Tetrahedron: *Asymmetry* 25 (2014) 709–717

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Tunable chiral monophosphines as ligands in enantioselective rhodium-catalyzed ring-opening of oxabenzonorbornadienes with amines

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ARTICLE INFO

Article history:
Received 20 August 2013
Revised 11 March 2014
Accepted 13 March 2014

ABSTRACT

A new tunable chiral monophosphine was used as a ligand for asymmetric rhodium-catalyzed ring-opening of oxabenzonorbornadiene with amines, providing a series of chiral ring-opened products in high yields (up to 97%) and with high enantioselectivities (>99%).The reaction can be performed at rt to obtain the desired product with high enantioselectivity.

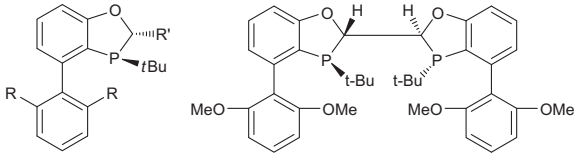
1. Introduction

Syntheses of chiral substituted dihydronaphthalene compounds have gained great interest due to their core structural relevance to different biological activities.[1] Although there are different chemical routes to synthesize such compounds, one of the most attractive synthetic strategies is the transition metal-catalyzed asymmetric ring-opening (ARO) of oxabenzonorbornadiene.

Ever since the pioneering study in this field reported by Lautens,[2] great progress has been achieved in the rhodium-catalyzed asymmetric ring-openings of oxabenzonorbornadiene with a wide range of nucleophiles.[3–10] Other metals such as copper,[11] palladium,[6,12] iron,[13] nickel,[14] and iridium[15,16] catalyzed asymmetric ring-opening reactions of oxabicyclic alkenes have also been reported on.

Although great progress has been achieved on the metal-catalyzed asymmetric ring-opening of oxabenzonorbornadiene,[17] the development of novel and efficient catalysts with less expensive transition metals, broader substrate scope, and low catalyst loadings continues to be of great importance.

Recently we have developed a series of chiral biaryl monophosphorus ligands used for palladium-catalyzed asymmetric Suzuki–Miyaura coupling reactions[18] and the ruthenium-catalyzed asymmetric additions of arylboronic acids to aryl aldehydes.[19] We speculated that the high tunability of these monophosphorus ligands could be used to investigate the asymmetric ring-opening reaction of oxabenzonorbornadiene with amines. Herein we report a new and efficient rhodium-**L2** (Fig. 1) catalyst, which is used in the asymmetric ring-openings of oxabenzonorbornadiene with amines providing high yields and enantioselectivities.



L1: R = H, R' = H
L2: R = OMe, R' = H
L3: R = OMe, R' = Me
L4: R = OMe, R' = P*t*-Bu$_2$

L5

Figure 1. Tunable chiral phosphorus ligands.

2. Results and discussions

2.1. Effect of ligands and additives

At first, we synthesized chiral phosphorus ligands according to the literature.[18] We also synthesized diphosphorus ligands **L4** and **L5** to study any differences from the monophosphorus ligand. With these ligands in hand, we next researched the asymmetric ring-opening reaction of oxabenzonorbornadiene with piperazine. The reaction was performed with 2.0 mol % $[Rh(cod)Cl]_2$ and 4.8 mol % of ligand as the catalytic system under nitrogen in THF at 80 °C for 6 h. Initial screening of the reaction conditions (Table 1, entries 1–5) demonstrated that the ligand structure (Fig. 1) and additive play a significant role both in terms of reactivity and

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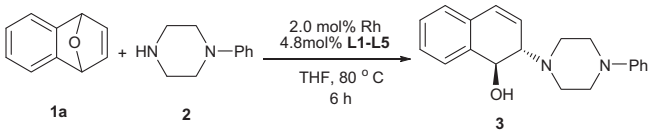
http://dx.doi.org/10.1016/j.tetasy.2014.03.017
0957-4166/

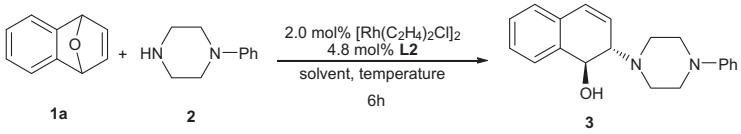
Table 1
Optimization of asymmetric rhodium-catalyzed ring-opening of oxabenzonorbornadiene with *N*-phenylpiperazine



Entry	Rh precursor	Additive	L*	Yield[a] (%)	ee[b] (%)
1	$[Rh(cod)Cl]_2$	no	—	<5	—
2	$[Rh(cod)Cl]_2$	NaI	—	85	—
3	$[Rh(cod)Cl]_2$	no	**L1**	<5	ND
4	$[Rh(cod)Cl]_2$	NaI	**L1**	97	83
5	$[Rh(cod)Cl]_2$	NaI	**L2**	95	86
6	$[Rh(cod)Cl]_2$	NaI	**L3**	95	12
7	$[Rh(cod)Cl]_2$	NaI	**L4**	93	70
8	$[Rh(cod)Cl]_2$	NaI	**L5**	81	55
9	$Rh(NBD)BF_4$	NaI	**L2**	93	90
10	$[Rh(coe)_2Cl]_2$	NaI	**L2**	95	93
11	$[Rh(C_2H_4)_2Cl]_2$	NaI	**L2**	97	93
12	$[Rh(C_2H_4)_2Cl]_2$	Bu_4NI	**L2**	95	78
13	$[Rh(C_2H_4)_2Cl]_2$	KI	**L2**	95	38
14[c]	$[Rh(C_2H_4)_2Cl]_2$	NaI	**L2**	91	92
15[d]	$[Rh(C_2H_4)_2Cl]_2$	NaI	**L2**	83	93

[a] Yield of the isolated product.
[b] The ee value was determined by HPLC analysis on a chiral phase (Chiralcel Amy-lose 2).
[c] 1.0 mol % $[Rh(C_2H_4)Cl]_2$ and 2.4 mol % **L2** were used.
[d] Performed at rt.

Table 2
Effects of solvents in the ring-opening reaction of oxabenzonorbornadiene with *N*-phenylpiperazine



Entry	Solvent	*T* (°C)	*T* (h)	Yield[a] (%)	ee[b] (%)
1	THF	80	8	95	93
2	Et_2O	40	7	95	92
3	MTBE	60	6	95	92
4	$CHCl_3$	60	6	95	92
5	CH_3CN	80	6	95	86
6	DCE	80	6	95	86
7	dioxane	90	8	95	81
8	DCM	40	7	95	87
9	hexane	80	6	95	84
10	toluene	90	8	95	65

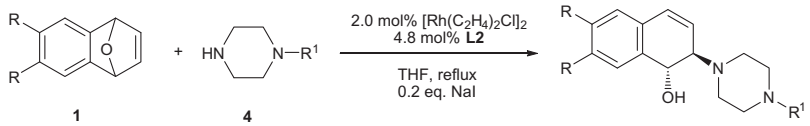
[a] Isolated product.
[b] Determined by HPLC (Chiralcel Lux Amylose-2 column).

selectivity.[6c,6d] Only <5% conversion was observed in the absence of NaI (Table 1, entries 1 and 3). High yields (85%) were obtained when 0.2 equiv of NaI were added (Table 1, entry 2). With $[Rh(cod)Cl]_2$ as the rhodium precursor, ligand **L1** gave the desired product with high yield and good ee (Table 1, entry 4). Upon further investigation of ligands, we found that the introduction of a bulky group at the R position of **L2** improved the enantioselectivity up to 86% (Table 1, entry 5). In contrast, the introduction of bulky substituents at the R' position of **L3**–**L5** led to a decrease of enantioselectivities (Table 1, entries 6–8). Having established that **L2** was the best ligand, we next studied rhodium precursors. An enantiomeric excess of 90% was obtained with $Rh(NBD)BF_4$ as the rhodium precursor (Table 1, entry 9). The same ees (up to 93% ee) were observed with $[Rh(C_2H_4)_2Cl]_2$ and $[Rh(coe)_2Cl]_2$ as the rhodium precursors (Table 1, entries 10 and 11). This could be due to the fast complex formation between the rhodium precursors and ligand **L2**. Different additives affected the performance of the catalyst. Only 78% ee and 38% ee were observed using additives such as Bu_4NI and KI, respectively (Table 1, entries 12 and 13). Almost the same enantioselectivity was observed at a catalyst loading of 1.0 mol % $[Rh(C_2H_4)_2Cl]_2$ and 2.4 mol % **L2** (Table 1, entry 14). The reaction can even be performed at room temperature to give the desired product with the same enantioselectivity (Table 1, entry 15).

