Tetrahedron: *Asymmetry* 22 (2011) 948–954

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Synthesis of optically active 1,4-benzoxazine derivatives using palladium-catalyzed coupling kinetic resolution

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ARTICLE INFO

Article history:
Received 4 April 2011
Accepted 2 June 2011
Available online 19 July 2011

ABSTRACT

A novel coupling kinetic resolution has been developed by employing commercially available reagents, such as $Pd(OOCCF_3)_2$–(*S*)-BINAP, which is a simple and convenient protocol that enables the formation of a highly important, novel class of optically active *trans*-1,4-benzoxazine derivatives and optically active *trans*-recovered starting materials with moderate selectivity (*s*).

1. Introduction

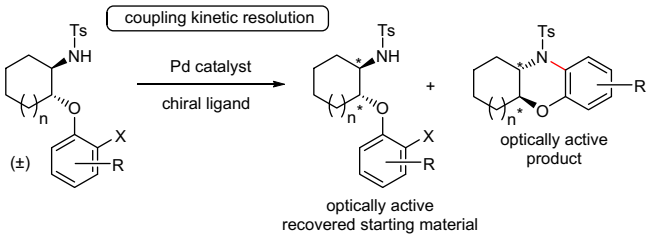
Developing novel methods to synthesize chiral molecules has become an important pursuit for synthetic organic chemists. Different enantiomers generally exhibit different biological activities. In biological systems, enzymes catalyze the reactions with excellent selectivity for the synthesis of a single enantiomer. These natural catalysts have inspired chemists to develop a variety of non-enzymatic synthetic catalysts, which can catalyze the reactions with excellent selectivity.[1]

For the past few years, great advances have been made in the development of cross-coupling methodology.[2] The leading application of cross-coupling chemistry, in particular C–N bond-forming reactions, are important in medicinal chemistry, pharmaceutical companies and in academic laboratories.

Organic compounds containing 1,4-benzoxazine and phenoxazine moieties have attracted interest due to their biological activities.[3] Generally, 1,4-benzoxazine compounds are synthesized via a multistep process, such as the cyclocondensation of *o*-aminophenols with suitable dihalo derivatives,[4] cyclocondensation of *o*-aminophenols with α-halo-acyl bromides followed by carbonyl group reduction with BH_3,[5] and alkylation of *o*-nitrophenol with a haloester followed by reductive cyclization.[6] Alternatively, these 1,4-benzoxazine moieties can be made via a ring opening of an epoxide with *o*-halosulfonamides followed by cyclization[7] or ring opening of an epoxide with *o*-aminophenols followed by cyclocondensation.[8]

As part of our ongoing research towards copper catalyzed coupling chemistry,[9] we have very recently developed a domino reaction, as an alternative to the conventional multistep process to prepare a 1,4-benzoxazine skeleton in a single process from readily available *o*-iodophenols and aziridines using a copper-catalyzed domino ring opening followed by a Goldberg cyclization.[10] However, all the aforementioned methods are achiral methodologies and provide racemic 1,4-benzoxazine derivatives. As a result development of a novel chiral method is highly desirable.

In order to devise a more efficient and simple chiral catalyst system for the synthesis of optically active *trans*-1,4-benzoxazines, we explored a novel kinetic resolution[11] method based on a coupling reaction (coupling kinetic resolution) by the use of simple and commercially available palladium as a metal source with the support of chiral chelating ligand (Scheme 1).



Scheme 1. Proposed scheme for the coupling kinetic resolution.

2. Results and discussion

In our initial studies, the palladium catalyzed coupling kinetic resolution was carried out using *trans*-*N*-(2-(2-iodophenoxy)-cyclohexyl)-4-methylbenzenesulfonamide (±)-**1** in the presence of 5 mol % of $Pd(OAc)_2$ and 10 mol % of (*S*)-BINAP in toluene at 110 °C. The reaction provided 10% ee and 58% isolated yield for the recovered starting material (+)-**1** and 16% ee, 36% yield for the corresponding product **4** (Table 1, entry 1).

In general, lowering the reactivity of the starting material, increased the selectivity. Hence, the more reactive iodo-starting material (±)-**1** was replaced by the corresponding less reactive

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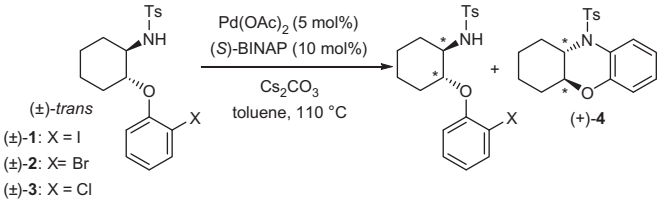
doi:10.1016/j.tetasy.2011.06.005

Table 1
Selection of starting material for the coupling kinetic resolution



Entry	Substrate	Time (h)	Recovered starting material		Product		Conversion (C) (%)	Selectivity factor (s)
			ee[a] (%)	Yield[b] (%)	ee[a] (%)	Yield[b] (%)		
1	(±)-**1**	8	10	58	16	36	38.5	1.5
2	(±)-**2**	7	34	42	26	55	56.7	2.3
3	(±)-**3**	48	02	81	10	13	16.8	1.2

[a] %Ee were calculated using HPLC chiral columns.
[b] Isolated yield.

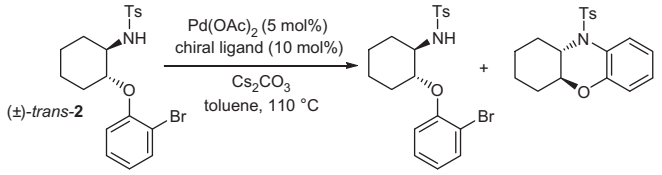
bromo-starting material (±)-**2**. As expected, replacing *trans*-(±)-**1** with (±)-**2** increased the enantiomeric excess up to 34% ee for the recovered starting material and 26% ee for the product with a selectivity of 2.3 (entry 2). However, decreasing the reactivity further by using the corresponding chloro precursor (±)-**3** reduced the selectivity to 1.2 (entry 3).

