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An efficient synthesis of enantiomerically pure aromatic-fused *N*-containing heterocycles from common chiral aziridines

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ABSTRACT

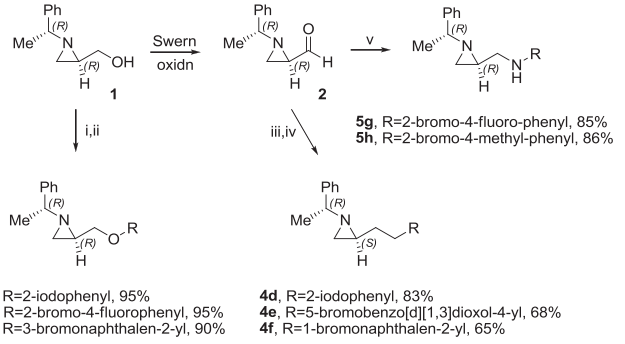
An efficient synthesis of enantiomerically pure aromatic-fused *N*-containing heterocycles was successfully achieved via Pd-catalyzed intramolecular C–N bond formation between the nitrogen originated from the aziridine and the halogen containing aromatic carbon. This reaction has a broad substrate scope to provide various enantiomerically pure (3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)methanols, 2-hydroxymethyl-1,2,3,4-tetrahydroquinolines and (1,2,3,4-tetrahydroquinoxalin-2-yl)methanols from common chiral aziridines in good yields.

1. Introduction

Recently, substituted 2-hydroxymethyl-1,2,3,4-tetrahydroquinolines and their analogous heterocycles turned out to be agonists or partial agonists of the 2C subtype of brain serotonin receptors.[1] They are also useful for the treatment of a variety of central nervous system disorders.[2] Moreover, their derivatives can play important roles as promoting angiogenesis of mesenchymal stem cells[3] and also as inhibitors of apoptosis for anti-cancer drugs.[4] The heterocyclic compounds containing 1,4-benzoxazines,[5] 1,2,3,4-tetrahydroquinolines,[6] and 1,2,3,4-tetrahydroquinoxalines[7] have attracted increasing interest from organic and medicinal chemists due to their various biological activities. Therefore, we were interested in the synthesis of enantiomerically pure substituted 2-hydroxymethyl-1,2,3,4-tetrahydroquinolines and their analogous heterocycles starting from common chiral aziridines. We found that chiral aziridines are valuable synthetic building blocks for chemical bond elaborations and functional group transformations.[8] Herein, we would like to report an efficient synthesis of various heterocyclic systems, such as 1,4-benzoxazines,[9] 1,2,3,4-tetrahydroquinolines,[10] and 1,2,3,4-tetrahydroquinoxalines[11] from 1-α-methylbenzyl-(2*R*)- and (2*S*)-aziridine-2-methanols via intramolecular Pd-catalyzed C–N bond formation.

2. Results and discussion

The synthesis of enantiomerically pure (3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)methanols commenced from commercially available 1-α-methylbenzyl-(2*R*)- and (2*S*)-aziridine-2-methanols. The reaction of aziridine-2-methanols and *p*-toluenesulfonyl chloride with TEA in DCM at room temperature afforded the tosylated compound,[12] which was reacted with various *o*-halophenols and K_2CO_3 in DMF/acetone to give the corresponding phenyl ethers **3a**–**c** in high yields (Scheme 1).



Scheme 1. Reagents and conditions: (i) *p*-TsCl, TEA, DMAP, DCM, 0 °C to rt; (ii) *o*-halophenols, K_2CO_3, DMF/acetone=1:1, reflux; (iii) corresponding phosphonium salts, LiHMDS, THF, 0 °C to rt; (iv) 2-nitrobenzenesulfonylhydrazide (NBSH), TEA, DCM, 0 °C to rt; (v) 2-bromoanilines, $NaBH(OAc)_3$, $MgSO_4$, DCE, rt.

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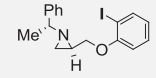
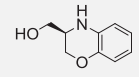
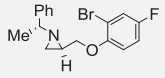
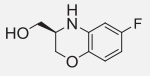
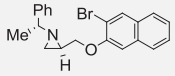
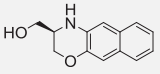
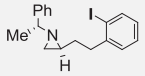
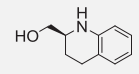
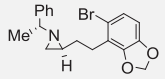
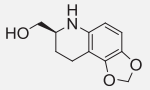
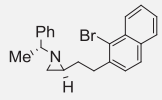
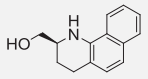
The synthesis of enantiomerically pure 2-alkylaziridines is also shown in Scheme 1. We reported the preparation of 1-α-methylbenzyl-(2*R*)- and (2*S*)-aziridine-2-carboxaldehydes[13] from the corresponding (2*R*)- and (2*S*)-aziridine-2-methalols by Swern oxidation.[14] The 2-alkenylaziridines[15] were obtained as a *cis*/*trans* mixture (~1:1—by NMR integration and they were not separated) from the Wittig reaction of the corresponding phosphonium salts and 1-α-methylbenzyl-(2*R*)- or (2*S*)-aziridine-2-carboxaldehyde in high yields. Even though the presence of a very labile vinyl substituted aziridine C(2)–N bond, the vinyl group was selectively reduced to provide the corresponding alkyl substituted products **4d**–**f** in 65–83% yields using *o*-nitrobenzenesulfonylhydrazide (NBSH) without forming any aziridine ring C(2)–N bond reduction product (Scheme 1).[16]

Table 1
Synthesis of enantiomerically pure 2-hydroxymethyl-1,2,3,4-tetrahydroquinolines and benzoxazine derivatives

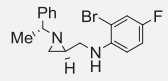
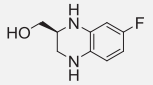
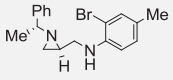
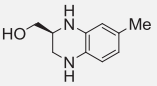
Compound		Yield (%)			Final product **8a**–**f**[c]
		6[a]	**7**[b]	**8**	
3a		88	87	92	
3b		60	48	90	
3c		90	55	97	
4d		86	61	90	
4e		85	58	97	
4f		68	59	98	

[a] Two steps yield.
[b] Three steps yield
[c] We easily obtained enantiomerically pure final heterocycles **8a**–**f** via debenzylation of α-methylbenzyl group from single diastereomers.

The synthesis of (1,2,3,4-tetrahydroquinoxalin-2-yl)methanols started from 1-α-methylbenzyl-(2*R*)- and (2*S*)-aziridine-2-carboxyaldehydes, which were reacted with the corresponding 2-bromoanilnes and $NaBH(OAc)_3$ in dichloroethane (DCE)[17] to obtain various 2-aminomethyl substituted aziridines **5g**–**h** in high yields (Scheme 1).

