colorless oil; yield = 95%; R_f = 0.35 (*n*-hexane/EtOAc = 20/1); IR (MeOH) υ 3072, 3028, 2860, 1445, 1302, 1200, 1044, 756, 700 cm^{-1}; $[\alpha]^{22}_D$ −18.8 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.93−2.02 (m, 1H), 2.17−2.26 (m, 1H), 2.73−2.96 (m, 2H), 3.96−4.01 (m, 1H), 4.54−4.81 (m, 5H), 7.09−7.37 (m, 14H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.6, 25.9, 70.9, 72.1, 72.2, 78.1, 125.9, 127.5, 127.6, 127.8, 127.9, 128.3, 129.6, 135.1, 137.0, 138.3, 138.6, 138.7; LC/MS (ESI) *m*/*z* 367.05 $(M + Na)^+$; HRMS (CI) calcd for $C_{24}H_{25}O_2$ $(M + H)^+$ 345.1855, found 345.1859; HPLC (Chiralcel OD column, *n*-hexane:*i*-PrOH = 98:2, 0.5 mL/min, 254 nm) R_t (major) = 14.03 min; ee = 99%.

General Procedure for the Reactions of Chiral Ethers with Chlorosulfonyl Isocyanate (CSI). To a stirred mixture of chiral ether (0.60 mmol) in anhydrous *n*-hexane (3 mL) was added Na_2CO_3 (1.80 mmol) at −40 °C under N_2. After being stirred for 20 min, chlorosulfonyl isocyanate (0.90 mmol) in anhydrous *n*-hexane (3 mL) was slowly added at −40 °C under N_2. The reaction mixture was stirred at −40 °C for 10 h, quenched with H_2O (10 mL) when the reaction was completed (TLC monitoring), and then extracted with EtOAc (2 × 25 mL). The organic layer was added to aqueous saturated solution of Na_2SO_3 (10 mL), and the reaction mixture was stirred for 14 h at room temperature. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc) afford the corresponding carbamate as a white solid.

*(S)-Benzyl 1,2,3,4-tetrahydronaphthalen-1-yl carbamate (**3a**):* white solid; yield = 78%; R_f = 0.13 (*n*-hexane/EtOAc = 10/1); $[\alpha]^{26}_D$ −27.3 (*c* 1.0, $CHCl_3$); mp 75−77 °C; IR (KBr) υ 3324, 3030, 2937, 1687, 1532, 1243, 1067, 1024 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.79−1.90 (m, 3H), 2.00−2.11 (m, 1H), 2.69−2.86 (m, 2H), 4.89−5.00 (m, 2H), 5.15 (s, 2H), 7.07−7.11 (m, 1H), 7.14−7.20 (m, 2H), 7.32−7.38 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.8, 29.2, 30.4, 49.3, 66.7, 126.2, 127.3, 128.1, 128.5, 128.7, 129.1, 136.5, 136.6, 137.4, 155.9; LC/MS (ESI) *m*/*z* 282.00 $(M + H)^+$; HRMS (EI) calcd for $C_{18}H_{19}NO_2$ $(M)^+$ 281.1416, found 281.1411; HPLC (Chiralcel OD column, *n*-hexane:*i*-PrOH = 80:20, 1.0 mL/min, 265 nm) R_t (major) = 9.64 min, R_t (minor) = 11.76 min; ee = 96%.