After selecting bromo derivative (±)-**2** as the starting material for the coupling kinetic resolution, we started our optimization process by changing several parameters. Initially, we screened several chiral ligands and the results are summarized in Table 2. Among them, (*S*)-BINAP provided a maximum selectivity ($s = 2.3$) for the coupling kinetic resolution (Table 2, entry 1). When chiral palladium carbene catalyst **5** was used alone, there was no reaction, whereas the chiral palladium carbene catalyst **5** in combination with PPh_3 catalyzed the coupling reaction but without any selectivity (entry 6). However, the chiral palladium carbene catalyst **5** in combination with (*S*)-BINAP provided an improved selectivity of 3.2 (entry 7). This observation clearly shows that the (*S*)-BINAP is important for the coupling kinetic resolution to give good selectivity.

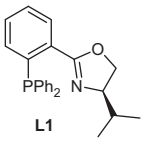
The coupling kinetic resolution was further optimized by changing the palladium source and the results are summarized in Table 3. Although several palladium salts catalyzed the coupling kinetic resolution reaction, the $Pd(OOCCF_3)_2$ turned out to be the optimal palladium salt in terms of selectivity ($s = 3.7$) (Table 3, entry 4). The reaction was further optimized by changing the solvents and bases to increase the efficiency of the coupling kinetic resolution. Among all the solvents examined, toluene provided the best results in terms of selectivity. The selectivity factor in the case of dioxane is only 1.7 while the reaction in DMF lowered the selectivity further to 1.2. The reaction in acetonitrile and in THF did not provide any selectivity. Among the bases K_2CO_3, K_3PO_4, Na_2CO_3 and Cs_2CO_3 screened, the Cs_2CO_3 continued to be the optimal base for the coupling kinetic resolution as it provided the maximum selectivity of 3.7 at 68.3% conversion in toluene using $Pd(OOCCF_3)_2$ (5 mol %)–(*S*)-BINAP (10 mol %).

Using the aforementioned optimized reaction conditions, we initiated our investigation into the scope of the chiral palladium catalyzed coupling kinetic resolution and the results are summarized in Table 4. The starting material *trans*-*N*-(2-(2-bromophenoxy)cyclohexyl)-4-methylbenzenesulfonamide (±)-**2** provided a

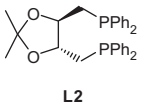
Table 2
Screening of Chiral Ligands for the coupling kinetic resolution



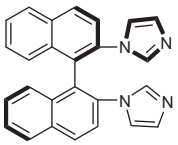
Entry	Ligands	Time (h)	Recovered starting material		Product		Conversion C (%)	Selectivity factor (s)
			ee[a] (%)	Yield[b] (%)	ee[a] (%)	Yield[b] (%)		
1	(*S*)-BINAP	7	34	42	26	55	56.7	2.3
2	**L1**	48	—	—	—	—	<5%	—
3	**L2**	48	—	>99	—	00	No rxn	—
4	**L3**	48	—	>99	—	00	No rxn	—
5	Catalyst **5**	48	—	>99	—	00	No rxn	—
6	Catalyst **5** PPh_3	4.5	00	62	00	33	38.0	—
7	Catalyst **5** (*S*)-BINAP	**5**	**12**	**72**	**48**	**19**	**20.0**	**3.2**



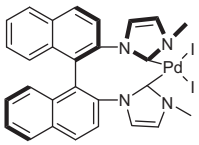
L1



L2



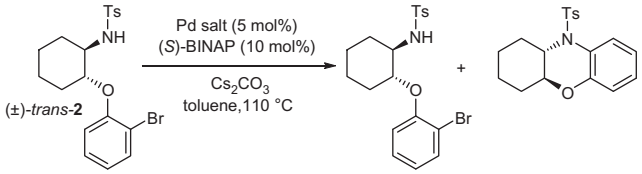
L3



catalyst **5**

[a] % Ee were calculated using HPLC chiral columns.
[b] Isolated yield.

Table 3
Screening of palladium salts for the coupling kinetic resolution



Entry	Pd salts	Time (h)	Recovered starting material		Product		Conversion C (%)	Selectivity factor (s)
			ee[a] (%)	Yield[b] (%)	ee[a] (%)	Yield[b] (%)		
1	$Pd(OAc)_2$	7	34	42	26	55	56.7	2.3
2	$PdCl_2$	72	52	9	6	72	10.3	3.4
3	Pd_2dba_3	7.5	53	13	11	81	82.8	1.9
4	**$Pd(OOCCF_3)_2$**	**3.5**	**69**	**32**	**32**	**62**	**68.3**	**3.7**
5	$Pd(acac)_2$	3.5	41	43	39	51	51.3	3.3
6	K_2PdCl_4	72	39	42	41	45	48.8	3.4
7	$Pd(OOCCF_3)_2$	4	96	10	12	85	88.9	3.6
8	$Pd(OOCCF_3)_2$	3 h 10 min	48	40	38	53	55.8	3.5

[a] % Ee were calculated using HPLC chiral columns.
[b] Isolated yield.

maximum selectivity of 3.7 with 69% ee for the recovered starting material and 32% ee for the product (entry 1). When the ring size was altered, the selectivity of the reaction was slightly reduced (entries 2 and 6). When electron withdrawing groups were present on the aromatic ring, a small reduction in selectivity (entries 3 and 5) was observed, while electron-donating groups reduced the selectivity further (entries 4 and 7). The enantiomerically enriched recovered starting material can be further reacted with an achiral palladium complex to obtain the other enantiomer of the cyclized product.