The aziridine ring was regioselectively cleaved by AcOH in dichloromethane (DCM) to furnish ring opening compounds in high yields and the crude products were used for the next reaction without further purification.[18] Saponification of the acetate proceeded smoothly with lithium hydroxide in THF, methanol, and water or potassium hydroxide in ethanol to give the corresponding amino alcohols and the hydroxyl group was protected with TBS. The TBS protected compounds were subsequently subjected to intramolecular C–N bond formation with $Pd_2(dba)_3$, X-Phos,[19] and NaO^tBu in toluene at 110 °C for 2–3 h. The same C–N bond forming reaction was applied for the preparation of (3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)methanols, 2-hydroxymethyl-1,2,3,4-tetrahydroquinolines, and (1,2,3,4-tetrahydroquinoxalin-2-yl)methanols (Scheme 2). The TBS group was deprotected by TBAF and the nitrogen protecting benzyl group was also cleaved by catalytic hydrogenation to provide the final compounds **8a**–**f** (Table 1) and **11g**–**h** (Table 2).

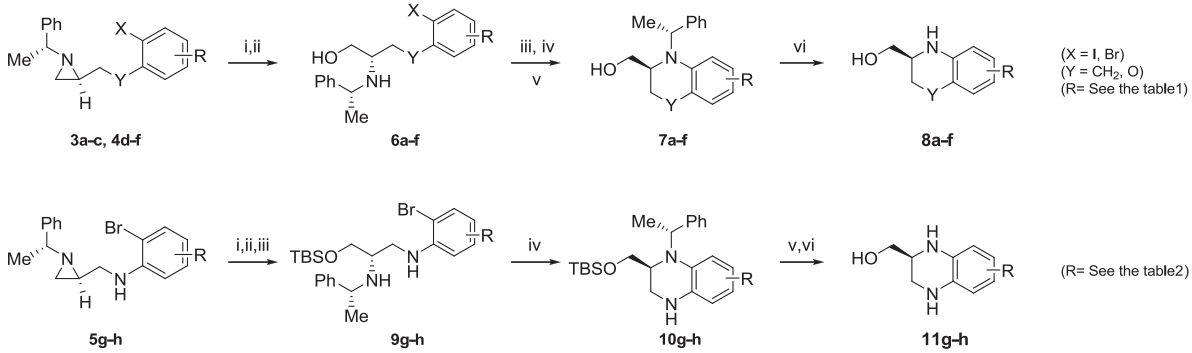
Table 2
Synthesis of enantiomerically pure 2-hydroxymethyl-1,2,3,4-tetrahydroquinoxalines

Compound		Yield (%)			Final product **11g**–**h**[c]
		9[b]	**10**	**11**[a]	
5g		63	56	79	
5h		68	72	52	

[a] Two steps yield.
[b] Three steps yield.
[c] We easily obtained enantiomerically pure final heterocycles **11g**–**h** via debenzylation of α-methylbenzyl group from single diastereomers.

3. Conclusions

Enantiomerically pure substituted 2,3-dihydro-3-hydroxymethyl-1,4-benzoxazines were prepared from chiral aziridine-2-methanols and *o*-halophenols, 2-hydroxymethyl-1,2,3,4-tetrahydroquinolines were synthesized from chiral aziridine-2-carboxaldeydes and *o*-halobenzylhalides and (1,2,3,4-tetrahydroquinoxalin-2-yl)methanols were prepared from chiral aziridine-2-carboxaldeydes and



Scheme 2. Reagents and conditions: (i) AcOH, DCM, rt; (ii) LiOH, MeOH/THF/H_2O=1:1:1, rt or KOH, EtOH, rt; (iii) TBSCl, TEA, DMAP, DCM, 0 °C to rt; (iv) $Pd_2(dba)_3$, X-Phos, NaO^tBu, toluene, 110 °C; (v) TBAF, THF, rt; (vi) $Pd(OH)_2$, H_2, MeOH, rt.

o-haloanilines in good yields. The synthesis of various *N*-containing heterocyclic compounds was successfully achieved from the common starting compounds, aziridine-2-methanols, via a Pd-catalyzed intramolecular C–N bond formation as the key step.

4. Experimental section

4.1. General method

All reactions were carried out under an atmosphere of nitrogen in oven-dried glasswares with magnetic stirring. Air sensitive reagents and solutions were transferred via syringe and were introduced to the apparatus through rubber septa. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates (60 F_{254}). Visualization was accomplished with either UV light, or by immersion in solutions of ninhydrin, *p*-anisaldehyde, or phosphomolybdic acid (PMA) followed by heating on a hot plate for about 10 s. Purification of reaction products was carried out by flash chromatography using Kieselgel 60 Art 9385 (230–400 mesh). ^{1}H NMR and ^{13}C NMR spectra were obtained using a Varian Gemini-300 (300 MHz for ^{1}H, and 75 MHz for ^{13}C), or a Varian Inova-500 (500 MHz for ^{1}H, and 125 MHz for ^{13}C) spectrometer. Chemical shifts are reported relative to chloroform (δ=7.26) for ^{1}H NMR and chloroform (δ=77.2) for ^{13}C NMR. Data are reported as (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet). Coupling constants are given in hertz. Ambiguous assignments were resolved on the basis of standard one dimensional proton decoupling experiments. Optical rotations were obtained using a Rudolph Autopol III digital polarimeter and optical rotation data was reported as follows: $[\alpha]_D^{24}$ (concentration *c*=g/100 mL, solvent). Elemental analyses were performed by the Organic Chemistry Research Center at Sogang University using a Carlo Erba EA 1180 elemental analyzer. High resolution mass spectra were recorded on a 4.7 Tesla IonSpec ESI-FTMS or a Micromass LCT ESI-TOF mass spectrometer. All commercially available compounds were used as received unless stated otherwise.

*4.1.1. (R)-2-[(2-Iodophenoxy)methyl]-1-[(R)-1-phenylethyl]-aziridine (**3a**).* To a solution of **1** (30 mg, 0.17 mmol) in DCM (0.90 mL) were added DMAP (2.0 mg, 0.017 mmol) and TEA (60 μL, 0.40 mmol) at 0 °C. After 30 min, TsCl (39 mg, 0.20 mmol) was added at room temperature. The reaction mixture was stirred for 4 h and then quenched with water. The mixture was extracted with DCM. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude tosylated compound. To a solution of the crude tosylate in DMF/acetone (1:1, 0.85 mL) were added 2-iodophenol (82 mg, 0.37 mmol) and K_2CO_3 (117 mg, 0.84 mmol). The reaction mixture was refluxed for 16 h and then cooled to room temperature. The reaction mixture was quenched with water and extracted with DCM. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by column silica gel chromatography provided 403 mg of **3a** in 95% yield (colorless oil); $[\alpha]_D^{24}$ +7.7 (*c* 0.35, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, 1H, *J*=7.8 Hz), 7.39–7.20 (m, 6H), 6.83 (d, 1H, *J*=7.8 Hz), 6.66 (t, 1H, *J*=6.9 Hz), 4.20 (dd, 1H, *J*=10.2, 3.6 Hz), 3.87–3.81 (m, 1H), 2.56 (q, 1H, *J*=6.6 Hz), 2.10–2.06 (m, 1H), 1.73 (d, 1H, *J*=3.0 Hz), 1.57 (d, 3H, *J*=6.6 Hz), 1.48 (d, 1H, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 144.6, 139.7, 129.6, 128.5, 127.2, 127.0, 122.7, 112.4, 86.7, 71.9, 70.0, 38.5, 31.2, 23.8; HRMS *m*/*z* calcd for $C_{17}H_{18}INO$ $[M+Na]^+$ 402.0331. Found 402.0329.