*(S)-Methyl 1-phenylethyl carbamate (**3b**):* white solid; yield = 70%; R_f = 0.24 (*n*-hexane/EtOAc = 5/1); $[\alpha]^{22}_D$ −88.7 (*c* 1.0, $CHCl_3$), lit.[24] $[\alpha]^{23}_D$ −83.2 (*c* 7.3, $CHCl_3$); mp 56−57 °C, lit.[25] mp 56−57 °C; IR (KBr) υ 3324, 3031, 2969, 1694, 1534, 1258, 1072, 1012 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (d, *J* = 6.9 Hz, 3H), 3.64 (s, 3H), 4.75−4.90 (br, 1H), 4.90−5.01 (br, 1H), 7.21−7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.4, 50.7, 52.0, 125.9, 127.3, 128.6, 143.5, 156.2; LC/MS (ESI) *m*/*z* 180.07 $(M + H)^+$; HRMS (EI) calcd for $C_{10}H_{13}NO_2$ $(M)^+$ 179.0946, found 179.0950; HPLC (Chiralcel OD column, *n*-hexane:*i*-PrOH = 95:5, 1.0 mL/min, 254 nm) R_t (major) = 13.36 min, R_t (minor) = 23.30 min; ee = 99%.

*(S)-Benzyl 1-phenylethyl carbamate (**3c**):* white solid; yield = 70%; R_f = 0.24 (*n*-hexane/EtOAc = 9/1); $[\alpha]^{25}_D$ −44.3 (*c* 1.0, $CHCl_3$), lit.[26] $[\alpha]^{24}_D$ −44.0 (*c* 0.59, $CHCl_3$); mp 60−62 °C; IR (KBr) υ 3304, 3029, 2972, 1692, 1539, 1493, 1257, 1110, 1059, 1005 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, *J* = 6.9 Hz, 3H), 4.84−4.89 (m, 1H), 4.97−5.10 (m, 1H), 5.05 (d, *J* = 12.0 Hz, 1H), 5.12 (d, *J* = 12.0 Hz, 1H), 7.26−7.37 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.4, 50.7, 66.7, 125.9, 127.3, 128.1, 128.2, 128.5, 128.6, 136.5, 143.4, 155.5; LC/MS (ESI) *m*/*z* 256.09 $(M + H)^+$; HRMS (EI) calcd for $C_{16}H_{17}NO_2$ $(M)^+$ 255.1259, found 255.1257; HPLC (Chiralcel OD column, *n*-hexane:*i*-PrOH = 85:15, 1.0 mL/min, 265 nm) R_t (major) = 7.60 min, R_t (minor) = 9.36 min; ee = 96%.

*(S)-Methyl 2,3-dihydro-1H-inden-1-yl carbamate (**3d**):* white solid; yield = 86%; R_f = 0.29 (*n*-hexane/EtOAc = 6/1); $[\alpha]^{24}_D$ −34.9 (*c* 1.0, $CHCl_3$); mp 94−97 °C; IR (KBr) υ 3302, 2944, 2850, 1695, 1541, 1252, 1061 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.74−1.86 (m, 1H), 2.56−2.65 (m, 1H), 2.79−3.02 (m, 2H), 3.72 (s, 3H), 4.80−4.92 (m, 1H), 5.08−5.28 (m, 1H), 7.20−7.33 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.7, 33.9, 51.7, 56.0, 123.7, 124.4, 126.4, 127.6, 142.8, 143.0, 156.6; LC/MS (ESI) *m*/*z* 192.06 $(M + H)^+$; HRMS (EI) calcd for $C_{11}H_{13}NO_2$ $(M)^+$ 191.0946, found 191.0948; HPLC (Chiralcel OD column, *n*-hexane:*i*-PrOH = 80:20, 1.0 mL/min, 254 nm) R_t (major) = 7.57 min, R_t (minor) = 12.48 min; ee = 96%.