2.2. Influence of the solvent

In order to obtain better reaction conditions, we next screened the effects of solvents (Table 2, entries 1–10). Among the solvents tested, THF was found to be the best solvent to give the best yield and enantioselectivity (Table 2, entry 1). Slightly lower enantioselectivities but high yields were observed with the solvents Et_2O, MTBE, and $CHCl_3$ (Table 2, entries 2–4). Almost the same enantioselectivities were obtained when the reactions were performed

Table 3
Substrates scope of rhodium-catalyzed ring-opening reaction of oxabenzonorbornadiene with piperazines



1a: R = H; **1b**: R = F; **1c**: R = OMe

Entry	R	R^1	*T* (h)	Yield[a] (%)	ee[b] (%)
1	**1a**	C_6H_5	8	95 **5aa**	93
2	**1a**	2-$MeOC_6H_4$	6	93(**5ab**)	95
3	**1a**	2-$CH_3C_6H_4$	6	95(**5ac**)	90
4	**1a**	2-FC_6H_4	10	90(**5ad**)	97
5	**1a**	3-ClC_6H_4	10	93(**5ae**)	95
6	**1a**	4-$CH_3C_6H_4$	6	95(**5af**)	96
7	**1a**	4-$CH_3OC_6H_4$	6	95(**5ag**)	98
8	**1a**	4-$CF_3C_6H_4$	10	87 **5ah**	>99
9	**1a**	2,4-di-$CH_3C_6H_3$	6	95 **5ai**	96
10	**1a**	3,4-di-ClC_6H_3	10	89 **5aj**	90
11	**1a**	3-Cl-Bn	6	95 **5ak**	>99
12	**1a**	Boc	6	91 **5al**	97
13	**1b**	C_6H_5	6	93 **5ba**	96
14	**1b**	2-FC_6H_4	8	91 **5bb**	96
15	**1b**	2-$CH_3OC_6H_4$	6	95 **5bc**	98
16	**1b**	4-$CH_3C_6H_4$	6	97 **5bd**	>99
17	**1b**	4-$CH_3OC_6H_4$	6	97 **5be**	97
18	**1b**	3,4-di-ClC_6H_3	8	90 **5bf**	83
19	**1b**	2,4-di-$CH_3C_6H_3$	6	95 **5bg**	95
20	**1c**	C_6H_5	16	91 **5ca**	94.5
21	**1c**	2-$MeOC_6H_4$	12	91 **5cb**	>99
22	**1c**	4-$CF_3C_6H_4$	12	90 **5cc**	96
23	**1c**	4-$CH_3OC_6H_4$	12	95 **5cd**	98

[a] Yield of the isolated product.
[b] The ee value was determined by HPLC analysis on a chiral phase (Chiralcel OD-H, AD-H or Lux Amylose-2 column).

with CH_3CN, DCE, dioxane, DCM, and hexane (Table 2, entries 5–9). Reactions in toluene afforded the desired product **3** in only 65% ee (Table 2, entry 10).

2.3. Scope and limitations of the catalytic system

Under the optimized reaction conditions, different oxabenzonorbornadienes were converted into the corresponding products in excellent yields and enantioselectivities (Table 3). As can be seen in Table 3, with 1,4-dihydro-1,4-epoxynaphthalene **1a** as the substrate, various piperazines with either electron-donating or electron-withdrawing substituents at the position phenyl afforded high yields and enantioselectivities (Table 3, entries 1–10). Other piperazines such as *N*-Boc piperazine and *N*-Bn piperazine were also used in this catalyst system and gave high yields and ees (Table 3, entries 11 and 12). Electron-withdrawing substrates such as 1,4-dihydro-6,7-difluoro-1,4-epoxynaphthalene **1b** could also be employed to provide high yields and enantioselectivities with various piperazines (Table 3, entries 13–19). High yields and *ees* were also obtained with bigger steric substrates such as 1,4-dihydro-6,7-dimethoxy-1,4-epoxynaphthalene **1c** (Table 3, entries 20–23).

With the optimized catalyst in hand, the asymmetric ring-opening reaction of oxabenzonorbornadiene was screened with other amines (Table 4). Using 1,4-dihydro-1,4-epoxynaphthalene **1a** as the substrate, various amines including primary or secondary aromatic amines (Table 4, entries 1, 2, and 4–8) and aliphatic amines (Table 4, entries 9 and 10) were used in the reaction to provide the desired ring-opening products in high yields and enantioselectivities. However, none of the desired products were observed when 2-chloro-*N*-methylaniline and pyrrole were employed in the reaction (Table 4, entries 3 and 11). These negative results may be attributed to the hindered *ortho*-substituted groups and the weak nucleophilicity of the nucleophiles.

Encouraged by the results of the rhodium-catalyzed ring-opening reaction of oxabenzonorbornadiene with amines, the ring-opening reaction of aza-benzonorbornadiene **8** with *N*-phenylpiperazine was also tested with the optimized reaction conditions. Unfortunately, moderate yields and enantioselectivities were obtained (Fig. 2). Further studies are currently in progress.

The X-ray structure of **5cc**, obtained by solvent evaporation from its solution in dichloromethane and petroleum ether, confirmed its absolute configuration to be (*R*,*R*)[20] as shown in Figure 3.

3. Conclusion

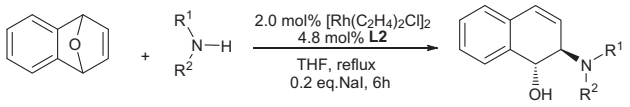
In conclusion, we have disclosed an efficient method for the Rh-**L2** catalyzed ring-opening of oxabenzonorbornadiene with amines, leading to the formation of a series of dihydronaphthalenes in high yields and enantioselectivities. The new monophosphorus ligand **L2** with a large steric chiral phosphine center is key to the success of this asymmetric transformation. Applications of this methodology for the synthesis of biologically active molecules are currently under investigation and will be reported in due course.

4. Experimental

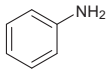
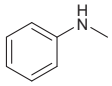
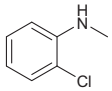
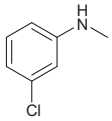
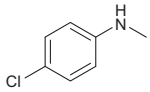
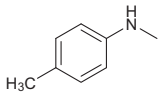
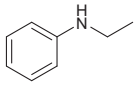
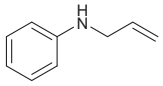
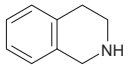
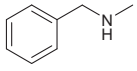
4.1. General

All reactions were carried out under a nitrogen atmosphere unless otherwise specified. THF (<0.02% water content), Et_2O, dioxane, MTBE, DCM, DCE, Xylene and toluene were purchased from Sigma Aldrich and used directly without further purification. Commercialized reagents were used without further purification. ^1H,

Table 4
Substrate scope of rhodium-catalyzed ring-opening reaction of oxabenzonorbornadiene with amines



1a 6 7

Entry	NHR^1R^2	Yield[a] (%)	ee[b] (%)
1		95 **7aa**	96
2		97 **7ab**	95
3		<5	ND
4		90 **7ac**	94
5		93 **7ad**	94
6		95 **7ae**	96
7		91 **7af**	94
8		97 **7ag**	97
9		95 **7ah**	94
10		95 **7ai**	96
11		<5	ND

[a] Yield of the isolated product.
[b] The ee value was determined by HPLC analysis on a chiral phase (Chiralcel OD-H or AD-H).

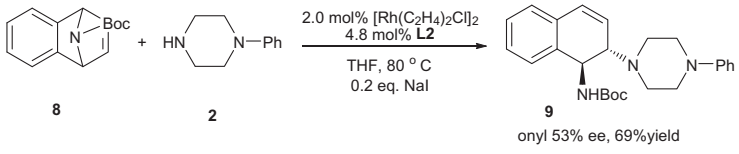


Figure 2. Rhodium-catalyzed ring-opening of piperazine to aza-norbornene.

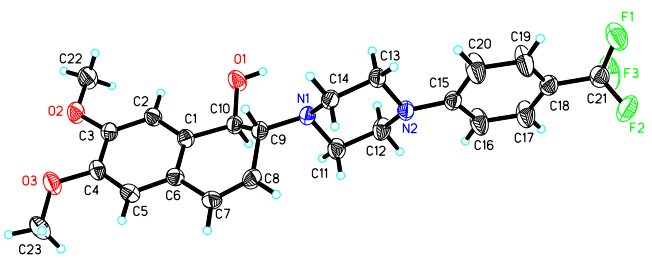


Figure 3. The X-ray structure of **5cc**; the absolute configuration of the stereogenic centers in **5cc** is (*R*,*R*).