A plausible reaction pathway is described in Scheme 2. Initially, the oxidative coupling takes place at the aryl-bromide bond of (±)-**2** with the chiral palladium catalyst; the selectivity is due to the diastereomeric transition state pair. The faster reacting enantiomer of (±)-**2** reacts first and produces intermediate **6** followed by nucleophilic displacement to give intermediate **7**. Intermediate **7**, upon reductive elimination releases the desired enantiomerically enriched product (+)-**4** and simultaneously regenerates the palladium(0) catalyst for the next cycle. When the reaction was stopped before completion, the fast reacting enantiomer of the (±)-**2** was converted into the product and slow reacting enantiomer of the (±)-**2** starting material remained in the reaction mixture in an enantiomerically enriched form.

3. Conclusion

In conclusion, a novel coupling kinetic resolution has been developed by employing commercially available (*S*)-BINAP–$Pd(OOCCF_3)_2$. This simple and convenient protocol enables us to access both enantiomers of a novel class of highly important optically active 1,4-benzoxazine derivatives and optically active *trans*-recovered starting materials with moderate selectivity factors (*s*).

4. Experimental

4.1. General information

All reactions were carried out in reaction tubes under a nitrogen atmosphere. Ligands, palladium salts and Cs_2CO_3 were purchased from Aldrich Chemical Company and used without further purification. Ligands **L1** and **L3** and catalyst **5** were prepared using literature procedures.[12] The starting materials for the coupling kinetic resolution were made by using aziridines and substituted *o*-bromophenols. Toluene was purchased from SRL Chemicals, India and dried over sodium wire (vacuum distillation). Reactions were performed by using Aldrich Stirrer, Thin-layer chromatography (TLC) was performed using Merck Silica Gel 60 F_{254} pre-coated plates (0.25 mm) and visualized by UV fluorescence quenching. Silica gel (particle size 100–200 mesh) purchased from SRL India was used for chromatography. ^1H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz instrument. ^1H NMR spectra were reported relative to Me_4Si (δ 0.0 ppm) or residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR were reported relative to $CDCl_3$ (δ 77.16 ppm). FTIR spectra were recorded on a Nicolet 6700 spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were recorded on Q-Tof Micro mass spectrometer. The enantiomeric excess (%ee) was determined by Shimadzu HPLC systems using Daicel chemical industries Ltd ChiralPAK AS-H column and ChiralPAK AD-H columns.

The selectivity factor (*s*) was determined using the following equation.[13]

$$(s) = (k_{fast}/k_{slow}) = \frac{\ln[(1-C)(1-ee_{RSM})]}{\ln[(1-C)(1+e_{RSM})]}$$

$$C = \text{Conversion} = \frac{ee_{RSM}}{ee_{RSM} + ee_{product}}$$

ee_{RSM} = enantiomeric excess of recovered starting material

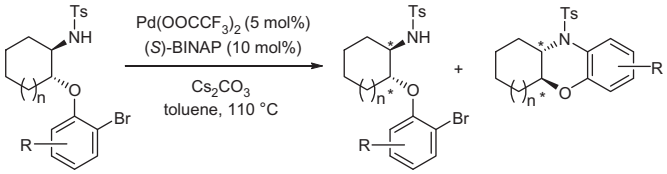
4.1.1. Typical experimental procedure for the synthesis of starting materials

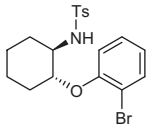
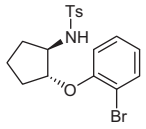
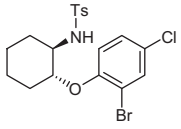
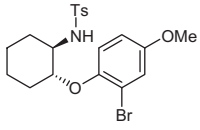
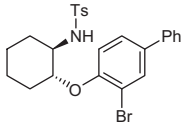
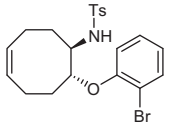
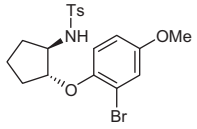
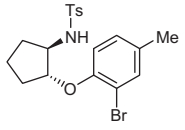
7-Tosyl-7-azabicyclo[4.1.0]heptane (1.004 g, 4.0 mmol), *o*-bromophenol (464 μL, 4.0 mmol) and Cs_2CO_3 (1.955 g, 6.0 mmol) were taken under a nitrogen atmosphere in a 20 mL reaction tube equipped with a septum. To this reaction mixture, toluene (8.0 mL) was added and heated at 110 °C for 12 h. After completion of the reaction (the reaction progress was monitored by TLC), the reaction mixture was allowed to cool, toluene was evaporated under rotavapor and the crude reaction mixture was purified directly using column chromatography on silica gel using ethyl acetate/hexane as eluents to afford *trans*-*N*-(2-(2-bromophenoxy)cyclohexyl)-4-methylbenzenesulfonamide (±)-**2**, 1.69 g (99%). The corresponding (±)-**1** and (±)-**3** starting materials were synthesized using a similar procedure.

4.1.2. Typical experimental procedure for the palladium catalyzed coupling kinetic resolution reaction

At first, $Pd(OOCCF_3)_2$ (4.2 mg, 0.0125 mmol), (*S*)-BINAP (15.6 mg, 0.025 mmol), (±)-**2** (106 mg, 0.25 mmol) and Cs_2CO_3

Table 4
Scope of the palladium catalyzed coupling kinetic resolution



Entry	Ligands	Time (h)	Recovered starting material		Product		Conversion C (%)	Selectivity factor (s)
			ee[a] (%)	Yield[b] (%)	ee[a] (%)	Yield[b] (%)		
1		3.5	69	32	32	62	68.3	3.7
2		27	22	58	40	35	35.5	2.9
3		3 h 50 min	20	61	36	30	35.7	2.6
4		3 h 50 min	16	56	26	36	38.1	2.0
5		4	20	53	39	31	33.9	2.8
6		4	10	67	43	16	18.9	2.8
7		24	28	42	24	49	53.6	2.1
8		6.5	18	63	42	23	30.0	2.9