*(S)-Benzyl 2,3-dihydro-1H-inden-1-yl carbamate (**3e**):* white solid; yield = 89%; R_f = 0.23 (*n*-hexane/EtOAc = 8/1); $[\alpha]^{25}_D$ −21.2 (*c* 1.0, $CHCl_3$); mp 112−114 °C; IR (KBr) υ 3307, 3035, 2920, 1682, 1532, 1249, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.76−1.88 (m, 1H), 2.54−2.66 (m, 1H), 2.80−3.02 (m, 2H), 4.88−4.98 (m, 1H), 5.16 (s, 2H), 5.22−5.30 (m, 1H), 7.21−7.39 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.1, 34.3, 56.5, 66.8, 124.0, 124.8, 126.7, 128.0, 128.1, 128.5, 136.5, 143.1, 143.1, 143.2, 156.2; LC/MS (ESI) *m*/*z* 268.23 $(M + H)^+$; HRMS (EI) calcd for $C_{17}H_{17}NO_2$ $(M)^+$ 267.1259, found 267.1256; HPLC (Chiralcel OD column, *n*-hexane:*i*-PrOH = 80:20, 1.0 mL/min, 265 nm) R_t (major) = 8.12 min, R_t (minor) = 10.52 min; ee = 97%.

*(S)-Benzyl 5-methyl-2,3-dihydro-1H-inden-1-yl carbamate (**3f**):* white solid; yield = 80%; R_f = 0.25 (*n*-hexane/EtOAc = 8/1); [α]29 D −21.8 (*c* 1.0, $CHCl_3$); mp 133−135 °C; IR (KBr) υ 3306, 3030, 2958, 1686, 1540, 1252, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.74−1.87 (m, 1H), 2.33 (s, 3H), 2.54−2.61 (m, 1H), 2.77−2.93 (m, 2H), 4.71−4.93 (m, 1H), 5.15 (s, 2H), 5.19−5.22 (m, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 7.05 (s, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.31−7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 29.9, 34.5, 56.2, 66.7, 123.7, 125.4, 127.6, 128.1, 128.5, 136.5, 137.9, 140.1, 143.4, 156.1; LC/MS (ESI) *m*/*z* 282.21 $(M + H)^+$; HRMS (CI) calcd for $C_{18}H_{20}NO_2$ $(M + H)^+$ 282.1494, found 282.1496; HPLC (Chiralcel OD column, *n*-hexane:*i*-PrOH = 80:20, 1.0 mL/min, 265 nm) R_t (major) = 6.72 min, R_t (minor) = 10.94 min; ee = 88%.

*(S)-Benzyl 5-bromo-2,3-dihydro-1H-inden-1-yl carbamate (**3g**):* white solid; yield = 80%; R_f = 0.24 (*n*-hexane/EtOAc = 8/1); $[\alpha]^{28}_D$ −37.4 (*c* 1.0, $CHCl_3$); mp 151−154 °C; IR (KBr) υ 3435, 3307, 3298, 3030, 2954, 1680, 1528, 1246, 1057 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.75−1.88 (m, 1H), 2.51−2.64 (m, 1H), 2.77−2.99 (m, 2H), 4.70−4.96 (m, 1H), 5.15 (s, 2H), 5.15−5.23 (m, 1H), 7.17 (d, *J* = 8.1 Hz, 1H), 7.26−7.37 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.9, 34.3, 55.9, 66.9, 121.9, 125.5, 128.0, 128.1, 128.2, 128.6, 129.9, 136.3, 142.2, 145.4, 156.1; LC/MS (ESI) *m*/*z* 346.16 $(M + H)^+$; HRMS (EI) calcd for $C_{17}H_{16}BrNO_2$ $(M)^+$ 345.0364, found 345.0363; HPLC (Chiralcel OD column, *n*-hexane:*i*-PrOH = 90:10, 1.0 mL/min, 274 nm) R_t (minor) = 22.97 min, R_t (major) = 30.45 min; ee = 94%.