^{31}P, and ^{13}C NMR data were recorded on a Bruker-Topspin DRX400 or 500 NMR Spectrometer with $CDCl_3$ as the solvent. ^1H shifts are referenced to $CDCl_3$ at 7.27 ppm. ^{31}P shifts are referenced to 85% H_3PO_4 in D_2O at 0.0 ppm as external standard and obtained with ^1H decoupling. ^{13}C shifts are referenced to $CDCl_3$ at 77.23 ppm and obtained with ^1H decoupling. MS was measured on Agilent 1100 Series LC/MSD mass spectrometer. Chiral HPLC analyses were performed on an Agilent 1200 system using a Chiralcel OD-H, Chiralpak AD-H column or Chiralcel Lu-Amy lose-2 column. Racemic compounds were prepared by a reaction using $[Rhcod)Cl]_2$ and NaI without using the ligand at 80 °C. Optical rotations were recorded on a Rudolph Research Automatic Polarimeter.

4.2. Procedures for the preparation of ligands

4.2.1. Synthesis of ligand L1

Ligand **L1** was synthesized from chiral **10** through a coupling reaction to give compound **12** followed by a stereospecific reduction of **12** mediated by PMHS/Ti(O*i*-Pr)$_4$. The synthetic procedures were published in a previous paper.[18] ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.71 (m, 2H), 7.42 (m, 2H), 7.35 (m, 2H), 6.99 (m, 1H), 6.90 (dd, J = 8.1, 0.8 Hz, 1H), 4.87 (dd, J = 12.7, 1.9 Hz, 1H), 4.57 (dd, J = 25.9, 12.7 Hz, 1H), 0.64 (d, J = 12.1 Hz, 9H); ^{31}P NMR (162 MHz, CD_2Cl_2): δ −11.2; ^{13}C NMR (100 MHz, CD_2Cl_2): δ 164.8, 146.5, 143.1, 131.9, 129.9, 129.8, 128.9, 127.9, 122.7 (d, J = 17.9 Hz), 122.3 (d, J = 3.1 Hz), 110.5, 70.5 (d, J = 26.9 Hz), 32.1 (d, J = 20.2 Hz), 27.0 (d, J = 13.8 Hz). ESI-MS: m/z 271 $[M+H]^+$.

4.2.2. Synthesis of ligand L2

Ligand **L2** was synthesized from the chiral compound **10** by a coupling reaction to give compound **13** followed by a stereospecific reduction of **13** mediated by PMHS/Ti(O*i*-Pr)$_4$. The synthetic procedures were published in a previous paper.[18] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (m, 2H), 6.87 (m, 2H), 6.65 (d, J = 8.2 Hz, 1H), 6.59 (d, J = 8.3 Hz, 1H), 4.81 (dd, J = 12.5, 1.8 Hz, 1H), 4.53 (dd, J = 25.2, 12.5 Hz, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 0.73 (d, J = 12.1 Hz, 9H); ^{31}P NMR (162 MHz, $CDCl_3$): δ −7.9; ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 157.9. 157.1, 138.4 (d, J = 22.3 Hz), 130.5, 129.0, 125.0 (d, J = 16.4 Hz), 123.8 (d, J = 5.4 Hz), 119.6, 109.5, 104.5, 103.6, 70.4 (d, J = 33.8 Hz), 55.9, 55.4, 30.9 (d, J = 23.2 Hz), 26.6 (d, J = 18.1 Hz); ESI-MS: m/z 331 $[M+H]^+$.

4.2.3. Synthesis of ligand L3

Ligand **L3** was synthesized from chiral compound **13** by a LDA-mediated homo-coupling reaction to give compound **14** followed by a stereospecific reduction of **14** mediated by PMHS/Ti(O*i*-Pr)$_4$. The synthetic procedures were published in a previous paper.[18] ^{1}H NMR (400 MHz,CD_2Cl_2): δ 7.35–7.20 (m, 2H), 6.85–6.75 (m, 2H), 6.64 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 8.4 Hz,1H), 4.97 (q, J = 7.0 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 1.40 (dd, J = 16.4, 7.0 Hz, 3H), 0.71 (d, J = 12.0 Hz, 9H); ^{31}P NMR (162 MHz, CD_2Cl_2): δ 9.9; ^{13}C NMR (100 MHz, CD_2Cl_2): δ 163.1, 158.2, 157.4, 139.5 (d, J = 17 Hz), 130.7, 129.4, 125.78, 125.0 (d, J = 6 Hz), 124.0, 120.0, 109.9, 104.6, 104.0, 79.2 (d, J = 24 Hz), 56.0 (d, J = 2 Hz), 31.1 (d, J = 19 Hz), 25.6, 21.6 (d, J = 29 Hz); HRMS calcd for $C_{20}H_{26}O_3P$ $[M+H]^+$: 345.1614; found: 345.1605.

4.2.4. Synthesis of ligand L4

Ligand **L4** was synthesized from chiral compound **13** by a LDA-mediated homo-coupling reaction to give compound **15** followed by a stereospecific reduction of **15** mediated by PMHS/Ti(O*i*-Pr)$_4$. The synthetic procedures were published in a previous paper.[18] ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.42 (m, 1H), 7.25 (m, 1H), 6.90 (m, 1H), 6.81 (d, J = 8.0 Hz, 1H), 5.60 (dd, J = 5.4, 4.4 Hz, 1H), 1.37 (d, J = 11.0 Hz, 9H), 1.18 (d, J = 11.1 Hz, 9H), 0.96 (d, J = 12.2 Hz, 9H); 31P NMR (162 MHz, CD_2Cl_2): δ 52.0 (d, $^3J_{PP}$ = 146.1 Hz), 12.2 (d, $^3J_{PP}$ = 146.4 Hz); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 164.7, 131.5, 131.3, 121.1 (dd, J = 64.3, 6.4 Hz), 121.0 (d, J = 6.1 Hz), 111.3, 80.2 (dd, J = 45.3, 37.4 Hz), 34.6 (d, J = 24.4 Hz), 34.1 (dd, J = 22.4, 11.3 Hz), 32.0 (dd, J = 22.5, 7.6 Hz), 31.5 (dd, J = 12.2, 3.6 Hz), 31.4 (d, J = 12.5 Hz), 26.3 (d, J = 14.7 Hz).

4.2.5. Synthesis of ligand L5

Ligand **L5** was synthesized from chiral compound **13** by a LDA-mediated homo-coupling reaction to give compound **16** followed by a stereospecific reduction of **16** mediated by PMHS/Ti(O*i*-Pr)$_4$. The synthetic procedures were published in a previous paper.[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.21 (m, 2H), 6.70–6.77 (m, 2H), 6.48–6.70 (m, 2H), 4.86 (s, 1H), 3.64 (s, 3H), 3.62 (s, 3H), 0.71 (t, J = 4.0, 8.0 Hz, 9H); ^{31}P NMR (162 MHz, $CDCl_3$) δ −0.3; ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.4 (d, J = 7.5 Hz), 56.0, 55.4, 31.6, 30.0 (d, J = 63.2 Hz), 27.1 (t, J = 7.5 Hz); ESI-MS: m/z 659.70 $[M+H]^+$.

4.3. General procedure for the asymmetric ring-opening of oxabenzonorbornadiene with amines

At first, THF (2.0 mL) was added to a mixture of oxabenzonorbornadiene **1** (0.347 mmol, 1.0 equiv), amine **4** or **6** (1.041 mmol, 3.0 equiv), NaI (10.34 mg, 0.069 mmol, 0.2 equiv), ligand **L2** (4.5 mg, 0.0167 mmol, 4.8 mol %) and $[Rh(C_2H_4)_2Cl]_2$ (2.7 mg, 0.0069 mmol, 2.0 mol %) under N_2. The mixture was then stirred at RT for 1 h and heated at reflux for 6–12 h after which the residue was subjected directly to silica gel column chromatography [ethyl acetate/hexanes (1:1–2:1 v/v) as the eluent] to afford the desired alcohol product **5** or **7**. The enantioselectivity was determined by chiral HPLC on a chiralcel OD-H, chiralcel AD-H, or Lux Amylose-2 column.

4.3.1. (1*R*,2*R*)-2-(4-Phenylpiperazin-1-yl)-1,2-dihydronaphthalen-1-ol 5aa

White solid (95% yield); 93% ee; $[\alpha]_D^{27}$ = −158.92 (*c* 0.53, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 7.50 (d, J = 7.1 Hz, 1H), 7.14–7.21 (m, 4H), 6.99–7.01 (m, 1H), 6.77–6.86 (m, 3H), 6.47 (dd, J = 2.5 Hz, J = 9.9 Hz, 1H), 6.04 (dd, J = 2.5 Hz, J = 9.9 Hz, 1H), 4.84 (d, J = 11.6 Hz, 1H), 3.45 (td, J = 2.5 Hz, J = 11.5 Hz, 1H), 3.28 (br, 1H), 3.08–3.19 (m, 4H), 2.85–3.08 (m, 2H), 2.60–2.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 151.42, 137.17, 131.91, 129.60, 129.32, 128.09, 127.65, 126.40, 124.97, 124.58, 120.13, 116.43, 67.91, 67.62 (d, J = 2.9 Hz), 49.98, 49.13; ESI-MS: m/z 307 $[M+H]^+$. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 12.22 min (minor), 13.22 min (major).