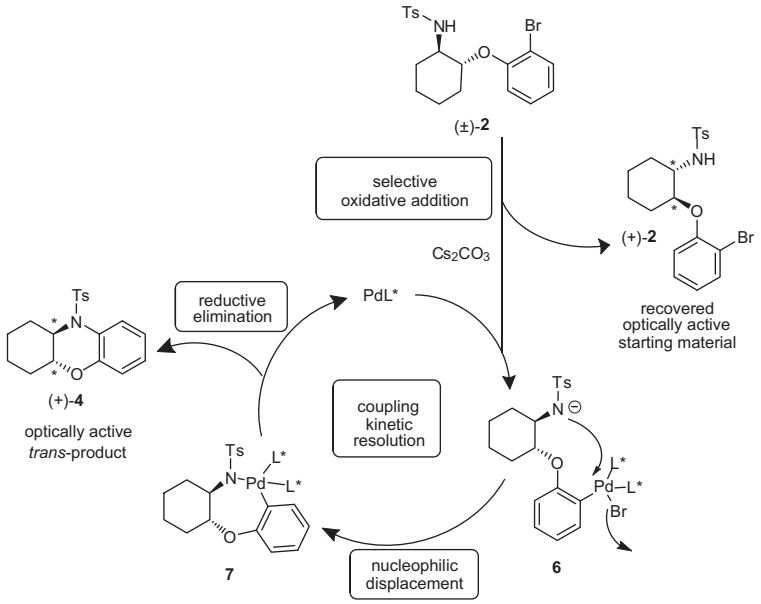
[a] % Ee were calculated using HPLC chiral columns.
[b] Isolated yield.

(163 mg, 0.5 mmol) were taken under a nitrogen atmosphere in a 10 mL reaction tube equipped with a septum. To this reaction mixture, toluene (2.2 mL) was added and heated at 110 °C for 3.5 h. After completion of the reaction (the reaction progress was monitored by TLC), the reaction mixture was allowed to cool, the toluene was evaporated under rotavapor and the crude reaction mixture was purified directly using column chromatography on silica gel using ethyl acetate/hexane as eluents to afford (+)-*trans*-10-tosyl-2,3,4,4a,10,10a-hexahydro-1*H*-phenoxazine 53 mg in 62%, and the starting material recovered (+)-**2** as 34 mg (32%) (Table 4, entry1).

4.1.3. Spectroscopic data for the products

4.1.3.1. (+)-*trans*-4a,10a-10-Tosyl-2,3,4,4a,10,10a-hexahydro-1*H*-phenoxazine (Table 4, entry 1).

White solid, mp 104–106 °C (lit.[7] 104–105 °C), R_f 0.63 (10% ethyl acetate/hexanes); $[\alpha]_D^{25} = +13.7$ (*c* 1.3, $CHCl_3$); IR ($CDCl_3$): 2932, 2861, 1593, 1485, 1453, 1352, 1255, 1164, 1057, 809, 733, 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.12–1.26 (m, 1H), 1.27–1.41 (m, 2H), 1.42–1.54 (m, 1H), 1.66–1.76 (m, 2H), 1.98–2.07 (m, 1H), 2.25 (s, 3H), 2.53–2.62 (m, 1H), 3.30 (ddd, *J* = 11.0, 10.6 and 4.0 Hz, 1H), 3.42 (ddd, *J* = 11.0, 10.5 and 3.2 Hz, 1H), 6.62 (dd, *J* = 7.6 and 1.6 Hz, 1H), 6.87–6.98 (m, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.71 (dd, *J* = 8.0 and 1.6 Hz, 1H); ^{13}C NMR (100 MHz): δ 21.7, 24.1, 24.7, 32.0, 33.6, 65.5, 81.0, 117.2, 122.2, 126.3, 126.4, 127.6, 127.9, 129.4, 133.5, 144.0, 152.9; MS (ESI, *m*/*z*): 344 $[MH]^+$; HRMS: calcd for $C_{19}H_{22}NSO_3$, $[MH]^+$ 344.1320, found 344.1316. The enantiomeric excess (% ee) was determined to be 32% by HPLC using a



Scheme 2. A plausible mechanistic explanation.

ChiralPAK AS-H column (4% *i*-PrOH/hexanes, 0.4 mL/min); t_R (minor, 27.4 min), t_R (major, 30.6 min).

4.1.3.2. (+)-*trans*-3a,9a-9-Tosyl-1,2,3,3a,9,9a-hexahydrobenz-o-[*b*]cyclopenta[*e*][1,4]oxazine (Table 4, entry 2)[10]. White solid, mp 140–142 °C, R_f 0.67 (10% ethyl acetate/hexanes); $[\alpha]_D^{25} = +29.4$ (*c* 1.3, $CHCl_3$); IR ($CDCl_3$) 2963, 2882, 1592, 1482, 1352, 1290, 1243, 1165, 1093, 811, 733, 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.59–1.70 (m, 1H), 1.78–2.11 (m, 4H), 2.36 (s, 3H), 2.50–2.60 (m, 1H), 3.30–3.38 (m, 1H), 3.85–3.94 (m, 1H), 6.78 (dd, *J* = 7.6 and 1.6 Hz, 1H), 6.91–7.03 (m, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 8.06, (dd, *J* = 8.4 and 1.6 Hz, 1H); ^{13}C NMR (100 MHz): δ 18.5, 21.7, 25.6, 28.4, 63.1, 80.4, 118.1, 121.9, 123.4, 125.5, 127.4, 127.8, 129.7, 133.9, 144.3, 149.4; MS (ESI, *m*/*z*): 352 $[MNa]^+$; HRMS: calcd for $C_{18}H_{19}NO_3NaS$, $[MNa]^+$ 352.0983, found 352.0980. The enantiomeric excess (% ee) was determined to be 40% by HPLC using a Chiralcel OJ column (10% *i*-PrOH/hexanes, 0.8 mL/min); t_R (major, 12.2 min), t_R (minor, 14.1 min).