*(S)-Methyl 1,2,3,4-tetrahydronaphthalen-1-yl carbamate (**3h**):* white solid; yield = 83%; R_f = 0.21 (*n*-hexane/EtOAc = 8/1); $[\alpha]^{23}_D$ −59.2 (*c* 1.0, $CHCl_3$), lit.[27] $[\alpha]^{20}_D$ −54.6 (*c* 1.0, $CHCl_3$); mp 85−87 °C; IR (KBr) υ 3321, 2941, 1695, 1530, 1317, 1248, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.82−1.87 (m, 3H), 2.01−2.05 (m, 1H), 2.71−2.84 (m, 2H), 3.71 (s, 3H), 4.80−4.90 (m, 2H), 7.07−7.10 (m, 1H), 7.12−7.21 (m, 2H), 7.32−7.35 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.8, 29.2, 30.4, 49.2, 52.1, 126.2, 127.3, 128.6, 129.1, 136.7, 137.4, 156.5; LC/MS (ESI) *m*/*z* 206.16 $(M + H)^+$; HRMS (EI) calcd for $C_{12}H_{15}NO_2$ $(M)^+$ 205.1103, found 205.1106; HPLC (Chiralcel OD column, *n*-hexane:*i*-PrOH = 90:10, 1.0 mL/min, 265 nm) R_t (major) = 8.66 min, R_t (minor) = 14.95 min; ee = 97%.

*(S)-Benzyl chroman-4-yl carbamate (**3i**):* white solid; yield = 75%; R_f = 0.13 (*n*-hexane/EtOAc = 4/1); $[\alpha]^{23}_D$ −41.7 (*c* 1.0, $CHCl_3$); mp 163−166 °C; IR (KBr) υ 3323, 3030, 2957, 1682, 1530, 1222, 1066 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.03−2.26 (m, 2H), 4.11−4.30 (m, 2H), 4.88−5.04 (m, 2H), 5.15 (s, 2H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 7.18 (t, *J* = 8.4 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.31−7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.2, 45.2, 63.0, 66.9, 117.1, 120.7, 121.8, 128.1, 128.2, 128.5, 129.4, 136.3, 154.9, 155.6; LC/MS (ESI) *m*/*z* 284.16 $(M + H)^+$; HRMS (EI) calcd for $C_{17}H_{17}NO_3$ $(M)^+$ 283.1208, found 283.1214; HPLC (Chiralcel OD column, *n*-hexane:*i*-PrOH = 95:5, 1.0 mL/min, 270 nm) R_t (major) = 15.90 min, R_t (minor) = 20.27 min; ee = 98%.

*Benzyl (1R,2R)-2-(benzyloxy)-2,3-dihydro-1H-inden-1-yl carbamate (**3j**):* white solid; yield = 75%; R_f = 0.14 (*n*-hexane/EtOAc = 9/1); $[\alpha]^{25}_D$ −17.4 (*c* 1.0, $CHCl_3$); mp 109−110 °C; IR (KBr) υ 3436, 3368, 3028, 2873, 1722, 1692, 1541, 1454, 1252, 1148 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.90 (dd, *J* = 16.0, 5.7 Hz, 1H), 3.26 (dd, *J* = 16.0, 6.9 Hz, 1H), 4.14 (dd, *J* = 12.1, 6.1 Hz, 1H), 4.69 (d, *J* = 12.2 Hz, 1H), 4.76 (d, *J* = 12.2 Hz, 1H), 4.60−4.93 (m, 1H), 5.14−5.28

(m, 3H), 7.16−7.38 (m, 14H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.9, 61.5, 66.9, 71.5, 85.7, 124.5, 125.0, 127.2, 127.6, 127.8, 128.1, 128.2, 128.3, 128.5, 128.6, 136.4, 136.5, 136.6, 138.3, 140.0, 140.2, 156.0; LC/MS (ESI) 374.19 $(M + H)^+$; HRMS (EI) calcd for $C_{24}H_{23}NO_3$ $(M)^+$ m/z 373.1678, found 373.1680; HPLC (Chiralcel OJ-RH column, CH_3CN:H_2O = 50:50, 1.0 mL/min, 210 nm) R_t (minor) = 22.55 min (1*S*,2*R*), R_t (major) = 27.41 min (1*R*,2*R*); de = 99%.