4.3.2. (1*R*,2*R*)-2-(4-(2-Methoxyphenylpiperazin-1-yl)-1,2-dihydronaphthalen-1-ol 5ab

White solid (93% yield); 95% ee; $[\alpha]_D^{27}$ = −131.8 (*c* 0.57, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 7.50 (d, J = 7.1 Hz, 1H), 7.12–7.20 (m, 2H), 6.98–7.00 (m, 1H), 6.90–6.94 (m, 1H), 6.81–6.87 (m, 2H), 6.76–6.78 (m, 1H), 6.46 (dd, J = 2.5 Hz, J = 9.9 Hz, 1H), 6.09 (dd, J = 2.5 Hz, J = 9.9 Hz, 1H), 4.84 (d, J = 11.5 Hz, 1H), 3.77 (s, 3H), 3.70 (s, 1H), 3.42 (td, J = 2.5 Hz, J = 11.5 Hz, 1H), 2.89–3.03 (m, 6H), 2.64–2.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 152.31, 141.23, 137.21, 131.92, 129.44, 127.95, 127.55, 126.31, 124.94, 124.91, 123.21, 121.11, 118.37, 112.21, 67.75, 67.55 (d, J = 2.9 Hz), 55.44 (d, J = 5.8 Hz), 51.27, 49.22; ESI-MS: m/z 337 $[M+H]^+$. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 11.07 min (major), 12.11 min (minor).

4.3.3. (1*R*,2*R*)-2-(4-*o*-Tolylpiperazin-1-yl)-1,2-dihydronaphthalen-1-ol 5ac

White solid (95% yield); 90% ee; $[\alpha]_D^{27}$ = −122.2 (*c* 0.37, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 7.52 (d, J = 7.2 Hz, 1H), 7.07–7.210 (m, 4H), 6.89–7.01 (m, 3H), 6.47 (dd, J = 2.5 Hz, J = 9.9 Hz, 1H), 6.11 (dd, J = 2.5 Hz, J = 9.9 Hz, 1H), 4.84 (d, J = 11.8 Hz, 1H), 3.42 (td, J = 2.4 Hz, J = 11.8 Hz, 1H), 3.27 (br, 1H), 2.85–2.91 (m, 6H), 2.59–2.63 (m, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 151.42, 137.19, 132.59, 131.86, 131.16, 129.33, 127.92, 127.48, 126.67, 126.24, 124.90, 127.77, 123.29, 119.05, 67.78, 67.58 (d, J = 3.2 Hz), 52.30, 49.51, 17.98; ESI-MS: m/z 321 $[M+H]^+$. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 7.37 min (minor), 8.37 min (major).

4.3.4. (1*R*,2*R*)-2-(4-(2-Fluorophenyl)piperazin-1-yl)-1,2-dihydronaphthalen-1-ol 5ad

White solid (90% yield); 97% ee; $[\alpha]_D^{27} = -154.7$ (*c* 0.67, $CHCl_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −119.71; ^1H NMR (400 MHz, $CDCl_3$) 7.49 (d, *J* = 7.1 Hz, 1H), 7.12–7.19 (m, 2H), 6.82–7.00 (m, 5H), 6.46 (dd, *J* = 2.5 Hz, *J* = 9.9 Hz, 1H), 6.05 (dd, *J* = 2.5 Hz, *J* = 9.9 Hz, 1H), 4.84 (d, *J* = 11.5 Hz, 1H), 3.41 (td, *J* = 2.5 Hz, *J* = 11.5 Hz, 1H), 3.25 (br, 1H), 2.98–3.07 (m, 4H), 2.85–2.90 (m, 2H), 2.61–2.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 157.08, 154.64, 140.20, 140.11, 137.16, 131.91, 129.51, 128.02, 127.61, 126.36, 124.96, 124.75, 124.64, 122.78, 122.70, 119.12, 116.37, 116.17, 67.83, 67.60 (d, *J* = 4.9 Hz), 51.22, 49.13. ESI-MS: *m*/*z* 325 $[M+H]^+$. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 9.87 min (major), 10.85 min (minor).

4.3.5. (1*R*,2*R*)-2-(4-(3-Chlorophenyl)piperazin-1-yl)-1,2-dihydronaphthalen-1-ol 5ae

White solid (93% yield); 95% ee; $[\alpha]_D^{27} = -153.7$ (*c* 0.43, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 7.49 (d, *J* = 7.1 Hz, 1H), 6.99–7.19 (m, 4H), 6.68–6.79 (m, 3H), 6.47 (dd, *J* = 2.4 Hz, *J* = 9.9 Hz, 1H), 6.01 (dd, *J* = 2.5 Hz, *J* = 9.9 Hz, 1H), 4.82 (d, *J* = 11.4 Hz, 1H), 3.42 (td, *J* = 2.3 Hz, *J* = 11.4 Hz, 1H), 3.20 (br, 1H), 3.09–3.21 (m, 4H), 2.81–2.86 (m, 2H), 2.57–2.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 152.40, 137.05, 135.10, 131.85, 130.22, 129.66, 128.11, 127.70, 126.42, 125.00, 124.38, 119.64, 116.07, 114.20, 67.89, 67.58, 49.42, 48.91. ESI-MS: *m*/*z* 341 $[M+H]^+$. Chiral HPLC conditions: Chiralcel AD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 14.39 min (minor), 15.65 min (major).

4.3.6. (1*R*,2*R*)-2-(4-*p*-Tolylpiperazin-1-yl)-1,2-dihydronaphthalen-1-ol 5af

White solid (95% yield); 96% ee; $[\alpha]_D^{27} = -120.9$ (*c* 0.38, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 7.50 (d, *J* = 7.2 Hz, 1H), 7.15–7.21 (m, 2H), 6.98–7.01 (m, 3H), 6.76–6.78 (m, 2H), 6.47 (dd, *J* = 2.5 Hz, *J* = 9.9 Hz, 1H), 6.04 (dd, *J* = 2.5 Hz, *J* = 9.9 Hz, 1H), 4.83 (d, *J* = 11.6 Hz, 1H), 3.42 (td, *J* = 2.4 Hz, *J* = 11.6 Hz, 1H), 3.24 (br, 1H), 3.04–3.12 (m, 4H), 2.85–2.90 (m, 2H), 2.59–2.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 149.32, 137.20, 131.92, 129.83, 129.65, 129.56, 128.06, 127.63, 126.38, 124.96, 124.64, 116.77, 67.87 (d, *J* = 3.5 Hz), 50.53, 49.13, 20.64 (d, *J* = 10.3 Hz). ESI-MS: *m*/*z* 321 $[M+H]^+$. Chiral HPLC conditions: Chiralcel Lu-Amy lose-2, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 12.92 min (minor), 14.33 min (major).

4.3.7. (1*R*,2*R*)-2-(4-(4-Methoxyphenyl)piperazin-1-yl)-1,2-dihydronaphthalen-1-ol 5ag

White solid (95% yield); 98% ee; $[\alpha]_D^{27} = -162.5$ (*c* 0.43, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 7.49 (d, *J* = 7.0 Hz, 1H), 7.13–7.20 (m, 2H), 6.99–7.01 (m, 1H), 6.75–6.83 (m, 4H), 6.47 (dd, *J* = 2.4 Hz, *J* = 9.9 Hz, 1H), 6.05 (dd, *J* = 2.5 Hz, *J* = 9.9 Hz, 1H), 4.83 (d, *J* = 11.8 Hz, 1H), 3.67 (s, 3H), 3.42 (td, *J* = 2.3 Hz, *J* = 11.5 Hz, 1H), 3.21 (br, 1H), 2.99–3.05 (m, 4H), 2.85–2.90 (m, 2H), 2.60–2.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 154.08, 145.72, 137.16, 131.90, 129.54, 128.04, 127.62, 126.37, 124.96, 124.64, 118.52, 114.57, 67.82, 67.53 (d, *J* = 3.1 Hz), 55.67 (d, *J* = 5.8 Hz), 51.38, 49.14. ESI-MS: *m*/*z* 337 $[M+H]^+$. Chiral HPLC conditions: Chiralcel AD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 16.27 min (minor), 18.17 min (major).