*4.1.2. (R)-2-[(2-Bromo-4-fluorophenoxy)methyl]-1-[(R)-1-phenylethyl]aziridine (**3b**).* Colorless oil, (95%); $[\alpha]_D^{24}$ +8.1 (*c* 0.40, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.25 (m, 5H), 7.00–6.87 (m, 3H), 4.19 (dd, 1H, *J*=3.9, 10.2 Hz), 3.81 (dd, 1H, *J*=7.8, 10.2 Hz), 2.54 (q, 1H, *J*=6.6 Hz), 1.72 (d, 1H, *J*=3.3 Hz), 1.58 (d, 1H, *J*=2.1 Hz), 1.52 (d, 3H, *J*=6.6 Hz), 1.47 (d, 1H, *J*=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 157.7, 155.8, 152.0, 144.4, 128.6, 127.3, 127.0, 120.7, 120.5, 114.8, 114.6, 113.9, 113.8, 112.3, 112.3; HRMS *m*/*z* calcd for $C_{17}H_{17}BrFNO$ $[M+Na]^+$ 372.0375. Found 372.0375.

*4.1.3. (R)-2-[(3-Bromonaphthalen-2-yloxy)methyl]-1-[(R)-1-phenylethyl]aziridine (**3c**).* Colorless oil, (90%); $[\alpha]_D^{24}$ +7.7 (*c* 0.30, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.68–7.64 (m, 2H), 7.40–7.16 (m, 8H), 4.31 (dd, 1H, *J*=9.9, 3.6 Hz), 3.96–3.89 (m, 1H), 2.56 (q, 1H, *J*=6.6 Hz), 2.13–2.11 (m, 1H), 1.77 (d, 1H, *J*=2.7 Hz), 1.56 (d, 1H, *J*=6.6 Hz), 1.50 (d, 1H, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 144.5, 133.6, 132.4, 129.6, 128.5, 127.2, 127.0, 126.9, 126.8, 126.7, 124.6, 113.9, 107.9, 71.7, 70.0, 38.5, 31.3, 23.5. Anal. Calcd for $C_{21}H_{20}BrNO$: C, 65.98; H, 5.27; Br, 20.90; N, 3.66; O, 4.19. Found: C, 65.91; H, 5.37; N, 3.49.

*4.1.4. (S)-2-(2-Iodophenylethyl)-1-[(R)-1-phenylethyl]aziridine (**4d**).* To a solution of (2-iodobenzyl)triphenylphosphonium bromide (830 mg, 1.48 mmol) in THF (2.80 mL) was added 1.0 M solution LiHMDS in THF (1.37 mL) at 0 °C. After 30 min, compound **2** (200 mg, 1.14 mmol) in THF (1.00 mL) was added at 0 °C. The reaction mixture was stirred for 24 h at room temperature and then quenched with water. The aqueous layer was extracted with DCM and the combined organic layer was dried over anhydrous $MgSO_4$, filtered then concentrated in vacuo. Purification by silica gel flash chromatography provided 403 mg of (*S*)-2-(2-iodostyryl)-1-[(*R*)-1-phenylethyl]aziridine (*cis*/*trans*=1:1 mixture). To a screw-cap vial was added above Wittig compound (200 mg, 0.53 mmol) in DCM (2.65 mL) and 2-nitrobenzenesulfonohydrazide (926 mg, 4.26 mmol) at room temperature. After 10 min, TEA (1.18 mL, 2.12 mmol) was added at 0 °C. The reaction mixture was stirred for overnight at room temperature and then diluted with ether (3 mL). The mixture was quenched with satd NH_4Cl solution and extracted with DCM. The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography provided 135 mg of **4d** in 83% yield (yellow oil); $[\alpha]_D^{24}$ +27.7 (*c* 0.75, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, 1H, *J*=7.8 Hz), 7.39–7.26 (m, 7H), 6.92–6.84 (m, 1H), 3.02–2.81 (m, 2H), 2.44 (q, 1H, *J*=6.6 Hz), 1.86–1.68 (m, 2H), 1.62–1.56 (m, 1H), 1.50–1.46 (m, 4H), 1.30 (d, 1H, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 144.5, 139.6, 129.3, 128.5, 128.4, 127.9, 127.1, 127.0, 100.9, 70.0, 40.2, 39.2, 33.8, 33.6, 23.5; HRMS *m*/*z* calcd for $C_{18}H_{20}IN$ $[M+Na]^+$ 400.0538. Found 400.0537.

*4.1.5. (S)-2-[2-(5-Bromobenzo[d][1,3]dioxol-4-yl)ethyl]-1-[(R)-1-phenylethyl]aziridine (**4e**).* Yellow oil, (68%); $[\alpha]_D^{24}$ +59.7 (*c* 1.30, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.23 (m, 5H), 7.00 (d, 1H, *J*=8.1 Hz), 6.56 (d, 1H, *J*=8.4 Hz), 5.95 (s, 2H), 2.98–2.77 (m, 2H), 2.42 (q, 1H, *J*=6.6 Hz), 1.94–1.65 (m, 2H), 1.58–1.51 (m, 1H), 1.46–1.43 (m, 4H), 1.25 (d, 1H, *J*=6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.8, 144.9, 128.4, 127.0, 127.0, 125.3, 123.7, 116.1, 107.6, 101.5, 70.0, 40.2, 33.4, 32.2, 28.0, 23.5; HRMS *m*/*z* calcd for $C_{19}H_{20}BrNO_2$ $[M+Na]^+$ 396.0575. Found 396.0573.

*4.1.6. (S)-2-[2-(1-Bromonaphthalen-2-yl)ethyl]-1-[(R)-1-phenylethyl]aziridine (**4f**).* Yellow oil, (65%); $[\alpha]_D^{24}$ +71.4 (*c* 1.55, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, 1H, *J*=8.1 Hz), 7.81–7.73 (m, 2H), 7.58 (t, 1H, *J*=7.2 Hz), 7.48 (t, 1H, *J*=7.2 Hz), 7.42–7.28 (m, 6H), 3.19 (t, 1H, *J*=7.5 Hz), 2.45 (q, 1H, *J*=6.3 Hz), 1.94–1.82 (m, 2H), 1.62–1.42 (m, 5H), 1.30 (d, 1H, *J*=6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 139.6, 133.4, 132.8, 128.5, 128.2, 128.1, 127.7, 127.5, 127.4, 127.1, 127.0, 126.0, 123.9, 70.0, 40.3, 35.7, 33.8,

33.6, 23.5; HRMS *m*/*z* calcd for $C_{22}H_{22}BrN$ $[M+Na]^+$ 402.0833. Found 402.0833.