*Benzyl (1R,2R)-2-(benzyloxy)-1,2,3,4-tetrahydronaphthalen-1-yl carbamate (**3k**):* white solid; yield = 85%; R_f = 0.27 (*n*-hexane/EtOAc = 10/1); $[\alpha]^{25}_D$ −71.3 (*c* 1.0, $CHCl_3$); mp 115−116 °C; lit.[14] 115.2 °C; IR (KBr) υ 3323, 3061, 3027, 2928, 2876, 1699, 1536, 1449, 1362, 1317, 1243, 1073, 1033 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98−2.03 (m, 2H), 2.67−2.76 (m, 1H), 2.94−3.04 (m, 1H), 3.76−3.83 (m, 1H), 4.63−4.74 (m, 2H), 4.85−4.95 (m, 2H), 5.16 (s, 2H), 7.07−7.36 (m, 14H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.5, 25.4, 52.9, 66.8, 70.6, 76.5, 126.4, 127.4, 127.5, 128.1, 128.1, 128.3, 128.5, 128.6, 129.6, 134.6, 134.6, 136.5, 136.5, 136.5, 136.7, 138.7, 155.9; LC/MS (ESI) m/z 388.19 $(M + H)^+$; HRMS (EI) calcd for $C_{25}H_{25}NO_3$ $(M)^+$ 387.1834, found 387.1838; HPLC (Chiralcel OJ-RH column, CH_3CN:H_2O = 50:50, 1.0 mL/min, 210 nm) R_t (minor) = 22.56 min (1*S*,2*R*), R_t (major) = 27.58 min (1*R*,2*R*); de = 99%.

*4-(3,4-Dichlorophenyl)-3,4-dihydronaphthalen-1(2H)-one (**5**).*[15] To a stirred solution of 1-naphthol (5.0 g, 34.68 mmol) in 1,2-dichlorobenzene (32 mL) and anhydrous $AlCl_3$ (11.56 g, 86.70 mmol) was added. The reaction mixture was stirred at 100 °C for 1.5 h under N_2. The reaction mixture was then cooled to room temperature and poured into ice and 1 N HCl (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The organic layer washed with H_2O, stirred with Celite (6.7 g) and activated carbon (5 g), then filtered. The solvent was concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 10/1) to afford 8.2 g (82%) of **5** as a white solid: R_f = 0.13 (*n*-hexane/EtOAc = 10/1); mp 99−101 °C; IR (KBr) υ 3422, 2859, 1675, 1591, 1470, 1286, 1203, 1029 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20−2.32 (m, 1H), 2.42−2.52 (m, 1H), 2.58−2.77 (m, 2H), 4.28 (dd, *J* = 8.0, 4.6 Hz, 1H), 6.95 (dd, *J* = 8.4, 2.0 Hz, 2H), 7.23 (d, *J* = 1.9 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.48 (dt, *J* = 7.2, 1.5 Hz, 1H), 8.13 (dd, *J* = 8.0, 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.6, 36.5, 44.5, 127.3, 127.5, 127.9, 129.2, 130.5, 130.6, 130.9, 132.6, 132.7, 133.8, 144.0, 144.8, 197.4; LC/MS (ESI) m/z 291.0 $(M + H)^+$; HRMS (EI) calcd for $C_{16}H_{12}Cl_2O$ $(M)^+$ 290.0265, found 290.0264.