4.3.8. (1*R*,2*R*)-2-(4-(4-(Trifluoromethyl)phenylpiperazin-1-yl)-1,2-dihydronaphthalen-1-ol 5ah

White solid (87% yield); >99% ee; $[\alpha]_D^{27} = -161.9$ (*c* 0.45, $CHCl_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.33; ^1H NMR (500 MHz, $CDCl_3$) 7.59–7.61 (m, 1H), 7.50–7.51 (m, 2H), 7.27–7.31(m, 2H), 7.11–7.12 (m, 1H), 6.94–6.96 (m, 2H), 6.59(dd, *J* = 2.4 Hz, *J* = 9.9 Hz, 1H), 6.11 (dd, *J* = 2.5 Hz, *J* = 9.9 Hz, 1H), 4.96 (d, *J* = 11.3 Hz, 1H), 3.57 (td, *J* = 2.4 Hz, *J* = 11.2 Hz, 1H), 3.33–3.37 (m, 4H), 3.27(br, 1H), 2.97–3.01 (2H, m), 2.73–2.77 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) 153.41, 137.01, 131.85, 129.95, 128.27, 127.84, 126.65 (td, *J* = 3.7 Hz), 126.55, 125.98, 125.15, 124.06, 114.96, 67.99, 67.78, 48.97, 48.80; ESI-MS: *m*/*z* 375 $[M+H]^+$. Chiral HPLC conditions: Chiralcel AD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 11.35 min (minor), 11.99 min (major).

4.3.9. (1*R*,2*R*)-2-(4-(2,4-Dimethylphenyl)piperazin-1-yl)-1,2-dihydronaphthalen-1-ol 5ai

White solid (95% yield); 96% ee; $[\alpha]_D^{27} = -160.8$ (*c* 0.55, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 7.50 (d, *J* = 7.2 Hz, 1H), 7.11–7.20 (m, 2H), 6.83–7.00 (m, 4H), 6.46 (dd, *J* = 2.5 Hz, *J* = 9.9 Hz, 1H), 6.09 (dd, *J* = 2.4 Hz, *J* = 9.9 Hz, 1H), 4.83 (d, *J* = 11.8 Hz, 1H), 3.41 (td, *J* = 2.4 Hz, *J* = 11.8 Hz, 1H), 3.21 (br, 1H), 2.81–2.87 (m, 6H), 2.57–2.62 (m, 2H), 2.19 (d, *J* =4.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 149.02, 137.25, 132.72, 132.52, 131.88, 129.31, 127.92, 127.48, 127.13, 126.24, 124.97, 124.79, 119.00, 67.79, 67.60 (d, *J* = 3.5 Hz), 52.52, 49.62, 20.80 (d, *J* = 5.0 Hz), 17.84 (d, *J* = 4.9 Hz). ESI-MS: *m*/*z* 335 $[M+H]^+$. Chiral HPLC conditions: Chiralcel AD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 230 nm, 6.58 min (minor), 7.20 min (major).

4.3.10. (1*R*,2*R*)-2-(4-(3,4-Dichlorophenyl)piperazin-1-yl)-1,2-dihydronaphthalen-1-ol 5aj

White solid (89% yield); 90% ee; $[\alpha]_D^{27} = -130.95$ (*c* 0.37, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 7.49 (d, *J* = 7.0 Hz, 1H), 7.14–7.21 (m, 3H), 6.99 (d, *J* = 6.8 Hz, 1H), 6.85 (d, *J* = 2.8 Hz, 1H), 6.63 (dd, *J* = 2.8 Hz, *J* = 8.9 Hz, 1H), 6.47 (dd, *J* = 2.4 Hz, *J* = 9.9 Hz, 1H), 5.99 (dd, *J* = 2.5 Hz, *J* = 9.9 Hz, 1H), 4.81 (d, *J* = 11.3 Hz, 1H), 3.42 (td, *J* = 2.4 Hz, *J* = 11.3 Hz, 1H), 3.18 (br, 1H), 3.05–3.10 (m, 4H), 2.80–2.85 (m, 2H), 2.56–2.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 150.63, 136.88, 132.82, 131.72, 130.51, 129.62, 128.04, 127.64, 126.35, 124.94, 124.16, 122.34, 117.39, 115.50, 67.80, 67.42, 49.27, 48.69. ESI-MS: *m*/*z* 375 $[M+H]^+$. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 16.12 min (minor), 17.96 min (major).

4.3.11. (1*R*,2*R*)-2-(4-(3-Chlorobenzyl)piperazin-1-yl)-1,2-dihydronaphthalen-1-ol 5ak

White solid (95% yield); >99% ee; $[\alpha]_D^{27} = -146.0$ (*c* 0.68, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 7.47 (d, *J* = 7.3 Hz, 1H), 7.26 (s, 1H), 7.09–7.18 (m, 5H), 6.96–6.98 (m, 1H), 6.44 (dd, *J* = 2.5 Hz, *J* = 9.9 Hz, 1H), 6.03 (dd, *J* = 2.5 Hz, *J* = 9.9 Hz, 1H), 4.77 (d, *J* = 11.5 Hz, 1H), 3.39 (s, 2H), 3.35 (td, *J* = 2.5 Hz, *J* = 11.5 Hz, 1H), 3.18 (br, 1H), 2.71–2.75 (m, 2H), 2.41–2.50 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 140.42, 137.24, 134.32, 131.92, 129.63, 129.36, 129.20, 127.94, 127.54, 127.42, 127.35, 126.30, 124.96, 124.90, 67.82, 67.42, 62.52, 53.67, 25.53.. ESI-MS: *m*/*z* 354 $[M+H]^+$. Chiral HPLC conditions: Chiralcel Lu-Amy lose-2, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 85:15, 254 nm, 7.34 min (minor), 8.32 min (major).

4.3.12. *tert*-Butyl 4-((1*R*,2*R*)-1-hydroxy-1,2-dihydronaph-thalen-2-yl)piperazine-1-carboxylate 5al

White solid (91% yield); 97% ee; $[\alpha]_D^{27} = -111.05$ (*c* 0.46, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 7.48 (d, *J* = 7.3 Hz, 1H), 7.14–7.21 (m, 2H), 6.99–7.01 (m, 1H), 6.46 (dd, *J* = 2.4 Hz, *J* = 9.9 Hz, 1H), 5.96 (dd, *J* = 2.6 Hz, *J* = 9.9 Hz, 1H), 4.81 (d, *J* = 11.2 Hz, 1H), 3.34–3.43 (m, 5H), 3.12 (br, 1H), 2.66–2.86 (m, 2H), 2.43–2.44 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 154.84, 137.04, 131.85, 129.64, 128.11, 127.71, 126.43, 125.03, 124.46, 79.95, 67.93, 67.83, 49.10, 28.60, 25.53. ESI-MS: *m*/*z* 331 $[M+H]^+$. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 85:15, 254 nm, 7.71 min (minor), 8.40 min (major).

4.3.13. (1*R*,2*R*)-6,7-Difluoro-2-(4-phenylpiperazin-1-yl)-1,2-dihydronaphthalen-1-ol 5ba

White solid (93% yield); 96% ee; $[\alpha]_D^{27} = -72.55$ (*c* 0.28, $CHCl_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −138.43, −140.87; ^1H NMR (400 MHz, $CDCl_3$) 7.41–7.44 (m, 1H), 7.26–7.31 (m, 2H), 6.88–6.96 (m, 4H), 6.45 (dd, *J* = 2.7 Hz, *J* = 9.9 Hz, 1H), 6.19 (dd, *J* = 1.8 Hz, *J* = 9.9 Hz, 1H), 4.84 (d, *J* = 12.5 Hz, 1H), 3.48 (td, *J* = 2.5 Hz, *J* = 11.5 Hz, 1H), 3.41 (br, 1H), 3.21–3.30 (m, 4H), 2.99–3.03 (m, 2H), 2.70–2.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 151.39, 148.65, 129.39, 127.94, 125.53, 125.52, 120.32, 116.54, 115.22, 115.08, 114.67, 114.52, 67.57, 67.33, 50.05, 49.29. ESI-MS: *m*/*z* 343 $[M+H]^+$. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 12.13 min (major), 15.16 min (minor).