4.1.3.3. (+)-*trans*-4a,10a-8-Chloro-10-tosyl-2,3,4,4a,10,10a-hexahydro-1*H*-phenoxazine (Table 4, entry 3)[10]. White solid; mp 117–119 °C R_f 0.52 (10% ethyl acetate/hexanes); $[\alpha]_D^{25} = +67.0$ (*c* 2.0, $CHCl_3$); FTIR (neat): 2925, 2858, 1593, 1478, 1345, 1259, 1166, 1050, 887, 814, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.28–1.57 (m, 4H), 1.74–1.85 (m, 2H), 2.07–2.20 (m, 1H), 2.35 (s, 3H), 2.62–2.71 (m, 1H), 3.36 (ddd, *J* = 10.6, 10.5 and 4.0 Hz, 1H), 3.48 (ddd, *J* = 10.6, 10.5 and 3.2 Hz, 1H), 6.61–6.66 (m, 1H), 6.96–7.01 (m, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* =8.0 Hz, 2H), 7.81 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 24.0, 24.6, 31.9, 33.5, 65.2, 81.1, 118.2, 125.9, 126.0, 126.9, 127.6, 128.9, 129.6, 133.5, 144.3, 151.2; MS (ESI, *m*/*z*): 400 $[MNa]^+$; HRMS: calcd for $C_{19}H_{20}NO_3SClNa$, $[MNa]^+$ 400.0750, found 400.0743. The enantiomeric excess (% ee) was determined to be 36% by HPLC using a ChiralPAK AS-H column (15% *i*-PrOH/hexanes, 0.8 mL/min); t_R (minor, 9.0 min), t_R (major, 10.1 min).

4.1.3.4. (+)-*trans*-8-Methoxy-10-tosyl-2,3,4,4a,10,10a-hexahydro-1*H*-phenoxazine (Table 4, entry 4). White solid, mp 88–90 °C, R_f 0.61 (10% ethyl acetate/hexanes); $[\alpha]_D^{25} = +10.9$ (*c* 0.2, $CHCl_3$); IR ($CDCl_3$): 2934, 2863, 1602, 1499, 1455, 1354, 1264, 1216, 1168, 1057, 815, 730, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.10–1.49 (m, 5H), 1.66–1.77 (m, 1H), 1.98–2.08 (m, 1H), 2.27 (s, 3H), 2.55–2.64 (m, 1H), 3.27 (t, *J* = 10.0 Hz, 1H), 3.41 (t, *J* = 10.8 Hz, 1H), 3.74 (s, 3H), 6.49–6.58 (m, 2H), 7.05 (d, *J* = 7.2 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.33 (s, 1H); ^{13}C NMR (100 MHz): δ 21.7, 24.2, 24.7, 32.0, 33.7, 56.0, 65.5, 81.3, 111.1, 112.4, 117.5, 127.6, 128.4, 129.4, 133.5, 144.0, 146.8, 154.5; MS (ESI, *m*/*z*): 374 $[MH]^+$; HRMS: calcd for $C_{20}H_{24}NO_4S$, $[MH]^+$ 374.1426, found 374.1432. The enantiomeric excess (% ee) was determined to be 26% by HPLC using a ChiralPAK AD-H column (10% *i*-PrOH/hexanes, 0.8 mL/min); t_R (minor, 11.7 min), t_R (major, 13.7 min).

4.1.3.5. (+)-*trans*-4a,10a-8-Phenyl-10-tosyl-2,3,4,4a,10,10a-hexahydro-1*H*-phenoxazine (Table 4, entry 5). White solid, mp 109–111 °C, R_f 0.68 (10% ethyl acetate/hexanes); $[\alpha]_D^{25} = +8.7$ (*c* 0.3, $CHCl_3$); IR ($CDCl_3$): 2931, 2861, 1600, 1482, 1353, 1268, 1166, 1059, 818, 703, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.16–1.30 (m, 2H), 1.30–1.45 (m, 2H), 1.45–1.58 (m, 2H), 1.69–1.79 (m, 2H), 2.03–2.11 (m, 1H), 2.26 (s, 3H), 2.57–2.66 (m, 1H), 3.36 (ddd, *J* = 10.8, 10.6 and 4.0 Hz, 1H), 3.46 (ddd, *J* = 11.0, 10.6 and 3.6 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.55 (d, *J* = 7.6 Hz, 2H), 8.0 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz): δ 21.7, 24.1, 24.7, 32.0, 33.6, 65.4, 81.1, 117.4, 124.7, 124.9, 127.0, 127.2, 127.7, 128.1, 128.9, 129.5, 133.6, 135.3, 140.4, 144.1, 152.2; MS (ESI, *m*/*z*): 420 $[MH]^+$; HRMS: calcd for $C_{25}H_{26}NO_3S$, $[MH]^+$ 420.1633, found 420.1652. The enantiomeric excess (% ee) was determined to be 39% by HPLC using a ChiralPAK AS-H column (15% *i*-PrOH/hexanes, 0.8 mL/min); t_R (minor, 11.1 min), t_R (major, 15.7 min).

4.1.3.6. (−)-*trans*-(5a,11a,*Z*)-12-Tosyl-6,7,10,11,11a,12-hexahydro-5a*H*-benzo[*b*]cyclooocta[*e*][1,4]oxazine (Table 4, entry 6)[10]. White solid, mp 97–99 °C, R_f 0.60 (10% ethyl acetate/hexanes); $[\alpha]_D^{25} = -12.0$ (*c* 0.6, $CHCl_3$); IR ($CDCl_3$): 2923, 2856, 1595, 1483, 1348, 1253, 1157, 1092, 812, 750, 662 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.20–1.35 (m, 1H), 1.55–1.77 (m, 1H), 1.82–1.95 (m, 1H), 2.01–2.31 (m, 4H), 2.35 (s, 3H), 3.64–3.73 (m, 1H), 4.32–4.42 (m, 1H), 5.61–5.75 (m, 2H), 6.76 (d, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 3H), 7.10–7.19 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz): δ 21.7, 22.8, 29.8, 33.8, 34.0,

62.5, 85.2, 117.4, 123.1, 127.2, 127.9, 128.6, 128.7, 129.3, 129.4, 129.5, 136.0, 143.6, 153.6; MS (ESI, *m*/*z*): 392 $[MNa]^+$; HRMS: calcd for $C_{21}H_{23}NO_3NaS$, $[MNa]^+$ 392.1296, found 392.1291. The enantiomeric excess (% ee) was determined to be 43% by HPLC using a ChiralPAK AS-H column (15% *i*-PrOH/hexanes, 0.8 mL/min); t_R (minor, 9.5 min), t_R (major, 10.6 min).