*4.1.7. 2-Bromo-4-fluoro-N-{(S)-1-[(S)-1-phenylethylaziridin-2-yl] methyl}aniline (**5g**).* To a solution of compound **2** (509 mg, 2.96 mmol) and 2-bromo-4-fluoroaniline (843 mg, 4.44 mmol) in DCE (14.8 mL) was treated with $NaBH(OAc)_3$ (1881 mg, 8.87 mmol) at room temperature and in nitrogen atmosphere. To the reaction mixture was added anhydrous $MgSO_4$ (712 mg, 5.92 mmol). After stirring 15 h, the reaction mixture was diluted with DCM and quenched with distilled water. The pH of the aqueous layer was adjusted to pH 7–8 with satd $NaHCO_3$ solution. The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure to give the crude product. The crude product was purified by silica gel flash chromatography using 15% EtOAc/hexane to give **5g** in 85% yield as a colorless oil; $[\alpha]_D^{24}$ +10.8 (*c* 2.213, $CHCl_3$); R_f=0.39 (30% EtOAc/Hex); ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.32 (m, 4H), 7.29–7.21 (m, 2H), 6.96–6.92 (td, 1H, *J*=8.5, 3.0 Hz), 6.66–6.64 (dd, 1H, *J*=8.5, 4.5 Hz), 4.54 (br, 1H), 3.51–3.46 (m, 1H), 2.93–2.88 (m, 1H), 2.50–2.46 (q, 1H, *J*=6.5 Hz), 1.91–1.86 (m, 1H), 1.69–1.68 (d, 1H, 3.5 Hz), 1.47–1.45 (d, 3H, *J*=6.0 Hz), 1.41–1.40 (d, 1H, *J*=6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 153.7, 144.4, 141.9, 128.6, 127.3, 126.9, 119.7, 119.6, 115.2, 114.9, 111.8, 111.7, 109.4, 109.3, 69.7, 47.0, 38.8, 32.2, 23.7; Anal. Calcd for $C_{17}H_{18}BrFN_2$: C, 58.46; H, 5.19; Br, 22.88; F, 5.44; N, 8.02. Found: C, 58.37; H, 5.09; N, 8.11.

*4.1.8. 2-Bromo-4-methyl-N-{(S)-1-[(S)-1-phenylethylaziridin-2-yl] methyl}aniline (**5h**).* Pale yellow solid, (86%); $[\alpha]_D^{24}$ −3.1 (*c* 2.188, $CHCl_3$); R_f=0.48 (30% EtOAc/Hex); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.30 (m, 5H), 7.24–7.22 (d, 1H, *J*=7.2 Hz), 7.00–6.97 (d, 1H, *J*=8.4 Hz), 6.64–6.61 (d, 1H, *J*=8.1 Hz), 4.56 (br, 1H), 3.52–3.44 (m, 1H), 2.97–2.89 (m, 1H), 2.49–2.42 (q, 1H, *J*=6.3 Hz), 2.22 (s, 3H), 1.91–1.84 (m, 1H), 1.68–1.67 (d, 1H, *J*=3.6 Hz), 1.47–1.45 (d, 3H, *J*=6.3 Hz), 1.39–1.37 (d, 1H, *J*=6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 142.9, 133.0, 129.1, 128.5, 127.6, 127.2, 126.9, 111.8, 110.1, 69.7, 46.8, 38.9, 32.2, 23.7, 20.2; HRMS *m*/*z* calcd for $C_{18}H_{21}BrN_2$ $[M+Na]^+$ 367.0786. Found 367.0783.

*4.1.9. (R)-3-(2-Iodophenoxy)-2-[(R)-1-phenylethylamino]propan-1-ol (**6a**).* To a solution of compound **3a** (370 mg, 0.98 mmol) in DCM (2.00 mL) was added AcOH (280 μL, 4.90 mmol) at room temperature. The reaction mixture was stirred for overnight at room temperature and then quenched with satd $NaHCO_3$ solution. The aqueous layer was extracted with DCM. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography provided 157 mg of the ring opening product. To a solution of the ring opening product in methanol/THF co-solvent (1:1, 2.5 mL) was added LiOH (159 mg in H_2O, 1.25 mL). The reaction mixture was stirred for 30 min at room temperature and the mixture was quenched with satd NH_4Cl solution, extracted with DCM. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography provided 266 mg of **6a** as a colorless oil in 88% yield (two steps yield): $[\alpha]_D^{24}$ +19.2 (*c* 0.50, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, 1H, *J*=7.2 Hz), 7.36–7.25 (m, 6H), 6.81 (d, 1H, *J*=8.1 Hz), 6.74 (t, 1H, *J*=7.2 Hz), 4.15–4.10 (m, 1H), 4.03–3.93 (m, 2H), 3.63–3.51 (m, 2H), 3.00–2.95 (m, 1H), 1.42 (d, 3H, *J*=6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 145.3, 139.5, 129.8, 128.8, 127.5, 127.0, 123.2, 112.3, 86.8, 68.0, 62.6, 55.8, 55.8, 25.4. Anal. Calcd for $C_{17}H_{20}INO_2$: C, 51.40; H, 5.07; I, 31.95; N, 3.53; O, 8.06. Found: C, 51.45; H, 5.13; N, 3.47.

*4.1.10. (R)-3-(2-Bromo-4-fluorophenoxy)-2-[(R)-1-phenylethylamino]propan-1-ol (**6b**).* Colorless oil, (60%); $[\alpha]_D^{24}$ +25.7 (*c* 0.50, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.22 (m, 6H), 6.98 (td, 1H, *J*=3.0, 8.7 Hz), 6.83 (dd, 1H, *J*=5.1, 9.0 Hz), 4.09 (dd, 1H, *J*=4.5, 9.3 Hz), 4.00 (q, 1H, *J*=6.3 Hz), 3.93 (dd, 1H, *J*=4.5, 9.3 Hz), 3.59–3.50 (m, 2H), 2.97 (quintet, 1H, *J*=4.8 Hz), 2.32 (s, 2H), 1.41 (d, 3H, *J*=6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 156.0, 151.8, 145.4, 128.8, 127.5, 126.9, 120.7, 120.5, 115.1, 114.9, 114.0, 114.0, 112.6, 112.5, 69.0, 62.5, 56.0, 55.8, 25.3. Anal. Calcd for $C_{17}H_{19}BrFNO_2$: C, 55.45; H, 5.20; Br, 21.70; F, 5.16; N, 3.80; O, 8.69. Found: C, 55.32; H, 5.17; N, 3.91.