4.3.14. (1*R*,2*R*)-6,7-Difluoro-2-(4-(2-fluorophenyl)piperazin-1-yl)-1, 2-dihydronaphthalen-1-ol 5bb

White solid (91% yield); 96% ee; $[\alpha]_D^{27} = -113.0$ (*c* 0.73, $CHCl_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.91, −138.47, −140.86; ^1H NMR (400 MHz, $CDCl_3$) 7.40–7.44 (m, 1H), 7.02–7.10 (m, 2H), 6.91–6.99 (m, 2H), 6.87–6.89 (m, 1H), 6.44 (dd, *J* = 2.7 Hz, *J* = 10.0 Hz, 1H), 6.22 (dd, *J* = 1.9 Hz, *J* = 10.0 Hz, 1H), 4.84 (d, *J* = 12.5 Hz, 1H), 3.48 (td, *J* = 2.5 Hz, *J* = 11.5 Hz, 1H), 3.43 (br, 1H), 3.12–3.21 (m, 4H), 3.00–3.04 (m, 2H), 2.72–2.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 156.92, 154.96, 150.73 (dd, *J* = 13.0 Hz, *J* = 23.4 Hz), 148.76(dd, *J* = 13.0 Hz, *J* = 21.0 Hz), 140.11 (d, *J* = 8.64 Hz), 134.37 (dd, *J* = 3.7 Hz, *J* = 5.7 Hz), 128.69 (dd, *J* = 4.0 Hz, *J* = 6.3 Hz), 127.87, 125.73 (d, *J* = 2.5 Hz), 124.71 (d, *J* = 3.6 Hz), 122.93 (d, *J* = 7.9Hzz), 119.21 (d, *J* = 3.0 Hz), 116.337 (d, *J* = 20.8 Hz), 114.84 (dd, *J* = 18.60 Hz, *J* = 70.1 Hz), 67.56, 67.27, 51.26 (d, *J* = 3.2 Hz), 49.32. ESI-MS: *m*/*z* 361 $[M+H]^+$. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 8.08 min (major), 9.79 min (minor).

4.3.15. (1*R*,2*R*)-6,7-Difluoro-2-(4-(2-methoxyphenyl)piperaz-in-1-yl)-1, 2-dihydronaphthalen-1-ol 5bc

White solid (95% yield); 98% ee; $[\alpha]_D^{27} = -110.0$ (*c* 0.68, $CHCl_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −138.59, −140.96; ^1H NMR (400 MHz, $CDCl_3$) 7.31–7.36 (m, 1H), 6.77–6.97 (m, 5H), 6.33–6.37 (m, 1H), 6.14–6.17 (m, 1H), 4.75 (d, *J* = 12.4 Hz, 1H), 3.80 (s, 3H), 3.43 (br, 1H), 3.38 (td, *J* = 2.5 Hz, *J* = 11.5 Hz, 1H), 2.94–3.06 (m, 6H), 2.65–2.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 152.39, 150.68(dd, *J* = 12.9 Hz, *J* = 22.6 Hz), 148.71(dd, *J* = 12.9 Hz, *J* = 20.2 Hz), 141.22, 134.46 (dd, *J* = 3.7 Hz, *J* = 5.6 Hz), 128.71 (dd, *J* = 4.0 Hz, *J* = 6.3 Hz), 127.74, 126.03 (d, *J* = 2.5 Hz), 123.35, 121.19, 118.43, 115.05 (d, *J* = 18.0 Hz), 114.52 (d, *J* = 19.2Hzz), 111.33, 67.51, 67.22, 55.53, 51.34, 49.40. ESI-MS: *m*/*z* 373 $[M+H]^+$. Chiral HPLC conditions: OD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 9.50 min (major), 11.03 min (minor).

4.3.16. (1*R*,2*R*)-6,7-Difluoro-2-(4-*p*-tolylpiperazin-1-yl)-1,2-dihydronaphthalen-1-ol 5bd

White solid (97% yield); >99% ee; $[\alpha]_D^{27} = -115.55$ (*c* 0.38, $CHCl_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −138.48, −140.92; ^1H NMR (400 MHz, $CDCl_3$) 7.32–7.37 (m, 1H), 7.01–7.03 (m, 2H), 6.78–6.84 (m, 3H), 6.36 (dd, *J* = 2.7 Hz, *J* = 10.0 Hz, 1H), 6.12 (dd, *J* = 1.8 Hz, *J* = 10.0 Hz, 1H), 4.76 (d, *J* = 12.6 Hz, 1H), 3.39 (td, *J* = 2.5 Hz, *J* = 11.5 Hz, 1H), 3.36 (br, 1H), 3.06–3.17 (m, 4H), 2.90–2.95 (m, 2H), 2.60–2.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 149.28, 145.87, 134.33, 129.91, 127.89, 125.62, 125.59, 116.87, 115.21, 115.04, 114.65, 114.46, 67.51, 67.29, 50.59, 49.27, 20.66. ESI-MS: *m*/*z* 357 $[M+H]^+$. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 8.24 min (major), 9.27 min (minor).

4.3.17. (1*R*,2*R*)-6,7-Difluoro-2-(4-(4-methoxyphenyl)-piperazin-1-yl)-1,2-dihydronaphthalen-1-ol 5be

White solid (97% yield); 97% ee; $[\alpha]_D^{27} = -113.9$ (*c* 0.89, $CHCl_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −138.47, −140.88; ^1H NMR (400 MHz, $CDCl_3$) 7.31–7.35 (m, 1H), 6.76–6.85 (m, 5H), 6.35 (dd, *J* = 2.6 Hz, *J* = 10.0 Hz, 1H), 6.11 (dd, *J* = 1.7 Hz, *J* = 10.0 Hz, 1H), 4.74 (d, *J* = 12.5 Hz, 1H), 3.69 (s, 3H), 3.40 (td, *J* = 2.5 Hz, *J* = 11.5 Hz, 1H), 3.37 (br, 1H), 3.00–3.10 (m, 4H), 2.88–2.93 (m, 2H), 2.60–2.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 154.20, 150.93 (dd, *J* = 13.0 Hz, *J* = 19.2 Hz), 148.47(dd, *J* = 12.7 Hz, *J* = 16.6 Hz), 145.67, 134.36 (dd, *J* = 3.7 Hz, *J* = 5.4 Hz), 128.66 (dd, *J* = 3.9 Hz, *J* = 6.2 Hz), 127.84, 125.64, 118.60, 115.09 (d, *J* = 18.1 Hz), 114.63, 114.44, 67.42, 67.24, 55.72, 51.43, 49.28. ESI-MS: *m*/*z* 373 $[M+H]^+$. Chiral HPLC conditions: OD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 13.40 min (major), 15.88 min (minor).

4.3.18. (1*R*,2*R*)-2-(4-(3,4-Dichlorophenyl)piperazin-1-yl)-6,7-difuoro-1,2-dihydronaphthalen-1-ol 5bf

White solid (90% yield); 83% ee; $[\alpha]_D^{27} = -117.5$ (*c* 0.39, $CHCl_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −138.27, −140.64; ^1H NMR (400 MHz, $CDCl_3$) 7.30–7.35 (m, 1H), 7.19 (d, *J* = 8.9 Hz, 1H), 6.87 (d, *J* = 2.8 Hz, 1H), 6.77–6.82 (m, 1H), 6.64–6.67 (m, 1H), 6.35 (dd, *J* = 2.6 Hz, *J* = 10.0 Hz, 1H), 6.05 (dd, *J* = 1.8 Hz, *J* = 10.0 Hz, 1H), 4.73 (d, *J* = 12.4 Hz, 1H), 3.38 (td, *J* = 2.5 Hz, *J* = 11.5 Hz, 1H), 3.27 (br, 1H), 3.07–3.17 (m, 4H), 2.85–2.90 (m, 2H), 2.57–2.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 150.95 (dd, *J* = 13.0 Hz, *J* = 19.0 Hz), 150.69, 148.49 (dd, *J* = 13.0 Hz, *J* = 16.6 Hz), 134.19 (dd, *J* = 3.7 Hz, *J* = 5.7 Hz), 132.97, 130.66, 128.60 (dd, *J* = 4.0 Hz, *J* = 6.3 Hz), 128.01, 125.21, 122.61, 117.58, 115.67, 115.15 (d, *J* = 18.0 Hz), 114.60 (d, *J* = 19.2 Hz), 67.46, 67.28, 49.41, 48.91. ESI-MS: *m*/*z* 411 $[M+H]^+$. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 10.60 min (major), 12.63 min (minor).

4.3.19. (1*R*,2*R*)-2-(4-(2,4-Dimethylphenyl)piperazin-1-yl)-6,7-difluoro-1,2-dihydronaphthalen-1-ol 5bg

White solid (95% yield); 95% ee; $[\alpha]_D^{27} = -129.3$ (*c* 0.94, $CHCl_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −138.54, −140.95; ^1H NMR (400 MHz, $CDCl_3$) 7.44–7.47 (m, 1H), 6.89–7.04 (m, 4H), 6.46 (dd, *J* = 2.7 Hz, *J* = 10.0 Hz, 1H), 6.27 (dd, *J* = 1.7 Hz, *J* = 9.9 Hz, 1H), 4.85 (d, *J* = 12.6 Hz, 1H), 3.60 (br, 1H), 3.48 (td, *J* = 2.5 Hz, *J* = 11.5 Hz, 1H), 2.93–3.01 (m, 6H), 2.69–2.72 (m, 2H), 2.32 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 150.68(dd, *J* = 12.9 Hz, *J* = 24.3 Hz), 149.02, 148.71(dd, *J* = 12.9 Hz, *J* = 21.9 Hz), 134.51 (dd, *J* = 3.7 Hz, *J* = 5.7 Hz), 132.94, 132.64, 132.03, 128.71 (dd, *J* = 4.0 Hz, *J* = 6.2 Hz), 127.68, 127.25, 126.03 (d, *J* = 2.5 Hz), 119.12, 115.04 (d, *J* = 18.0 Hz), 114.52 (d, *J* = 19.2 Hz), 67.53, 67.25, 52.61, 49.76, 20.88, 17.90. ESI-MS: *m*/*z* 371 $[M+H]^+$. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 5.51 min (major), 6.57 min (minor).