4.1.3.7. (+)-*trans*-3a,9a-7-Methoxy-9-tosyl-1,2,3,3a,9,9a-hexahydrobenzo[*b*]cyclopenta[*e*][1,4]oxazine (Table 4, entry 7). White solid, mp 103–105 °C, R_f 0.64 (10% ethyl acetate/hexanes); $[\alpha]_D^{25} = +48.7$ (*c* 1.0, $CHCl_3$); IR ($CDCl_3$): 2924, 1608, 1496, 1356, 1267, 1215, 1168, 1097, 952, 733, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.49–1.61 (m, 1H), 1.73–1.90 (m, 3H), 1.91–2.02 (m, 1H), 2.29 (s, 3H), 2.44–2.54 (m, 1H), 3.21–3.31 (m, 1H), 3.73 (s, 3H), 3.76–3.86 (m, 1H), 6.49 (dd, *J* = 8.8 and 2.8 Hz, 1H), 6.62 (d, *J* = 8.8 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR (100 MHz): δ 18.5, 21.7, 25.5, 28.6, 56.0, 63.1, 80.8, 108.1, 111.7, 118.4, 127.8, 129.7, 133.9, 143.4, 144.3, 154.3; MS (ESI, *m*/*z*): 360 $[MH]^+$; HRMS: calcd for $C_{19}H_{22}NO_4S$, $[MH]^+$ 360.1270, found 360.1261. The enantiomeric excess (% ee) was determined to be 24% by HPLC using a ChiralPAK AS-H column (15% *i*-PrOH/hexanes, 0.8 mL/min); t_R (minor, 14.4 min), t_R (major, 19.8 min).

4.1.3.8. (+)-*trans*-7-Methyl-9-tosyl-1,2,3,3a,9,9a-hexahydrobenzo[*b*]cyclopenta[*e*][1,4]oxazine (Table 4, entry 8). White solid, mp 118–121 °C, R_f 0.64 (10% ethyl acetate/hexanes); $[\alpha]_D^{25} = +16.9$ (*c* 0.2, $CHCl_3$); IR ($CDCl_3$): 2924, 1599, 1496, 1354, 1257, 1167, 1096, 814, 761, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.48–1.61 (m, 1H), 1.72–1.91 (m, 3H), 1.91–2.02 (m, 1H), 2.34 (s, 3H), 2.28 (s, 3H), 2.41–2.51 (m, 1H), 3.21–3.30 (m, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.79 (s, 1H); ^{13}C NMR (100 MHz): δ 18.5, 21.1, 21.7, 25.6, 28.4, 63.1, 80.4, 117.6, 123.7, 126.1, 127.0, 127.8, 129.6, 131.3, 134.0, 144.2, 147.2; MS (ESI, *m*/*z*): 343 $[M]^+$; HRMS: calcd for $C_{19}H_{21}NO_3S$, $[MH]^+$ 343.1242, found 343.1242. The enantiomeric excess (% ee) was determined to be 42% by HPLC using a ChiralPAK AD-H column (15% *i*-PrOH/hexanes, 1 mL/min); t_R (major, 8.8 min), t_R (minor, 10.8 min).

4.1.3.9. (+)-*trans*-*N*-(2-(2-Bromophenoxy)cyclohexyl)-4-methylbenzenesulfonamide (Table 4, entry 1). White solid, mp 89–91 °C, R_f 0.35 (20% ethyl acetate/hexanes); $[\alpha]_D^{25} = +33.7$ (*c* 0.2, $CHCl_3$); IR ($CDCl_3$): 3276, 2927, 2858, 1586, 1469, 1321, 1276, 1154, 1090, 1036, 813, 743, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.13–1.49 (m, 3H), 1.28–1.42 (m, 1H), 1.44–1.54 (m, 1H), 1.69–1.78 (m, 1H), 1.93–2.02 (m, 1H), 2.23–2.33 (m, 1H), 2.4 (s, 3H), 3.24–3.32 (m, 1H), 4.16 (ddd, *J* = 7.8, 7.8 and 3.6 Hz, 1H), 5.09 (d, *J* = 4.4 Hz, 1H), 6.82–6.87 (m, 2H), 7.21 (ddd, *J* = 8.0, 7.9 and 1.2 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.50 (dd, *J* = 8.2, 1.6 Hz,, 1H), 7.77 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz): δ 21.7, 22.3, 22.7, 28.5, 29.9, 55.0, 78.5, 113.8, 116.0, 122.8, 127.4, 128.5, 129.8, 133.7, 137.1, 143.5, 153.5; MS (ESI, *m*/*z*): 424 $[MH]^+$; HRMS: calcd for $C_{19}H_{23}NO_3SBr$, $[MH]^+$ 424.0582, found 424.0581. The enantiomeric excess (% ee) was determined to be 69% by HPLC using a ChiralPAK AD-H column (15% *i*-PrOH/hexanes, 1 mL/min); t_R (minor, 9.5 min), t_R (major, 12.3 min).