*(1S,4S)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-ol (**7**).* To a stirred mixture of (*R*)-(+)-2-methyl-CBS-oxazaborolidine catalyst **6** (82 μL, 0.08 mmol) in anhydrous toluene (4 mL) was added *N*,*N*-diethylaniline borane (0.49 mL, 2.74 mmol) at room temperature. A mixture of **5** (400 mg, 1.37 mmol) in anhydrous toluene (5 mL) was slowly added via a syringe pump over 5 h. The reaction mixture was stirred at 25 °C for 1 h and carefully quenched with MeOH (1 mL) and 1 N HCl (1 mL), then extracted with EtOAc (2 × 50 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 5/1) to afford 193 mg (48%) of **7** as a colorless oil: R_f = 0.29 (*n*-hexane/EtOAc = 5/1); $[\alpha]^{25}_D$ +50.5 (*c* 1.0, $CHCl_3$); IR (neat) υ 3331, 3059, 2938, 2864, 1561, 1468, 1264, 1396, 1131, 1030, 765 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96−2.13 (m, 5H), 3.99 (t, *J* = 6.8 Hz, 1H), 4.86 (t, *J* = 4.6 Hz, 1H), 6.82 (d, *J* = 7.2 Hz, 1H), 6.99 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.17 (dt, *J* = 7.2, 1.5 Hz, 1H), 7.26 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.27 (dd, *J* = 1.9 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 30.1, 45.1, 67.8, 127.0, 128.1, 128.2, 129.0, 129.7, 130.2, 130.3, 130.7, 132.4, 138.4, 138.9, 146.9; LC/MS (ESI) m/z 292.00 $(M + H)^+$; HRMS (EI) calcd for $C_{16}H_{14}Cl_2O$ $(M)^+$ 292.0422, found 292.0420; HPLC (Chiralcel OD-RH column, CH_3CN:H_2O = 10:90 to 100:0, 1.0 mL/min, 265 nm) R_t (major) = 18.66 min (1*S*,4*S*), R_t (minor) = 19.64 min (1*R*,4*R*); ee = 99.5%.

*(1S,4S)-1-(Benzyloxy)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalene (**8**).* To a stirred solution of 7 (432 mg, 1.47 mmol) in anhydrous THF (14 mL) and DMF (3.5 mL) was added NaH (88 mg, 2.21 mmol, 60% in mineral oil) at 0 °C. After being stirred for 30 min, benzyl bromide (0.52 mL, 4.41 mmol) was added at 0 °C under N_2. The reaction mixture was stirred at room temperature for 12 h under N_2 and quenched with H_2O (30 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 30/1) to afford 461 mg (82%) of **8** a colorless oil: R_f = 0.37 (*n*-hexane/EtOAc = 20/1); $[\alpha]^{25}_D$ +39.8 (*c* 1.0, $CHCl_3$); IR (neat) υ 3062, 3028, 2938, 2863, 1468, 1394, 1130, 1088, 1029, 743, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85−1.94 (m, 1H), 2.04−2.24 (m, 3H), 4.00 (dd, *J* = 8.4, 6.1 Hz, 1H), 4.55 (t, *J* = 4.2 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.73 (d, *J* = 11.9 Hz, 1H), 6.82 (d, *J* = 6.9 Hz, 1H), 6.98 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.13−7.25 (m, 2H), 7.28−7.44 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.3, 28.3, 45.0, 70.3, 74.1, 126.5, 127.6, 127.8, 128.1, 128.3, 128.4, 129.8, 129.8, 130.1, 130.3, 130.7, 132.3, 136.9, 138.7, 138.9, 147.3; LC/MS (ESI) m/z 383.04 $(M + H)^+$; HRMS (CI) calcd for $C_{23}H_{19}Cl_2O$ $(M - H)^+$ 381.0813, found 381.0814.