*4.1.11. (R)-3-(3-Bromonaphthalen-2-yloxy)-2-[(R)-1-phenylethylamino]propan-1-ol (**6c**).* Colorless oil, (90%); $[\alpha]_D^{24}$ +13.5 (*c* 0.15, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.72–7.69 (m, 2H), 7.49–7.23 (m, 7H), 7.16 (s, 1H), 4.26 (dd, 1H, *J*=4.2, 9.3 Hz), 4.13–4.03 (m, 2H), 3.66–3.53 (m, 2H), 3.06 (quintet, 1H, *J*=4.8 Hz), 2.21 (s, 2H), 1.43 (d, 3H, *J*=6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6, 145.4, 133.6, 132.4, 129.7, 128.8, 127.5, 127.0, 126.9, 126.9, 126.8, 124.9, 113.8, 107.9, 68.3, 62.7, 56.0, 55.8, 25.3. Anal. Calcd for $C_{21}H_{22}BrNO_2$: C, 63.01; H, 5.54; Br, 19.96; N, 3.50; O, 7.99. Found: C, 63.05; H, 5.59; N, 3.57.

*4.1.12. (S)-4-(2-Iodophenyl)-2-[(R)-1-phenylethylamino]butan-1-ol (**6d**).* Yellow oil, (86%); $[\alpha]_D^{24}$ +4.0 (*c* 0.40, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, 1H, *J*=7.5, 1.5 Hz), 7.33–7.23 (m, 6H), 7.17 (dd, 1H, *J*=7.5, 1.5 Hz), 6.89 (td, 1H, *J*=7.5, 1.5 Hz), 3.98 (q, 1H, *J*=6.5 Hz), 3.54 (dd, 1H, *J*=10.5, 4.0 Hz), 3.30 (dd, 1H, *J*=10.5, 7.5 Hz), 2.75–2.56 (m, 3H), 1.65–1.57 (m, 2H), 1.37 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 139.8, 129.5, 128.9, 128.8, 128.7, 128.1, 127.6, 127.0, 100.6, 64.0, 56.3, 55.7, 37.4, 31.8, 24.7; HRMS *m*/*z* calcd for $C_{18}H_{22}INO$ $[M+Na]^+$ 396.0824. Found 396.0822.

*4.1.13. (S)-4-(5-Bromobenzo[d][1,3]dioxol-4-yl)-2-[(R)-1-phenylethylamino]butan-1-ol (**6e**).* Colorless oil, (85%); $[\alpha]_D^{24}$ +6.8 (*c* 0.15, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.22 (m, 5H), 7.02 (d, 1H, *J*=8.1 Hz), 6.58 (d, 1H, *J*=8.4 Hz), 5.92 (d, 1H, *J*=1.5 Hz), 5.81 (d, 1H, *J*=1.2 Hz), 3.95 (q, 1H, *J*=6.6 Hz), 3.59 (dd, 1H, *J*=11.1, 3.9 Hz), 3.36 (dd, 1H, *J*=7.5, 10.5 Hz), 2.76–2.50 (m, 4H), 1.74–1.62 (m, 2H), 1.42 (d, 3H, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5, 144.5, 128.6, 127.3, 126.8, 125.2, 123.1, 115.6, 107.7, 104.4, 101.4, 63.9, 56.1, 55.5, 29.7, 26.0, 24.5; HRMS *m*/*z* calcd for $C_{19}H_{22}BrNO_3$ $[M+H]^+$ 392.0861. Found 392.0863.

*4.1.14. (S)-4-(1-Bromonaphthalen-2-yl)-2-[(R)-1-phenylethylamino] butan-1-ol (**6f**).* Colorless oil, (68%); $[\alpha]_D^{24}$ +37.3 (*c* 0.35, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, 1H, *J*=8.5 Hz), 7.82 (d, 1H, *J*=8.0 Hz), 7.74 (d, 1H, *J*=8.0 Hz), 7.61 (t, 1H, *J*=8.0 Hz), 7.52 (t, 1H, *J*=8.0 Hz), 7.31–7.21 (m, 6H), 3.99 (q, 1H, *J*=6.5 Hz), 3.63 (dd, 1H, *J*=4.0, 10.5 Hz), 3.39 (dd, 1H, *J*=7.5, 10.5 Hz), 3.04–2.98 (m, 1H), 2.94–2.87 (m, 1H), 2.64–2.61 (m, 1H), 2.25 (br s, 2H), 2.02–1.96 (m, 1H), 1.82–1.75 (m, 1H), 1.40 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 139.5, 133.4, 132.8, 128.7, 128.2, 128.1, 128.0, 127.6, 127.4, 127.3, 126.9, 126.1, 123.7, 64.3, 56.1, 55.6, 34.0, 31.9, 25.0; HRMS *m*/*z* calcd for $C_{22}H_{24}BrNO$ $[M+Na]^+$ 420.0939. Found 420.0936.

*4.1.15. (S)-N^1-(2-Bromo-4-fluorophenyl)-3-(tert-butyldimethylsilyloxy)-N^2-[(R)-1-phenylethyl]propane-1,2-diamine (**9g**).* To a round bottom flask was added **5g** (762 mg, 2.18 mmol) in DCM (7.30 mL). AcOH (0.75 mL, 13.10 mmol) was added to the solution at room temperature and the mixture was stirred for 8 h. The reaction was quenched with satd $NaHCO_3$ solution, extracted with DCM, and concentrated in vacuo. The crude product was dissolved in EtOH (6.1 mL) and KOH (309 mg, 5.51 mmol) was added to the reaction mixture. After stirring for 20 min at room temperature, the solvent was removed under reduced pressure to give a crude product. The crude product was diluted with DCM and added distilled water. The

aqueous layer was extracted with DCM, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was dissolved in DCM (8.0 mL) and added TBSCl (361 mg, 2.39 mmol) at a temperature of 0 °C. To the reaction mixture were added TEA (0.67 mL, 4.79 mmol) and DMAP (19 mg, 0.160 mmol) and stirred for 1.5 h at room temperature in nitrogen atmosphere. The reaction was quenched with distilled water and the aqueous layer was extracted with DCM. The combined organic layer was dried over anhydrous $MgSO_4$ and concerted in vacuo. Purification by column chromatography on silica gel using 10% EtOAc/hexane to give **9g** in 63% yield as a colorless oil; $[\alpha]_D^{24}$ +23.6 (*c* 1.147, $CHCl_3$); R_f=0.52 (20% EtOAc/Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.20 (m, 5H), 7.17–7.13 (dd, 1H, *J*=8.1, 2.7 Hz), 6.87–6.80 (td, 1H, *J*=8.7, 2.7 Hz), 6.45–6.40 (dd, 1H, *J*=9.3, 5.4 Hz), 4.90 (br, 1H), 3.84–3.77 (q, 1H, *J*=6.6 Hz), 3.59–3.50 (m, 2H), 3.13–3.06 (m, 1H), 2.94–2.87 (m, 1H), 2.84–2.77 (m, 1H), 1.79 (br, 1H), 1.33–1.31 (d, 3H, *J*=6.6 Hz), 0.83 (s, 9H), −0.02 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 153.5, 145.9, 142.6, 128.6, 127.1, 126.6, 119.6, 119.4, 115.1, 114.9, 111.5, 111.5, 109.3, 109.3, 64.3, 55.1, 54.8, 44.5, 26.0, 24.9, 18.4, −5.3, −5.3; HRMS *m*/*z* calcd for $C_{23}H_{34}BrFN_2OSi$ $[M+Na]^+$ 503.1506. Found 503.1508.