4.1.3.10. (−)-*trans*-*N*-(2-(2-Bromophenoxy)cyclopentyl)-4-methyl-benzenesulfonamide (Table 4, entry 2). White solid, mp 94–96 °C, R_f 0.35 (20% ethyl acetate/hexanes); $[\alpha]_D^{25} = -22.9$ (*c* 3.5, $CHCl_3$); IR ($CDCl_3$): 3262, 2960, 1586, 1471, 1438, 1279, 1154, 1089, 813, 747, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.39–1.49 (m, 1H), 1.68–1.91 (m, 3H), 1.96–2.07 (m, 1H), 2.11–2.22 (m, 1H), 2.38 (s, 3H), 3.65–3.71 (m, 1H), 4.59–4.63 (m, 1H), 4.89 (d, *J* = 6.0 Hz, 1H), 6.82 (ddd, *J* = 7.6, 7.6 and 1.2 Hz, 1H), 6.87 (dd, *J* = 8.2 and 1.2 Hz, 1H), 7.18–7.26 (m, 3H), 7.49 (dd, *J* = 7.6 and 1.6 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz): δ 21.4, 21.5, 29.7, 31.2, 59.3, 84.2, 113.0, 115.1, 122.2, 127.3, 128.4, 129.8, 133.4, 136.8, 143.6, 153.8; MS (ESI, *m*/*z*): 432 $[MNa]^+$; HRMS: calcd for $C_{18}H_{20}NO_3SNaBr$, $[MNa]^+$ 432.0245, found 432.0259; The enantiomeric excess (% ee) was determined to be 22% by HPLC using a ChiralPAK AD-H column (15% *i*-PrOH/hexanes, 1 mL/min); t_R (minor, 7.7 min), t_R (major, 9.3 min).

4.1.3.11. (−)-*trans*-*N*-(2-(2-Bromo-4-chlorophenoxy)cyclohexyl)-4-methylbenzenesulfonamide (Table 4, entry 3). White solid, mp 98–100 °C, R_f 0.35 (20% ethyl acetate/hexanes); $[\alpha]_D^{25} = -21.1$ (*c* 3.5, $CHCl_3$); IR ($CDCl_3$): 3275, 2936, 2863, 1592, 1467, 1321, 1272, 1153, 1091, 1040, 811, 734, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.17–1.34 (m, 3H), 1.38–1.54 (m, 2H), 1.59–1.69 (m, 1H), 1.8–1.89 (m, 1H), 2.04–2.15 (m, 1H), 2.32 (s, 3H), 3.19–3.28 (m, 1H), 4.03–4.11 (m, 1H), 5.29 (d, *J* = 5.6 Hz, 1H), 6.70 (d, *J* = 8.8 Hz, 1H), 7.07 (dd, *J* = 8.8 and 2.8 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz): δ 21.6, 22.1, 22.5, 28.3, 29.8, 54.6, 78.8, 114.2, 116.5, 126.8, 127.2, 128.3, 129.8, 133.0, 137.2, 143.5, 152.4; MS (ESI, *m*/*z*): 480 $[MNa]^+$; HRMS: calcd for $C_{19}H_{21}NO_3NaSClBr$, $[MNa]^+$ 480.0012, found 480.0020; The enantiomeric excess (% ee) was determined to be 20% by HPLC using ChiralPAK AD-H column (15% *i*-PrOH/hexanes, 1 mL/min); t_R (minor, 8.3 min), t_R (major, 11.1 min).

4.1.3.12. (+)-*trans*-*N*-(2-(2-Bromo-4-methoxyphenoxy)-cyclohexy-l)-4-methylbenzenesulfonamide (Table 4, entry 4). White solid, mp 93–95 °C, R_f 0.35 (20% ethyl acetate/hexanes); $[\alpha]_D^{25} = +13.3$ (*c* 0.3, $CHCl_3$); IR ($CDCl_3$): 3277, 2936, 2862, 1601, 1487, 1446, 1270, 1212, 1152, 1089, 1033, 808, 737, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.12–1.41 (m, 4H), 1.46–1.58 (m, 1H), 1.59–1.69 (m, 1H), 1.81–1.91 (m, 1H), 2.16–2.27 (m, 1H), 2.33 (s, 3H), 3.10–3.20 (m, 1H), 3.69 (s, 3H), 3.89 (ddd, *J* = 8.4, 8.2 and 3.6 Hz, 1H), 5.15 (d, *J* = 3.2 Hz, 1H), 6.66–6.75 (m, 2H), 6.99 (d, *J* = 2.8 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz): δ 21.6, 22.6, 22.9, 28.8, 30.3, 55.6, 56.0, 79.8, 114.0, 114.6, 118.4, 118.6, 127.7, 137.1, 143.4, 147.4, 154.9; MS (ESI, *m*/*z*): 454 $[MH]^+$; HRMS: calcd for $C_{20}H_{25}NO_4SBr$, $[MH]^+$ 454.0688, found 454.0671; The enantiomeric excess (% ee) was determined to be 16% by HPLC using a ChiralPAK AD-H column (15% *i*-PrOH/hexanes, 1 mL/min); t_R (minor, 8.8 min), t_R (major, 10.9 min).

4.1.3.13. (+)-*trans*-*N*-(2-(3-Bromobiphenyl-4-yloxy)cyclohexyl)-4-methylbenzenesulfonamide (Table 4, entry 5). White solid, mp 131–134 °C, R_f 0.35 (20% ethyl acetate/hexanes); $[\alpha]_D^{25} = +5.0$ (*c* 0.2, $CHCl_3$); IR ($CDCl_3$): 3245, 2936, 1597, 1475, 1266, 1154, 1088, 1043, 815, 734, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.21–1.36 (m, 3H), 1.41–1.58 (m, 2H), 1.62–1.72 (m, 1H), 1.88–1.98 (m, 1H), 2.11–2.26 (m, 1H), 2.31 (s, 3H), 3.21–3.30 (m, 1H), 4.09–4.18 (m, 1H), 5.18 (d, *J* = 4.4 Hz, 1H), 6.84 (dd, *J* = 8.4 and 1.2 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 2H), 7.23–7.29 (m, 1H), 7.31–7.38 (m, 3H), 7.41–7.46 (m, 2H), 7.66 (t, *J* = 2.0 Hz, 1H), 7.71 (dd, *J* = 8.0 and 1.6 Hz, 2H); ^{13}C NMR (100 MHz): δ 21.7, 22.3, 22.7, 28.6, 29.9, 55.0, 78.7, 114.1, 116, 126.9, 127.0, 127.4, 127.5, 129.0, 129.8, 132.1, 136.1, 137.1, 139.4, 143.5, 152.8; MS (ESI, *m*/*z*): 522 $[MNa]^+$; HRMS: calcd for $C_{25}H_{26}NO_3NaBrS$, $[MNa]^+$ 522.0714, found 522.0721; The enantiomeric excess (% ee) was determined to be 20% by HPLC using chiralcel OD-H column (15% *i*-PrOH/hexanes, 1 mL/min); t_R (major, 9.5 min), t_R (minor, 10.8 min).