*Benzyl (1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl carbamate (**9**).* To a stirred solution of **8** (340 mg, 0.89 mmol) in anhydrous *n*-hexane (8 mL) was added Na_2CO_3 (283 mg, 2.67 mmol) at −40 °C under N_2. After being stirred for 30 min, chlorosulfonyl isocyanate (0.23 mL, 2.67 mmol) in anhydrous *n*-hexane (2 mL) was slowly added at −40 °C under N_2. The reaction mixture was stirred at −40 °C for 40 h and quenched with H_2O (20 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL). The organic layer was added to aqueous saturated solution of Na_2SO_3 (20 mL), and the reaction mixture was stirred for 12 h at room temperature. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 6/1) to afford 301 mg (80%) of **9** as a white solid: R_f = 0.33 (*n*-hexane/EtOAc = 6/1); $[\alpha]^{25}_D$ +25.4 (*c* 1.0, $CHCl_3$); mp 76−77 °C; IR (KBr) υ 3426, 2934, 1690, 1530, 1466, 1239, 1069, 1028 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83−2.02 (m, 3H), 2.10−2.17 (m, 1H), 4.03 (t, *J* = 7.2 Hz, 1H), 4.93−4.99 (m, 1H), 5.09 (d, *J* = 8.0 Hz, 1H), 5.16 (s, 2H), 6.82 (d, *J* = 7.2 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 1.9 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.32−7.42 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.6, 29.2, 44.6, 49.2, 66.9, 127.2, 127.9, 128.1, 128.2, 128.2, 128.6, 129.1, 129.9, 130.3, 130.6, 132.4, 136.3, 137.0, 138.4, 146.7, 155.7; LC/MS (ESI) m/z 426.07 $(M + H)^+$; HRMS (EI) calcd for $C_{24}H_{21}Cl_2NO_2$ $(M)^+$ 425.0949, found 425.0952; HPLC (Chiralcel OD-RH column, CH_3CN:H_2O (0.1% TFA) = 60:40, 1.0 mL/min, 265 nm) R_t (major) = 22.94 min (1*S*,4*S*), R_t (minor) = 25.51 min (1*R*,4*S*); de = 99%.

*Benzyl (1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl(methyl) carbamate (**10**).* To a stirred solution of **9** (113 mg, 0.27 mmol) in anhydrous THF (4 mL) and DMF (1 mL) was added NaH (22 mg, 0.54 mmol, 60% in mineral oil) at 0 °C. After stirring for 30 min, CH_3I (68 ul, 1.10 mmol) was added at 0 °C under N_2. The reaction mixture was stirred at room temperature for 6 h under N_2 and quenched with H_2O (10 mL). The aqueous layer was extracted with EtOAc (2 × 25 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 8/1) to afford 116 mg (99%) of **10** a colorless oil: R_f = 0.29 (*n*-hexane/EtOAc = 8/1); $[\alpha]^{25}_D$ +24.6 (*c* 1.0, $CHCl_3$); IR (MeOH) υ 2933, 1694, 1397, 1314, 1131 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) Note: *a splitting or broadening of some peaks was observed due to rotamers* δ 1.68−1.82 (m, 2H), 1.97−2.03 (m, 1H), 2.20−2.36 (m, 1H), 2.71 and 2.74 (s, 3H), 4.16−4.18 (m, 1H), 5.19 (d, *J* = 12.9 Hz, 1H), 5.25 (d, *J* = 12.9 Hz, 1H), 5.36−5.55 (m, 1H), 6.78 and 6.82 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.95 (d, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 2.2 Hz, 1H), 7.16−7.27 (m, 3H), 7.29−7.43 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 30.0, 43.1, 55.1, 67.3, 127.2, 127.4, 127.5, 127.81, 128.0, 128.5, 130.1, 130.6, 130.8, 132.3, 136.1, 136.8, 138.1, 147.1, 157.2; LC/MS (ESI) m/z 440.11 $(M + H)^+$; HRMS (EI) calcd for $C_{25}H_{23}Cl_2NO_2$ $(M)^+$ 439.1106, found 439.1102.