*4.1.16. (S)-N^1-(2-Bromo-4-methylphenyl)-3-(tert-butyldimethylsilyloxy)-N^2-[(R)-1-phenylethyl]propane-1,2-diamine (**9h**).* Colorless oil, (68%); $[\alpha]_D^{24}$ +26.6 (*c* 0.948, $CHCl_3$); R_f=0.56 (20% EtOAc/Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.29 (m, 5H), 7.28–7.25 (m, 1H), 7.01–6.98 (d, 1H, *J*=7.2 Hz), 6.54–6.51 (d, 1H, *J*=8.4 Hz), 4.96 (br, 1H), 3.94–3.87 (q, 1H, *J*=6.6 Hz), 3.69–3.59 (m, 2H), 3.25–3.15 (m, 1H), 3.08–3.00 (m, 1H), 2.93–2.86 (m, 1H), 2.26 (s, 3H), 1.89 (br, 1H), 1.42–1.40 (d, 3H, *J*=6.6 Hz), 0.93 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.0, 143.5, 132.9, 129.0, 128.6, 127.1, 127.0, 126.6, 111.7, 110.1, 64.4, 55.1, 54.9, 44.3, 26.1, 25.0, 20.2, 18.4, −5.3, −5.3; HRMS *m*/*z* calcd for $C_{24}H_{37}BrN_2OSi$ $[M+Na]^+$ 499.1757. Found 499.1757.

*4.1.17. {(R)-4-[(R)-1-Phenylethyl]-3,4-dihydro-2H-benzo[b]-[1,4]oxazin-3-yl}methanol (**7a**).* To a screw-cap vial were added **6a** (347 mg, 0.68 mmol) and NaO^{t}Bu (163 mg, 1.69 mmol) in toluene (6.80 mL). The reaction mixture was degassed for 10 min and quickly added $Pd_2(dba)_3$ (37 mg, 0.041 mmol) and X-Phos (29 mg, 0.061 mmol). The reaction mixture was stirred for 30 min at 110 °C. The mixture was cooled to room temperature, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography provided 230 mg of cyclized product in 88% yield. To a solution of the product (230 mg, 0.60 mmol) in THF (3.00 mL) was added 0.63 ml of 1.0 M solution of TBAF at room temperature. The reaction mixture was stirred for 5 h at room temperature and then quenched with water. The mixture was extracted with DCM and the combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography provided 159 mg of **7a** as a colorless oil in 99% yield: $[\alpha]_D^{24}$ +66.1 (*c* 0.50, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.22 (m, 5H), 7.00 (d, 1H, *J*=7.5 Hz), 6.88 (t, 1H, *J*=7.5 Hz), 6.80 (d, 1H, *J*=7.5 Hz), 6.69 (t, 1H, *J*=7.5 Hz), 5.12 (q, 1H, *J*=6.6 Hz), 4.05 (d, 1H, *J*=10.5 Hz), 3.52 (d, 2H, *J*=7.2 Hz), 3.33–3.30 (m, 1H), 3.05 (d, 1H, *J*=10.5 Hz), 1.89 (br s, 1H), 1.69 (d, 3H, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 140.5, 133.1, 128.6, 127.7, 127.1, 121.9, 118.7, 117.1, 117.0, 62.6, 61.1, 58.9, 52.0, 18.4; HRMS *m*/*z* calcd for $C_{17}H_{19}NO_2$ $[M+Na]^+$ 292.1314. Found 292.1311.

*4.1.18. {(R)-6-Fluoro-4-[(R)-1-phenylethyl]-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl}methanol (**7b**).* Yellow oil, (60/80%); $[\alpha]_D^{24}$ +5.5 (*c* 0.85, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.25 (m, 5H), 6.74–6.63 (m, 2H), 6.36 (m, 1H), 5.05 (q, 1H, *J*=7.5 Hz), 4.12 (d, 1H, *J*=6.6 Hz), 3.57–3.54 (m, 2H), 3.35–3.29 (m, 1H), 3.12 (d, 1H, *J*=6.0 Hz), 1.69 (d, 3H, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 157.4, 140.3, 139.9, 134.1, 134.1, 128.8, 127.9, 127.1, 117.4, 117.3, 104.3, 104.1, 102.8, 102.6, 62.9, 61.4, 58.6, 52.0, 18.2; HRMS *m*/*z* calcd for $C_{17}H_{18}FNO_2$ $[M+Na]^+$ 310.1219. Found 310.1217.

*4.1.19. {(R)-4-[(R)-1-Phenylethyl]-3,4-dihydro-2H-naphtho[2,3-b][1,4]oxazin-3-yl}methanol (**7c**).* Yellow oil, (77/71%); $[\alpha]_D^{24}$ +86.9 (*c* 0.45, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (t, 2H, *J*=7.5 Hz), 7.28–7.10 (m, 9H), 5.26 (q, 1H, *J*=6.9 Hz), 4.29 (d, 1H, *J*=10.8 Hz), 3.62–3.60 (m, 2H), 3.53–3.49 (m, 1H), 3.34–3.29 (m, 1H), 2.11 (br s, 1H), 1.71 (d, 3H, *J*=6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 141.0, 134.4, 130.5, 128.7, 127.7, 127.4, 127.1, 126.2, 125.7, 124.2, 122.9, 112.0, 108.9, 63.7, 61.3, 57.6, 51.6, 18.0; HRMS *m*/*z* calcd for $C_{21}H_{21}NO_2$ $[M+Na]^+$ 342.1470. Found 342.1471.

*4.1.20. {(S)-1-[(R)-1-Phenylethyl]-1,2,3,4-tetrahydroquinolin-2-yl}methanol (**7d**).* Yellow oil, (73/83%); $[\alpha]_D^{24}$ +109.6 (*c* 4.25, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.24 (m, 5H), 7.07 (t, 1H, *J*=7.8 Hz), 6.98 (d, 1H, *J*=7.2 Hz), 6.90 (d, 1H, *J*=8.1 Hz), 6.69 (t, 1H, *J*=7.2 Hz), 5.11 (q, 1H, *J*=6.6 Hz), 3.53–3.35 (m, 3H), 2.74–2.54 (m, 2H), 2.71–2.68 (m, 4H), 1.20–1.09 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9, 141.9, 129.9, 128.5, 127.3, 127.1, 127.0, 123.7, 117.6, 116.7, 63.1, 59.5, 53.0, 23.5, 21.1, 18.6; HRMS *m*/*z* calcd for $C_{18}H_{21}NO$ $[M+Na]^+$ 290.1521. Found 290.1522.