4.1.3.14. (−)-*trans*-*N*-((*Z*)-8-(2-Bromo-4-phenoxy)cyclooct-4-enyl)-4-methylbenzenesulfonamide (Table 4, entry 6). R_f 0.35

(20% ethyl acetate/hexanes); $[\alpha]_D^{25} = -6.9$ (*c* 0.2, $CHCl_3$); IR ($CDCl_3$): 3310, 2930, 1586, 1474, 1436, 1274, 1157, 1091, 1035, 815, 747, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.47–1.65 (m, 2H), 1.84–1.99 (m, 2H), 1.99–2.09 (m, 1H), 2.09–2.21 (m, 1H), 2.30–2.53 (m, 2H), 2.35 (s, 3H), 3.63–3.72 (m, 1H), 4.45 (ddd, *J* = 7.3, 7.2 and 2.4 Hz, 1H), 5.35 (d, *J* = 7.2 Hz, 1H), 5.63–5.77 (m, 2H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.76–6.82 (m, 1H), 7.13–7.20 (m, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.46 (dd, *J* = 7.8 and 1.6 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz): δ 21.5, 21.7, 23.4, 29.9, 32.7, 54.8, 78.6, 113.5, 115.0, 122.8, 127.4, 128.7, 129.8, 130.9, 131.2, 133.8, 137.5, 143.5, 153.5; MS (ESI, *m*/*z*): 450 $[MH]^+$; HRMS: calcd for $C_{21}H_{25}NO_3SBr$, $[MH]^+$ 450.0739, found 450.0744; The enantiomeric excess (% ee) was determined to be 10% by HPLC using a ChiralPAK AD-H column (15% *i*-PrOH/hexanes, 1 mL/min); t_R (minor, 9.5 min), t_R (major, 12.3 min).

4.1.3.15. (−)-*trans*-*N*-(2-(2-Bromo-4-methoxyphenoxy)-cyclopent-yl)-4-methylbenzenesulfonamide (Table 4, entry 7). White solid, mp 74–76 °C, R_f 0.35 (20% ethyl acetate/hexanes); $[\alpha]_D^{25} = -11.2$ (*c* 1.3, $CHCl_3$); IR ($CDCl_3$): 3245, 2936, 1597, 1475, 1266, 1154, 1088, 1043, 815, 734, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.31–1.41 (m, 1H), 1.57–1.82 (m, 3H), 1.83–1.92 (m, 1H), 2.02–2.13 (m, 1H), 2.32 (s, 3H), 3.69 (s, 3H), 3.54–3.61 (m, 1H), 4.40–4.45 (m, 1H), 4.89 (d, *J* = 5.6 Hz, 1H), 6.68 (dd, *J* = 9.0 and 3.2 Hz, 1H), 6.74 (d, *J* = 9.2 Hz, 1H), 6.99 (d, *J* = 2.8 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz): δ 21.4, 21.6, 29.7, 31.2, 56.0, 59.3, 85.3, 113.8, 113.9, 117.0, 118.7, 127.4, 129.9, 136.9, 143.7, 148.2, 154.6; MS (ESI, *m*/*z*): 440 $[MH]^+$; HRMS: calcd for $C_{19}H_{23}NO_4SBr$, $[MH]^+$ 440.0531, found 440.0523; The enantiomeric excess (% ee) was determined to be 28% by HPLC using a ChiralPAK AD-H column (15% *i*-PrOH/hexanes, 1 mL/min); t_R (minor, 11.3 min), t_R (major, 13.3 min).

4.1.3.16. (−)-*trans*-*N*-(2-(2-Bromo-4-methylphenoxy)cyclopentyl)-4-methylbenzenesulfonamide (Table 4, entry 8). R_f 0.35 (20% ethyl acetate/hexanes); $[\alpha]_D^{25} = -19.5$ (*c* 3.5, $CHCl_3$); IR ($CDCl_3$): 3264, 2963, 1602, 1489, 1259, 1154, 1090, 810, 734, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.31–1.41 (m, 1H), 1.60–1.83 (m, 3H), 1.87–1.99 (m, 1H), 2.03–2.17 (m, 1H), 2.19 (s, 3H), 2.31 (s, 3H), 3.55–3.63 (m, 1H), 4.45–4.50 (m, 1H), 4.62 (d, *J* = 5.6 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 7.15–7.21 (m, 2H), 7.24 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz): δ 20.3, 21.4, 21.6, 29.7, 31.2, 59.4, 84.5, 113.0, 115.5, 127.4, 129.0, 129.9, 132.2, 133.8, 136.9, 143.7, 151.8; MS (ESI, *m*/*z*): 446 $[MNa]^+$; HRMS: calcd for $C_{19}H_{22}NO_3NaBrS$, $[MNa]^+$ 446.0401, found 446.0410; The enantiomeric excess (% ee) was determined to be 18% by HPLC using a ChiralPAK AD-H column (15% *i*-PrOH/hexanes, 1 mL/min); t_R (minor, 9.2 min), t_R (major, 11.0 min).

Acknowledgments

We thank DST (Project No.: SR/S1/OC-06/2008), New Delhi, for the financial support, and R.K.R. thanks CSIR, New Delhi, for a senior research fellowship.

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