(1S,4S)-4-(3,4-Dichlorophenyl)-N-methyl-1,2,3,4-tetrahydronaphthalen-1-amine. To a stirred solution of **10** (50 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) and MeOH (8 mL) was added Raney Ni (20 mg, wet basis) at room temperature. The reaction mixture was stirred for 5 h

under H_2 balloon at room temperature. The resulting mixture was filtered through Celite pad and concentrated in vacuo. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH = 10/1) to afford 30 mg (89%) of (+)-sertraline as a free base form: R_f = 0.29 (CH_2Cl_2/MeOH = 10/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (br, 1H), 1.77−1.87 (m, 1H), 1.96−2.12 (m, 3H), 2.54 (s, 3H), 3.72 (t, J = 4.2 Hz, 1H), 3.98 (dd, J = 9.3, 5.6 Hz, 1H), 6.79 (d, J = 7.7 Hz, 1H), 6.97 (dd, J = 8.2, 2.1 Hz, 1H), 7.11 (dt, J = 7.6, 1.5 Hz, 1H), 7.20 (t, J = 7.2 Hz, 1H), 7.25 (d, J = 2.1 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.35 (dd, J = 7.6, 1.1 Hz, 1H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.68−1.75 (m, 1H), 1.91−2.08 (m, 3H), 2.38 (s, 3H), 3.69 (t, J = 4.2 Hz, 1H), 4.10 (dd, J = 8.8, 5.7 Hz, 1H), 6.69 (d, J = 7.6 Hz, 1H), 7.11 (dt, J = 7.2, 1.5 Hz, 1H), 7.13−7.21 (m, 3H), 7.39 (d, J = 7.6 Hz, 1H), 7.42 (d, J = 1.9 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.7, 28.4, 34.4, 45.4, 57.3, 126.6, 127.2, 128.2, 129.2, 129.8, 130.0, 130.3, 130.7, 132.2, 138.6, 139.5, 147.5; LC/MS (ESI) m/z 306.06 $(M + H)^+$; HRMS (EI) calcd for $C_{17}H_{17}Cl_2N$ $(M)^+$ 305.0738, found 305.0734.

(1S,4S)-4-(3,4-Dichlorophenyl)-N-methyl-1,2,3,4-tetrahydronaphthalen-1-amine hydrochloride (1). (+)-Sertraline as a free base (30 mg, 0.098 mmol) was dissolved in anhydrous ether, and dry HCl gas was passed through the solution to from the hydrochloride salt. The precipitate was filtered and washed with anhydrous ether and dried to afford 29 mg (83%) of (+)-sertraline-HCl (**1**) as a white solid: $[\alpha]^{25}_D$ +32.5 (c 1.0, MeOH), lit.[2b] $[\alpha]^{23}_D$ +37.9 (c 2.0, MeOH); mp 244−246 °C, lit.[6] mp 243−245 °C; IR (KBr) υ 3427, 2940, 2676, 2468, 1582, 1469, 1402, 1136, 825, 789 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.98−2.28 (m, 4H), 2.65 (s, 3H), 4.16 (dd, J = 9.5, 5.7 Hz, 1H), 4.42 (m, 1H), 6.76 (d, J = 8.7 Hz, 1H), 7.25−7.37 (m, 3H), 7.59−7.69 (m, 3H), 9.40 (br, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 22.8, 26.4, 30.3, 54.9, 126.5, 129.0, 129.1, 129.7, 130.3, 130.4, 130.9, 131.0, 131.1, 139.9, 147.7; LC/MS (ESI) m/z 306.06 $(M + H)^+$; HRMS (FAB) calcd for $C_{17}H_{18}Cl_2N$ $(M + H)^+$ 306.0816, found 306.0812.; HPLC (Chiralcel OD-RH column, CH_3CN:H_2O (0.1% TFA) = 10:90 to 100:0, 1.0 mL/min, 210, 225, and 265 nm) R_t (major) = 11.03 min (1*S*,4*S*); ee = 99% (C18 XTerra column, CH_3CN:H_2O (0.1% TFA) = 10:90 to 100:0, 1.0 mL/min, 225 nm; chemical purity > 99%).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR copies for compounds (alcohols (**i**−**vi**), **1**, **2a**−**k**, **3a**−**k**, **5** and **7**−**10**) and HPLC analysis data for alcohols (**i**−**vi**), **1**, **2a**−**k**, **3a**−**k**, **7**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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