*4.1.21. {(S)-6-[(R)-1-Phenylethyl]-6,7,8,9-tetrahydro-[1,3]-dioxolo[4,5-f]quinolin-7-yl}methanol (**7e**).* Brown oil, (64/90%); $[\alpha]_D^{24}$ +35.0 (*c* 1.30, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.18 (m, 5H), 7.64 (d, 1H, *J*=8.4 Hz), 6.44 (d, 1H, *J*=8.7 Hz), 5.89 (s, 2H), 5.00 (q, 1H, *J*=6.9 Hz), 3.50–3.34 (m, 3H), 2.55–2.33 (m, 2H), 1.85–1.82 (m, 1H), 1.65 (d, 3H, *J*=6.9 Hz), 1.54–1.48 (m, 1H), 1.01–0.92 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.5, 141.9, 140.3, 139.2, 128.5, 127.4, 127.1, 110.0, 108.6, 106.7, 101.0, 62.5, 61.1, 52.3, 19.6, 19.0, 17.1; HRMS *m*/*z* calcd for $C_{19}H_{21}NO_3$ $[M+Na]^+$ 334.1419. Found 334.1420.

*4.1.22. {(S)-1-[(R)-1-Phenylethyl]-1,2,3,4-tetrahydrobenzo[h]-quinolin-2-yl}methanol (**7f**).* Green oil, (72/82%); $[\alpha]_D^{24}$ +58.8 (*c* 0.30, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, 1H, *J*=8.1 Hz), 7.84 (d, 1H, *J*=7.8 Hz), 7.56–7.43 (m, 3H), 7.25–7.18 (m, 3H), 7.06 (d, 1H, *J*=8.4 Hz), 6.87–6.85 (m, 2H), 4.93 (q, 1H, *J*=7.2 Hz), 3.57–3.55 (m, 1H), 3.29–3.26 (m, 2H), 2.52–2.40 (m, 2H), 2.33–2.24 (m, 1H), 1.86 (d, 3H, *J*=7.2 Hz), 1.28–1.14 (m, 1H), 0.77–0.69 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3, 140.1, 134.2, 129.6, 129.0, 128.3, 127.9, 127.7, 127.6, 126.6, 125.7, 125.2, 123.2, 122.8, 63.2, 61.9, 51.8, 23.7, 20.3, 18.7; HRMS *m*/*z* calcd for $C_{22}H_{23}NO$ $[M+Na]^+$ 340.1677.Found 340.1675.

*4.1.23. (S)-2-[(tert-Butyldimethylsilyloxy)methyl]-7-fluoro-1-[(R)-1-phenylethyl]-1,2,3,4-tetrahydroquinoxaline (**10g**).* To a solution of **9g** (664 mg, 1.38 mmol) in anhydrous toluene (27.6 mL) was added NaO^{t}Bu (332 mg, 3.45 mmol) at room temperature and in nitrogen atmosphere. The reaction mixture was degassed for 10 min and were added $Pd_2(dba)_3$ (76 mg, 0.08 mmol) and X-Phos (59 mg, 0.12 mmol). The reaction mixture was refluxed and stirred for 3 h in nitrogen atmosphere. After the reaction was completed, the reaction mixture was cooled to room temperature, filtered with glass filter on a pad of Celite. The residue was concentrated in vacuo to give a crude product. Purification by column chromatography on silica gel using 5% EtOAc/hexane to give of **10g** in 56% yield as a dark brown oil; $[\alpha]_D^{24}$ −4.9 (*c* 0.500, $CHCl_3$); R_f=0.46 (10% EtOAc/Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.21 (m, 5H), 6.48–6.40 (m, 2H), 6.28–6.22 (td, 1H, *J*=8.4, 2.4 Hz), 5.02–4.95 (q, 1H, *J*=6.9 Hz), 3.61–3.55 (t, 1H, *J*=9.6 Hz), 3.49–3.44 (m, 2H), 3.31–3.23 (m, 2H), 2.56–2.51 (dd, 1H, *J*=11.1, 3.3 Hz), 1.68–1.65 (d, 3H, *J*=7.2 Hz), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 156.3, 141.4, 134.6, 134.5, 429.5, 128.6, 127.4, 127.1, 114.7, 114.6, 102.9, 102.7, 101.3,

101.0, 62.7, 57.9, 52.9, 39.1, 26.1, 18.2, −5.2, −5.2; HRMS *m*/*z* calcd for $C_{23}H_{33}FN_2OSi$ $[M+Na]^+$ 423.2244. Found 423.2248.

*4.1.24. (S)-2-[(tert-Butyldimethylsilyloxy)methyl]-7-methyl-1-[(R)-1-phenylethyl]-1,2,3,4-tetrahydroquinoxaline (**10h**).* Brown oil, (72%); $[\alpha]_D^{24}$ −42.8 (*c* 1.160, $CHCl_3$); R_f=0.58 (10% EtOAc/Hex); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 6.68 (s, 1H), 6.52–6.49 (d, 1H, *J*=7.8 Hz), 6.46–6.44 (d, 1H, *J*=7.5 Hz), 5.20–5.13 (q, 1H, *J*=6.9 Hz), 3.66–3.59 (t, 1H, *J*=9.9 Hz), 3.54 (br, 1H), 3.52–3.47 (dd, 1H, *J*=9.6, 4.8 Hz), 3.31–3.21 (m, 2H), 2.54–2.49 (dd, 1H, *J*=10.5, 2.7 Hz), 2.28 (s, 3H), 1.73–1.71 (d, 3H, *J*=6.9 Hz), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.5, 131.2, 128.4, 128.1, 127.3, 127.2, 117.9, 115.0, 114.8, 62.8, 57.6, 52.5, 38.7, 26.1, 21.3, 18.3, −5.1, −5.2; HRMS *m*/*z* calcd for $C_{24}H_{36}N_2OSi$ $[M+Na]^+$ 419.2495. Found 419.2496.

*4.1.25. (R)-(3,4-Dihydro-2H-benzo[b][1,4]oxazin-3-yl)methanol (**8a**).* To a solution of **7a** (53 mg, 0.20 mmol) in methanol (0.70 mL) was added $Pd(OH)_2$ (30 wt %) at room temperature under 100 psi of H_2 (g). The reaction mixture was filtered and the filtrate was concentrated in vacuo. Purification by silica gel flash column chromatography provided 30 mg of **8a** as a white solid in 92% yield: $[\alpha]_D^{24}$ +9.4 (*c* 0.30, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 6.81–6.62 (m, 5H), 4.19 (dd, 1H, *J*=2.7, 10.8 Hz), 4.06 (dd, 1H, *J*=5.7, 10.8 Hz), 3.72 (dd, 1H, *J*=5.1, 10.2 Hz), 3.63 (dd, 1H, *J*=6.9, 10.2 Hz), 3.57–3.50 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 132.8, 121.8, 119.2, 116.9, 116.1, 66.0, 62.9, 51.3; HRMS *m*/*z* calcd for $C_9H_{11}NO_2$ $[M+Na]^+$ 188.0688. Found 188.0689.

*4.1.26. (R)-(6-Fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl) methanol (**8b**).* Red solid, (90%); $[\alpha]_D^{24}$ +7.1 (*c* 0.40, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ 6.72–6.67 (m, 1H), 6.36–6.30 (m, 2H), 4.14 (dd, 1H, *J*=3.0, 10.8 Hz), 4.03 (dd, 1H, *J*=5.1, 10.8 Hz), 3.73 (dd, 1H, *J*=5.1, 10.8 Hz), 3.66–3.60 (m, 1H), 3.58–3.51 (m, 1H), 2.98 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 157.1, 139.8, 139.7, 133.7, 133.6, 117.2, 117.2, 104.8, 104.7, 102.4, 102.2, 65.7, 62.9, 51.1; HRMS *m*/*z* calcd for $C_9H_{10}FNO_2$ $[M+Na]^+$ 206.0593. Found 206.0597.

*4.1.27. (R)-(3,4-Dihydro-2H-naphtho[2,3-b][1,4]oxazin-3-yl)methanol (**8c**).* Yellow solid, (97%); $[\alpha]_D^{24}$ +9.5 (*c* 0.35, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ 7.50–7.44 (m, 2H), 7.17–7.06 (m,3H), 6.90 (s, 1H), 4.26 (dd, 1H, *J*=3.0, 10.8 Hz), 4.10 (dd, 1H, *J*=5.7, 10.8 Hz), 3.62–3.60 (m, 2H), 3.55–3.47 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 146.2, 136.1, 132.0, 129.4, 127.3, 126.1, 124.7, 123.1, 112.2, 109.5, 67.4, 63.1, 52.4; HRMS *m*/*z* calcd for $C_{13}H_{13}NO_2$ $[M+Na]^+$ 238.0844. Found 238.0844.

*4.1.28. (S)-(1,2,3,4-Tetrahydroquinolin-2-yl)methanol (**8d**)*[10,20]. Yellow oil, (90%); $[\alpha]_D^{24}$ +54.0 (*c* 0.85, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.00–6.95 (m, 2H), 6.63 (t, 1H, *J*=6.9 Hz), 6.53 (d, 1H, *J*=7.8 Hz), 3.73 (dd, 1H, *J*=3.6, 10.2 Hz), 3.57–3.51 (m, 1H), 3.48–3.40 (m, 1H), 2.89–2.70 (m, 2H), 1.92–1.87 (m, 1H), 1.76–1.63 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 129.4, 127.0, 121.6, 117.6, 114.7, 66.9, 52.9, 26.0, 24.5; HRMS *m*/*z* calcd for $C_{10}H_{13}NO$ $[M+Na]^+$ 186.0895. Found 186.0896.

*4.1.29. (S)-(6,7,8,9-Tetrahydro-[1,3]dioxolo[4,5-f]quinolin-7-yl)methanol (**8e**).* Brown oil, (97%); $[\alpha]_D^{24}$ +71.2 (*c* 1.10, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 6.51 (d, 1H, *J*=8.1 Hz), 6.03 (d, 1H, *J*=8.1 Hz), 5.85 (d, 2H, *J*=3.9 Hz), 3.74 (dd, 1H, *J*=3.9, 10.5 Hz), 3.55 (dd, 1H, *J*=7.8, 10.5 Hz), 3.35 (br s, 1H), 2.86 (br s, 1H), 2.80–2.58 (m, 3H), 1.93–1.86 (m, 1H), 1.73–1.59 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.6, 140.0, 139.2, 106.7, 106.1, 106.0, 100.8, 66.7, 53.0, 23.9, 20.0; HRMS *m*/*z* calcd for $C_{11}H_{13}NO_3$ $[M+Na]^+$ 230.0793. Found 230.0795.

*4.1.30. (S)-(1,2,3,4-Tetrahydrobenzo[h]quinolin-2-yl)methanol (**8f**).* Green oil, (98%); $[\alpha]_D^{24}$ +104.0 (*c* 1.00, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.77–7.72 (m, 2H), 7.43–7.38 (m, 2H), 7.24–7.10 (m, 2H), 3.84 (dd, 1H, *J*=3.6, 10.2 Hz), 3.70–3.64 (m, 1H), 3.59–3.48 (m, 1H), 3.06–2.81 (m, 2H), 2.00–1.94 (m, 1H), 1.87–1.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 133.2, 128.7, 128.3, 125.2, 125.0, 123.4, 119.7, 117.6, 115.9, 66.8,53.3, 26.5, 24.4; HRMS *m*/*z* calcd for $C_{14}H_{15}NO$ $[M+Na]^+$ 236.1051. Found 236.1052.

*4.1.31. (S)-(7-Fluoro-1,2,3,4-tetrahydroquinoxalin-2-yl)methanol (**11g**).* To a solution of **10g** (239 mg, 0.50 mmol) in anhydrous THF (2.5 mL) was added 0.52 ml of 1.0 M solution of TBAF at room temperature in nitrogen atmosphere. The reaction mixture was stirred for 2 h and then diluted with EtOAc. The reaction was quenched with distilled water and the aqueous layer was extracted with DCM, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure to give a crude product. The crude product was purified by column chromatography on silica gel using 40% EtOAc/hexane. A mixture of the desilylated product and Pd $(OH)_2$ (80 mg) in MeOH (2.5 mL) was stirred at room temperature under H_2 atmosphere for 2 h. After the reaction was completed the reaction mixture was filtered to remove $Pd(OH)_2$, concentrated in vacuo. Purification by column chromatography to give of **11g** as a brown oil in 79% yield; $[\alpha]_D^{24}$ +20.5 (*c* 0.705, $CHCl_3$); R_f=0.37 (100% EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 6.45–6.40 (m, 1H), 6.31–6.25 (m, 2H), 3.74–3.69 (dd, 1H, *J*=10.5, 4.5 Hz), 3.64–3.57 (m, 1H), 3.56–3.51 (m, 1H), 3.31–3.26 (dd, 1H, *J*=11.1, 3.0 Hz), 3.20–3.14 (dd, 1H, *J*=10.8, 5.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 156.4, 134.4, 134.3, 128.9, 128.9, 115.3, 115.2, 104.2, 104.1, 101.7, 101.4, 65.1, 51.7, 42.9; HRMS calcd for $C_9H_{11}FN_2O$ $[M+Na]^+$ 205.0753. Found 205.0753.

*4.1.32. (S)-(7-Methyl-1,2,3,4-tetrahydroquinoxalin-2-yl)methanol (**11h**).* Dark brown oil, (52%); $[\alpha]_D^{24}$ +40.2 (*c* 1.800, $CHCl_3$); R_f=0.33 (100% EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 6.45–6.40 (m, 2H), 6.38 (s, 1H), 3.72–3.69 (dd, 1H, *J*=10.5, 5.0 Hz), 3.64–3.60 (dd, 1H, *J*=11.0, 7.0 Hz), 3.54 (br, 1H), 3.29 (br, 1H), 3.21 (br, 3H), 2.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.1, 130.7, 129.1, 119.3, 115.8, 115.1, 65.0, 51.9, 43.1, 20.8; HRMS calcd for $C_{10}H_{14}N_2O$ $[M+Na]^+$ 201.1004. Found 201.1003.

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