4.3.20. (1*R*,2*R*)-6,7-dimethoxy-2-(4-phenylpiperazin-1-yl)-1,2-dihydronaphthalen-1-ol 5ca

White solid (91% yield); 94.5% ee; $[\alpha]_D^{27} = -225.3$ (*c* 0.62, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 7.17–7.21 (m, 2H), 7.06 (s, 1H), 6.77–6.86 (m, 3H), 6.56 (s, 1H), 6.39 (dd, *J* = 2.4 Hz, *J* = 9.9 Hz, 1H), 5.95 (dd, *J* = 2.6 Hz, *J* = 9.9 Hz, 1H), 4.78 (d, *J* = 11.8 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.39 (td, *J* = 2.4 Hz, *J* = 11.2 Hz, 1H), 3.29 (br, 1H), 3.08–3.18 (m, 4H), 2.83–2.88 (m, 2H), 2.60–2.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 151.35, 148.71, 148.12, 129.92, 129.25, 129.05, 124.69, 122.52, 120.06, 116.35, 110.08, 108.77, 67.83, 67.72, 56.17, 56.14, 49.91, 49.11. ESI-MS: *m*/*z* 367 $[M+H]^+$. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/

min, hexane/isopropanol: 75:25, 254 nm, 14.10 min (major), 18.81 min (minor).

4.3.21. (1*R*,2*R*)-6,7-Dimethoxy-2-(4-(2-methoxyphenyl)-piperazin-1-yl)-1,2-dihydronaphthalen-1-ol 5cb

White solid (91% yield); >99% ee; $[\alpha]_D^{27} = -199.4$ (*c* 0.82, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 7.06 (s, 1H), 6.91–6.94 (m, 1H), 6.84–6.87 (m, 2H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.56 (s, 1H), 6.40 (dd, *J* = 2.4 Hz, *J* = 9.9 Hz, 1H), 6.00 (dd, *J* = 2.7 Hz, *J* = 9.8 Hz, 1H), 4.79 (d, *J* = 11.1 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.43 (br, 1H), 3.39 (td, *J* = 2.4 Hz, *J* = 11.1 Hz, 1H), 3.02–3.06 (m, 4H), 2.88–2.92 (m, 2H), 2.66–2.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 152.18, 148.57, 148.00, 141.12, 129.90, 128.82, 124.63, 123.05, 122.77, 120.97, 118.21, 111.07, 109.99, 108.76, 67.58, 60.36, 56.03 (d, *J* = 1.5 Hz), 55.31, 51.15, 21.02, 14.19. ESI-MS: *m*/*z* 397 $[M+H]^+$. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 75:25, 254 nm, 10.86 min (major), 17.55 min (minor).

4.3.22. (1*R*,2*R*)-6,7-Dimethoxy-2-(4-(4-(trifluoromethyl)-phenyl)-piperazin-1-yl)-1,2-dihydronaphthalen-1-ol 5cc

White solid (90% yield); 96% ee; $[\alpha]_D^{27} = -198.4$ (*c* 1.23, $CHCl_3$);[19] F NMR (376 MHz, $CDCl_3$) δ −61.45; ^1H NMR (400 MHz, $CDCl_3$) 7.40 (d, *J* = 8.6 Hz, 1H), 7.06 (s, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 6.57 (s, 1H), 6.41 (dd, *J* = 2.1 Hz, *J* = 9.9 Hz, 1H), 5.91 (dd, *J* = 2.6 Hz, *J* = 9.8 Hz, 1H), 4.78 (d, *J* = 11.0 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.49 (td, *J* = 2.4 Hz, *J* = 11.2 Hz, 1H), 3.27 (br, 1H), 3.17–3.26 (m, 4H), 2.82–2.86 (m, 2H), 2.61–2.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 153.38, 148.86, 148.29, 129.29, 129.83, 129.26, 126.57, 126.54, 124.71, 122.21, 114.80, 110.21, 108.97, 67.98, 67.78, 56.22, 56.19, 48.91, 48.72. ESI-MS: *m*/*z* 435 $[M+H]^+$. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 75:25, 254 nm, 12.46 min (major), 15.23 min (minor).

4.3.23. (1*R*,2*R*)-6,7-Dimethoxy-2-(4-(4-methoxyphenyl)-piperazin-1-yl)-1,2-dihydronaphthalen-1-ol 5cd

Colorless liquid (95% yield); 98% ee; $[\alpha]_D^{27} = -204.2$ (*c* 1.12, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 7.14 (s, 1H), 6.83–6.91 (m, 4H), 6.64 (s, 1H), 6.47 (dd, *J* = 2.3 Hz, *J* = 9.9 Hz, 1H), 6.04 (dd, *J* = 2.5 Hz, *J* = 9.9 Hz, 1H), 4.86 (d, *J* = 11.3 Hz, 1H), 3.92 (s, 3H), 3.879 (s, 3H), 3.76 (s, 3H), 3.47 (td, *J* = 2.3 Hz, *J* = 11.3 Hz, 1H), 3.28 (br, 1H), 3.06–3.14 (m, 4H), 2.92–2.96 (m, 2H), 2.69–2.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 154.06, 148.75, 148.16, 145.74, 130.00, 129.02, 124.74, 122.65, 118.47, 114.57, 110.15, 108.83, 67.84, 67.73, 56.19, 56.17, 55.67, 51.40, 49.22. ESI-MS: *m*/*z* 397 $[M+H]^+$. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 60:40, 254 nm, 10.18 min (major), 12.86 min (minor).

4.3.24. (1*R*,2*R*)-2-(Phenylamino)-1,2-dihydronaphthalen-1-ol 7aa

White solid (95% yield); 96% ee; $[\alpha]_D^{27} = -138.4$ (*c* 0.32, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) 7.49–7.51 (m, 1H), 7.16–7.33 (m, 5H), 6.73–6.81 (m, 3H), 6.58 (dd, *J* = 1.7 Hz, *J* = 9.6 Hz, 1H), 6.04 (dd, *J* = 3.6 Hz, *J* = 9.6 Hz, 1H), 4.87 (d, *J* = 7.8 Hz, 1H), 4.45 (td, *J* = 2.7 Hz, *J* = 9.8 Hz, 1H), 3.66 (s, 1H), 2.46 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 146.85, 135.76, 132.07, 129.65, 128.70, 128.63, 128.13, 127.11, 126.89, 118.57, 114.25, 71.67, 55.75. ESI-MS: *m*/*z* 238 $[M+H]^+$. Chiral HPLC conditions: Chiralcel AD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 13.48 min (minor), 17.51 min (major).

4.3.25. (1*R*,2*R*)-2-[Methyl(phenyl)amino]-1,2-dihydro-naphthalen-1-ol 7ab

Colorless liquid (97% yield); 95% ee; $[\alpha]_D^{27} = -112.9$ (0.72, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) 7.52–7.54 (m, 1H), 7.22–7.27 (m, 4H), 7.09–7.11 (m, 1H), 6.94–6.95 (m, 1H), 6.77–6.80 (m, 1H), 6.57 (dd, *J* = 2.5 Hz, *J* = 9.8 Hz, 1H), 5.91 (dd, *J* = 3.0 Hz, *J* = 9.8 Hz, 1H), 5.08 (d, *J* = 9.8 Hz, 1H), 4.72 (td, *J* = 2.7 Hz, *J* = 9.8 Hz, 1H), 2.83 (s, 3H), 2.38 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 150.44, 136.72, 132.16, 129.86, 129.46, 128.29, 128.13, 127.95, 126.65, 125.80, 118.29, 114.85, 70.27, 63.70, 33.56. ESI-MS: *m*/*z* 252 $[M+H]^+$. Chiral HPLC conditions: Chiralcel AD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 9.80 min (major), 11.30 min (minor).

4.3.26. (1*R*,2*R*)-2-((3-Chlorophenyl)(methyl)amino)-1,2-dihydronaphthalen-1-ol 7ac

Colorless liquid (90% yield); 94% ee; $[\alpha]_D^{27} = -143.7$ (*c* 0.92, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) 7.54–7.56 (m, 1H), 7.30–7.31 (m, 2H), 7.14–7.18 (m, 2H), 6.91–6.92 (m, 1H), 6.83–6.85 (m, 1H), 6.76–6.77 (m, 1H), 6.64 (dd, *J* = 2.4 Hz, *J* = 9.8 Hz, 1H), 5.91 (dd, *J* = 3.1 Hz, *J* = 9.8 Hz, 1H), 5.09 (d, *J* = 9.3 Hz, 1H), 4.73 (td, *J* = 2.8 Hz, *J* = 9.4 Hz, 1H), 2.84 (s, 3H), 2.27 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 151.46, 136.47, 135.37, 132.06, 130.32, 130.20, 128.46, 128.35, 127.45, 126.82, 125.97, 117.85, 114.32, 112.54, 70.40, 63.36, 33.60. ESI-MS: *m*/*z* 286 $[M+H]^+$. Chiral HPLC conditions: Chiralcel AD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 9.21 min (minor), 10.27 min (major).

4.3.27. (1*R*,2*R*)-2-((4-Chlorophenyl)(methyl)amino)-1,2-dihydronaphthalen-1-ol 7ad

White solid (93% yield); 94% ee; $[\alpha]_D^{27} = -112.0$ (*c* 0.82, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) 7.53–7.54 (m, 1H), 7.29–7.31 (m, 2H), 7.20–7.22 (m, 2H), 7.14–7.16 (m, 1H), 6.86–6.88 (m, 2H), 6.63 (dd, *J* = 2.5 Hz, *J* = 9.8 Hz, 1H), 5.91 (dd, *J* = 3.1 Hz, *J* = 9.8 Hz, 1H), 5.08 (d, *J* = 9.5 Hz, 1H), 4.68 (td, *J* = 2.8 Hz, *J* = 9.5 Hz, 1H), 2.82 (s, 3H), 2.38 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 148.82, 136.37, 131.91, 129.93, 129.04, 128.24, 128.12, 127.32, 126.61, 125.73, 122.81, 115.67, 70.12, 63.57, 33.53. ESI-MS: *m*/*z* 286 $[M+H]^+$. Chiral HPLC conditions: Chiralcel AD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 11.09 min (major), 13.05 min (minor).

4.3.28. (1*R*,2*R*)-2-(Methyl(*p*-tolyl)amino)-1,2-dihydro-naphthalen-1-ol 7ae

Colorless liquid (95% yield); 96% ee; $[\alpha]_D^{27} = -132.4$ (*c* 0.62, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) 7.58–7.60 (m, 1H), 7.27–7.31 (m, 2H), 7.10–7.15 (m, 3H), 6.91–6.93 (m, 2H), 6.60 (dd, *J* = 2.5 Hz, *J* = 9.8 Hz, 1H), 5.96 (dd, *J* = 2.9 Hz, *J* = 9.8 Hz, 1H), 5.13 (d, *J* = 10.1 Hz, 1H), 4.69 (td, *J* = 2.7 Hz, *J* = 10.1 Hz, 1H), 2.85 (s, 3H), 2.51 (s, 1H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 148.41, 136.83, 132.19, 129.96, 129.77, 128.22, 128.02, 127.92, 126.59, 125.64, 115.50, 70.11, 64.36, 33.71, 20.47. ESI-MS: *m*/*z* 266 $[M+H]^+$. Chiral HPLC conditions: Chiralcel AD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 9.61 min (major), 10.28 min (minor).

4.3.29. (1*R*,2*R*)-2-(Ethyl(phenyl)amino)-1,2-dihydro-naphthalen-1-ol 7af

Colorless liquid (91% yield); 94% ee; $[\alpha]_D^{27} = -160.7$ (*c* 0.85, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) 7.56–7.58 (m, 1H), 7.28–7.33 (m, 4H), 7.16–7.18 (m, 1H), 6.99–7.00 (m, 2H), 6.81–6.84 (m, 1H), 6.64 (dd, *J* = 2.4 Hz, *J* = 9.8 Hz, 1H), 6.00 (dd, *J* = 3.2 Hz, *J* = 9.8 Hz, 1H), 5.15 (d, *J* = 9.8 Hz, 1H), 4.71 (td, *J* = 2.8 Hz, *J* = 9.2 Hz, 1H), 3.39 (q, *J* = 7.0 Hz, 2H), 2.47 (s, 1H), 5.15 (t, *J* = 7.08 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 148.40, 136.57, 132.16, 129.61, 129.48, 128.81, 128.24, 128.21, 126.71, 126.19, 117.80, 114.95, 70.47, 63.39, 41.72, 14.67. ESI-MS: *m*/*z* 266 $[M+H]^+$. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 7.39 min (major), 8.28 min (minor).

4.3.30. (1*R*,2*R*)-2-(Allyl(methyl)amino)-1,2-dihydro-naphthalen-1-ol 7ag

Colorless liquid (97% yield); 97% ee; $[\alpha]_D^{27} = -83.4$ (*c* 0.28, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) 7.42–7.44 (m, 1H), 7.14–7.20 (m, 4H), 7.03–7.05 (m, 1H), 6.84–6.86 (m, 2H), 6.68–6.71 (m, 1H), 6.54 (dd, *J* = 2.2 Hz, *J* = 9.8 Hz, 1H), 5.86 (dd, *J* = 3.1 Hz, *J* = 9.8 Hz, 1H), 5.77–5.81 (m, 1H), 5.00–5.16 (m, 3H), 4.68–4.70 (m, 1H), 3.80–3.84 (m, 2H), 2.25 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 141.97, 135.24, 134.94, 130.91, 128.88, 128.18, 127.12, 125.56, 125.12, 123.96, 119.23, 116.75, 115.03, 113.45, 69.31, 61.31, 49.08. ESI-MS: *m*/*z* 278 $[M+H]^+$. Chiral HPLC conditions: Chiralcel AD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 13.01 min (minor), 16.84 min (major).

4.3.31. (1*R*,2*R*)-2-(3,4-Dihydroisoquinolin-2(1H)-yl)-1,2-dihydronaphthalen-1-ol 7ah

Colorless liquid (95% yield); 94% ee; $[\alpha]_D^{27} = -134.9$ (*c* 0.82, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) 7.62–7.63 (m, 1H), 7.27–7.31 (m, 2H), 7.06–7.18 (m, 4H), 6.60 (dd, *J* = 2.6 Hz, *J* = 9.8 Hz, 1H), 6.17 (dd, *J* = 2.4 Hz, *J* = 9.9 Hz, 1H), 5.04 (d, *J* = 12.0 Hz, 1H), 4.04 (d, *J* = 14.9 Hz, 1H), 3.83 (d, *J* = 14.9 Hz, 1H), 3.68 (td, *J* = 2.5 Hz, *J* = 12.0 Hz, 1H), 3.45 (s, 1H), 3.16–3.18 (m, 1H), 2.95–2.98 (m, 2H), 2.81–2.83 (m, 1H), 1.68 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 137.15, 134.85, 134.48, 131.84, 129.66, 128.86, 127.93, 127.43, 126.71, 126.27, 126.21, 125.75, 124.76, 124.68, 68.12, 67.86, 52.03, 46.97, 30.01. ESI-MS: *m*/*z* 278 $[M+H]^+$. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 11.04 min (major), 12.74 min (minor).

4.3.32. (1*R*,2*R*)-2-(Benzyl(methyl)amino)-1,2-dihydro-naphthalen-1-ol 7ai

Colorless liquid (95% yield); 95% ee; $[\alpha]_D^{27} = -118.2$ (*c* 0.32, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) 7.61–7.62 (m, 1H), 7.25–7.36 (m, 7H), 7.09–7.11 (m, 1H), 6.59 (dd, *J* = 2.7 Hz, *J* = 9.9 Hz, 1H), 6.16 (dd, *J* = 2.4 Hz, *J* = 9.9 Hz, 1H), 4.98 (d, *J* = 12.0 Hz, 1H), 3.89 (d, *J* = 13.3 Hz, 1H), 3.62–3.65 (m, 1H), 3.42 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 139.04, 137.30, 132.02, 129.72, 129.03, 128.63, 127.99, 127.50, 127.43, 126.28, 125.20, 124.75, 68.85, 66.43, 58.94, 38.00. ESI-MS: *m*/*z* 266 $[M+H]^+$. Chiral HPLC conditions: Chiralcel AD-H, 25 °C, flow rate: 1.0 mL/min, hexane/isopropanol: 90:10, 254 nm, 13.61 min (major), 14.20 min (minor).

Acknowledgements

We are grateful to the start fund of the School of Pharmaceutical Sciences, Gannan Medical University (QD201303).

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20. CCDC 943665 **5cb** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk)