Tetrahedron: *Asymmetry* 21 (2010) 2177–2182

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Halogenative kinetic resolution of β-aryloxy cyclic alcohols: chiral BINAP-mediated S_N2 displacement of hydroxy groups by chlorides with inversion of stereochemistry

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ARTICLE INFO

Article history:
Received 15 June 2010
Accepted 25 June 2010
Available online 23 July 2010

ABSTRACT

A series of optically active cyclic *trans*-β-aryloxy alcohols have been obtained by non-enzymatic kinetic resolution of the corresponding racemic aryloxy cyclic alcohols using commercially available (*S*)-BINAP and NCS by S_N2 halogenation of a hydroxy group. The product, *cis*-β-aryloxy chlorides, was also obtained in optically active form with inversion of the stereochemistry.

1. Introduction

Enantiopure alcohols are very important structural units for the synthesis of a wide range of natural products, chiral ligands, and biologically active compounds.[1] Recent efforts directed toward the synthesis of biologically active molecules have pointed out the need for a variety of chiral auxiliaries that are easy to synthesize. Among the various chiral auxiliaries, the cyclohexane-based chiral auxiliaries[2] such as (+) and (−)-menthol,[3] (−)-8-phenylmenthol,[4] (+) and (−)-*trans*-2-phenylcyclohexanol[5] are some of the more commonly used chiral auxiliaries for asymmetric transformations. Since the structurally related *trans*-2-aryloxycyclohexan-1-ol derivatives have also gained some interest as chiral auxiliaries in organic synthesis, various methods have been developed for their synthesis in enantiomerically pure form. Basavaiah et al. used pig liver acetone powder (PLAP) for the enzymatic-enantioselective hydrolysis of racemic *trans*-1-acetoxy-2-aryloxycyclohexanes to produce the optically active *trans*-2-aryloxycyclohexan-1-ols and their acetates in high enantiomeric purities.[6] Non-enzymatic kinetic resolution (NKR) is a versatile and hence an attractive alternative for the enzymatic process. Herein, we report the first NKR of racemic-2-aryloxy cyclic alcohols to produce both the optically active recovered alcohol and the product chloride using chiral chlorinating agent.

Recently, we reported that the NKR of racemic *trans*-β-amino alcohols by halogenation of a hydroxyl group using the chiral BINAP and *N*-chlorosuccinimide (NCS) as the chlorinating agent.[7] In this kinetic resolution, the reaction produced racemic chloride with *trans* stereochemistry through an aziridinium ion intermediate (through double S_N2 reaction; Scheme 1). We found that having a highly electron-withdrawing group such as a tosyl group on a nitrogen or an electronegative oxygen atom instead of nitrogen at the β-position will provide *cis*-chloride with inversion of configuration.[8] Herein, we report enantioselective non-enzymatic kinetic resolution of β-aryloxy cyclic alcohols through S_N2 displacement of the hydroxy group by chlorides with commercially available chiral BINAP and NCS, which produces both the optically active recovered *trans*-aryloxy alcohols and *cis*-chloride with inversion of configuration (Scheme 2).

2. Results and discussion

First, racemic *trans*-2-(4-chlorophenoxy)cyclohexanol (±)-*trans*-**1** was chosen as the model substrate and subjected to kinetic resolution with NCS and (*S*)-BINAP in CH_2Cl_2 at room temperature (Scheme 3). After 24 h, 51% of optically active (−)-*trans*-β-2-(4-chlorophenoxy) cyclohexanol (30% ee) and 18% of optically active (−)-*cis*-β-1-chloro-4-(2-chlorocyclohexyloxy)benzene (35% ee) were isolated. The selectivity factor *s* ($k_{(fast)}/k_{(slow)}$)[9] is 2.7 at 46.2% conversion. The *cis* stereochemistry of the product (−)-*cis*-**2** was deduced from the coupling constant of the methine proton (dt, J = 8.0, 3.0 and 2.8 Hz) at 4.36 ppm (–C*H*–OAr) in the ^{1}H NMR spectrum. In this reaction, the slow reacting enantiomer (−)-*trans*-**1** was recovered with 30% ee. Here, the hydroxy group of the (+)-enantiomer of the racemic aryloxy alcohol was selectively replaced by a chloride ion through an S_N2 reaction to produce optically active *cis*-β-aryloxy chloride (−)-*cis*-**2**. The *trans*-chloride was not observed in the reaction. During the reaction and work-up procedure, the (*S*)-BINAP was converted to the corresponding (*S*)-BINAPO and it was recovered in 92% yield without any racemization,[10] which can be reused after reduction.[11]

In order to improve the selectivity (*s*) of the kinetic resolution, the reaction was screened with different solvents, temperatures,

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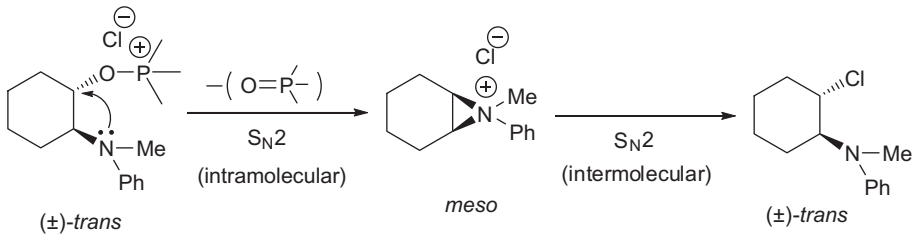
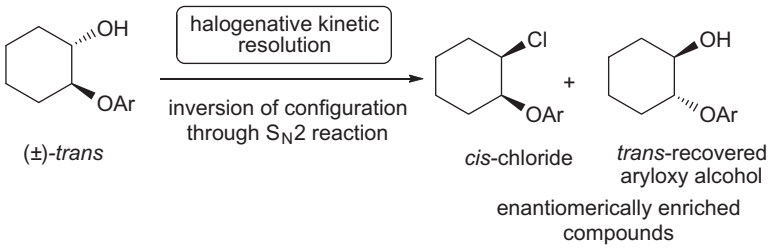
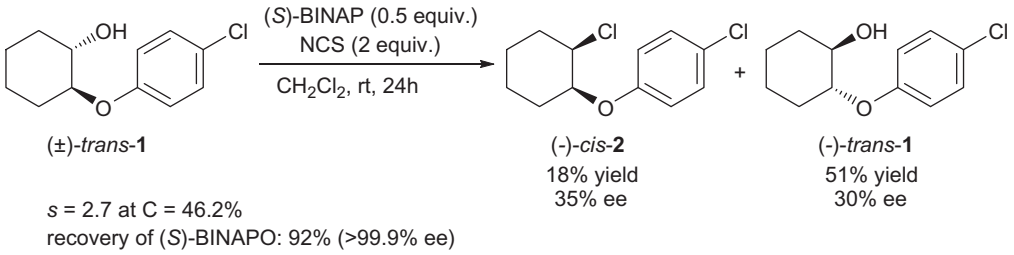
doi:10.1016/j.tetasy.2010.06.034



Scheme 1. Halogenative kinetic resolution of (±)-β-amino alcohols with retention of configuration.



Scheme 2. Halogenative kinetic resolution of (±)-β-aryloxy cyclic alcohols with inversion of configuration.



Scheme 3. HKR of *trans*-2-(4-chlorophenoxy)cyclohexanol (±)-*trans*-**1**.

and different ratios of (*S*)-BINAP and NCS; the results are summarized in Table 1. Among the solvents examined, THF turned out to be the solvent of choice as it provided a maximum of $s = 2.9$ at $C = 61.5\%$ (entry 6). When the reaction temperature was increased to 60 °C, the selectivity increased slightly to 3.0 (entry 7). Lowering the temperature to 10 °C or −10 °C increased the selectivity to 3.7 and 3.6, respectively (entries 8 and 9). Next, the effect of the ratio of chiral BINAP and NCS in the HKR of (±)-*trans*-2-(4-chlorophenoxy)cyclohexanol was carried out and it was observed that the selectivity and conversion were highly dependent on the amount of BINAP and NCS used. A maximum selectivity of 3.9 was obtained when 0.4 equiv of (*S*)-BINAP and 0.9 equiv of NCS were used at 10 °C to room temperature (entry 14).

Using the optimized reaction conditions, a wide range of *trans*-β-aryloxy-substituted cyclic alcohols were resolved and the results are summarized in Table 2. *trans*-β-Aryloxy substituted- cyclohexanols with electron-withdrawing (entries 1–3 and 8) and electron-releasing groups (entries 4–7) on the phenyl group were resolved with moderate selectivities. The substrates with sensitive functional groups, such as an acyl group at the *para*- and *meta*-positions of the phenyl group, were resolved with selectivities of 4.6 and 3.7, respectively. It was observed that when the substitution was a methoxy group at the *meta*-position, the selectivity increased to 6.9 (entry 7). When the same methoxy group was present at the *para*-position the selectivity was slightly reduced to $s = 5.2$ (entry 4). In all the reactions, the halogenative kinetic resolution provided optically active *cis*-chloride (inversion of configuration) through S$_N$2 substitution reaction and in none of the cases was *trans*-chloride (retention of configuration) isolated. In the cases of entries 2 and 4–7, the recovered *trans*-β-aryloxy cyclohexanols had (1*R*,2*R*)-absolute stereochemistry.[12] In these reactions, the (1*S*,2*S*)-enantiomers of the racemates reacted faster than the (1*R*,2*R*)-enantiomers and the (1*R*,2*R*)-enantiomers were recovered as unreacted major enantiomers. Based on the same analogy, we assumed that for entries 1, 3, and 8, the same (1*S*,2*S*)-enantiomers of the racemates reacted faster to give the corresponding *cis*-(1*S*,2*R*)-chlorides as product.

3. Conclusion

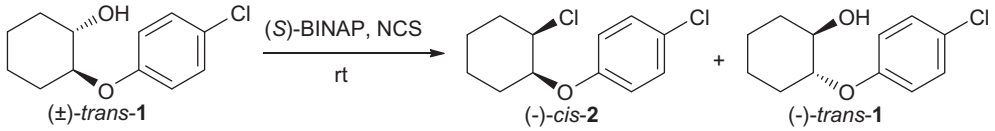
In conclusion, we have demonstrated the enantioselective non-enzymatic kinetic resolution of racemic *trans*-β-aryloxy cyclic alcohols using commercially available chiral BINAP and NCS. Using this NKR, a wide range of *trans*-β-aryloxy-substituted cyclic alcohols were resolved including *trans*-β-aryloxy alcohol having sensitive groups such as acyl substitution. By substituting the electron-withdrawing group such as aryloxy group instead of the electron-releasing amine, we were able to successfully prevent the neighboring group participation to produce the optically active *cis*-chlorides.

4. Experimental

4.1. General information

All the reactions were carried out in the reaction tubes under a nitrogen atmosphere. All the solvents used in the experiments

Table 1
Optimization study of NKR of 2-(4-chlorophenoxy)cyclohexanol (±)-*trans*-**1**



Entry	Solvent	Molar ratio of alcohol/BINAP/NCS	Time (h)	% ee[a]		*C* (%)	*s*
				Alcohol	Chloride		
1	DCM	1:0.5:2	24	30	35	46.2	2.7
2	Toluene	1:0.5:2	30	03	12	16.7	1.3
3	1,4-Dioxane	1:0.5:2	36	02	30	06.3	1.9
4	$CHCl_3$	1:0.5:2	33	07	26	19.2	2.8
5	Benzene	1:0.5:2	29	06	22	21.4	1.7
6	THF	1:0.5:2	02	48	30	61.5	2.9
7	THF	1:0.5:2	01	30	38	44.0	3.0[b]
8	THF	1:0.5:2	14	16	52	23.5	3.7[c]
9	THF	1:0.5:2	12	16	50	24.0	3.6[d]
10	THF	1:0.5:1	10	39	41	48.7	3.4
11	THF	1:0.3:0.9	17	14	44	24.1	3.0
12	THF	1:0.3:1	18	13	48	21.3	3.2
13	THF	1:0.4:0.9	18	30	44	40.5	3.4
14	THF	1:0.4:0.9	10	38	46	45.0	3.9[c]

[a] Determined by HPLC analysis using chiral columns.
[b] Reaction temperature is 60 °C.
[c] 10 °C to rt.
[d] −10 °C to rt.

were obtained from Merck, and dried by Vogel's procedure. Reactions were monitored by TLC plates (Silica Gel 60 F_{254}, obtained from Merck) using an appropriate mixture of ethyl acetate and hexanes.

Product purification was done by using silica gel (100–200 mesh) column chromatography using hexanes and ethyl acetate mixture as eluent. (*S*)-BINAP and NCS were obtained from Sigma-Aldrich company. Racemic aryloxy alcohols were synthesized using the literature procedures.[13] All the products were characterized by ^{1}H and ^{13}C NMR (Bruker 400 MHz), FT-IR (Thermo Nicolet 6700), mass spectra (Q-Tof micro hybrid quadruple time of flight mass spectrometer), and melting points (Toshniwal melting point apparatus). ^{1}H NMR spectra were reported relative to Me_4Si (δ 0.0 ppm) or residual $CHCl_3$ peak (δ 7.26 ppm). ^{13}C NMR spectra were reported relative to $CDCl_3$ (δ 77.16 ppm). All yields reported in this publication refer to isolated yields of compounds. Enantioselectivities were determined by HPLC using JASCO PU-2080 with Diacel chiral columns (ChiralPAK/Chiralcel AS-H, OD-H, AD-H and OJ columns).

4.2. General procedure for the halogenative kinetic resolution of racemic β-aryloxy cyclic alcohols

trans-2-(4-Chlorophenoxy)cyclohexanol (±)-*trans*-**1** (56.7 mg, 0.25 mmol), *N*-chlorosuccinimide (30.0, 0.225 mmol), and (*S*)-BINAP (62.3 mg, 0.1 mmol) were taken in a 10 mL reaction tube capped with a septum. The tube was evacuated and back-filled with nitrogen. Dry THF (2 mL) was added to the reaction mixture at room temperature. The reaction mixture was stirred at 10 °C to rt until 50–60% completion of the reaction had taken place (monitored by TLC). After that, the solvent was evaporated by rotary evaporator. The crude residue was purified by silica gel column chromatography to provide the corresponding *cis*-chloride (28.9 mg, 51%) and the recovered *trans*-alcohol (20.2 mg, 33%). The enantiopurity of the product and recovered phenoxy alcohols was measured by HPLC using chiral column.

4.2.1. Spectroscopic data for recovered alcohol: 2-(4-chlorophenoxy)cyclohexanol (Table 2, entry 1)

White solid; mp 84–86 °C; R_f 0.31 (10% ethyl acetate in hexanes); $[\alpha]_D^{25} = -11.9$ (*c* 0.5, $CHCl_3$); IR (neat): 1237, 1488, 2861, 2935, 3414 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22–1.46 (m, 4H), 1.70–1.81 (m, 2H), 2.05–2.15 (m, 2H), 2.58 (s, 1H), 3.66–3.74 (m, 1H), 3.94 (td, *J* = 9.2, 9.2, 4.4 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 24.1, 29.2, 32.2, 73.5, 82.8, 117.8, 126.2, 129.5, 156.6; HRMS (ESI): *m*/*z* calcd for $C_{12}H_{15}O_2NaCl$ [M+Na$^+$]: 249.0658; found: 249.0652. The enantiomeric excess (% ee) was determined to be 38% by HPLC using Diacel Chiralcel OJ column (3% *i*-PrOH/hexanes, 1 mL/min, 220 nm). Retention time: 14.900 min (minor); 12.850 min (major).

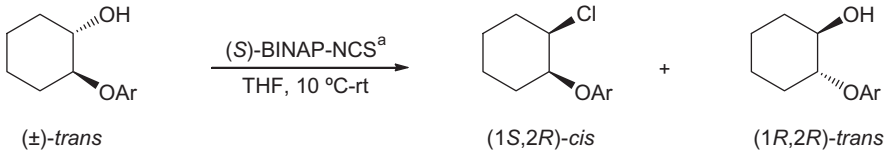
4.2.2. Spectroscopic data for product: 1-chloro-4-(2-chlorocyclohexyloxy)benzene (Table 2, entry 1)

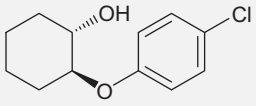
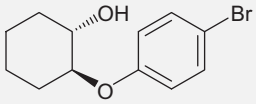
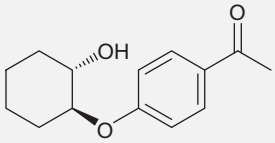
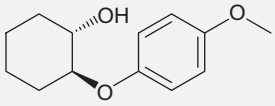
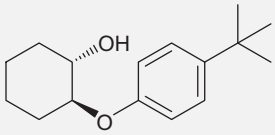
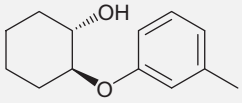
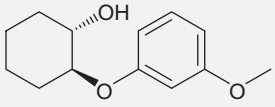
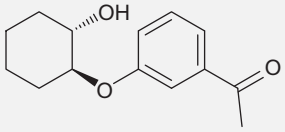
Colorless viscous liquid; R_f 0.51 (5% ethyl acetate in hexanes); $[\alpha]_D^{25} = -10.2$ (*c* 1.0, $CHCl_3$); IR (neat): 823, 971, 1056, 1236, 1487, 1594, 2864, 2360 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34–1.51 (m, 2H), 1.65–1.93 (m, 4H), 1.98–2.09 (m, 1H), 2.10–2.21 (m, 1H), 4.29–4.34 (m, 1H), 4.36 (dt, *J* = 8.0, 3.0, 2.8 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 22.2, 27.6, 32.1, 60.9, 77.7, 118.5, 126.6, 129.6, 156.2; HRMS (ESI): *m*/*z* calcd for $C_{12}H_{15}OCl_2$ [M+H$^+$]: 245.0500; found: 245.0498. The enantiomeric excess (% ee) was determined to be 46% by HPLC using Diacel Chiralcel OJ column (3% *i*-PrOH/hexanes, 0.35 mL/min, 220 nm). Retention time: 19.967 min (minor); 22.100 min (major).

4.2.3. 2-(4-Bromophenoxy)cyclohexanols[6] (Table 2, entry 2)

White solid; mp 92–94 °C; R_f 0.58 (30% ethyl acetate in hexane); $[\alpha]_D^{25} = -7.4$ (*c* 1.0, acetone); IR (neat): 1237, 1484, 2860, 2932, 3388 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22–1.46 (m, 4H), 1.70–1.80 (m, 2H), 2.06–2.14 (m, 2H), 2.31 (br s, 1H), 3.67–3.74 (m, 1H), 3.91–3.98 (m, 1H), 6.83 (d, *J* = 9.2 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 24.1, 29.2,

Table 2
NKR of various (±)-*trans*-β-aryloxy cyclohexanols with (*S*)-BINAP and NCS



Entry	Substrates	Time (h)	*C* (%)	Yield[b] (%)		% ee[c]		*s*
				Alcohol	Chloride	Alcohol	Chloride	
1		10	45.0	51	33	38	46	3.9
2		50	36.3	59	35	26	46	3.5[d,e]
3		20	19.0	67	18	14	60	4.6
4		24	47.5	44	35	48	53	5.2[e]
5		50	40.5	52	40	34	50	4.2[d,e]
6		43	23.5	45	21	19	62	5.4[e]
7		52	19.5	65	19	17	70	6.9[e]
8		50	29.6	40	25	21	50	3.7[d]

[a] Molar ratio of alcohol/BINAP/NCS = 1.0:0.4:0.9.
[b] Isolated yield.
[c] Determined by HPLC analysis using chiral columns.
[d] Reaction carried out at room temperature.
[e] Absolute configuration for recovered alcohol is determined as (1*R*,2*R*) by comparing its sign of specific rotation with the literature value.

32.2, 73.5, 82.8, 113.6, 118.3, 132.5, 157.2; HRMS (ESI): *m*/*z* calcd for $C_{12}H_{15}O_2BrNa$ [M+Na$^+$]: 293.0153; found: 293.0150. The enantiomeric excess (% ee) was determined to be 26% by HPLC using Diacel Chiralcel OJ column (3% *i*-PrOH/hexanes, 1 mL/min, 220 nm). Retention time: 17.350 min (minor); 14.758 min (major).

4.2.4. 1-Bromo-4-(2-chlorocyclohexyloxy)benzene (Table 2, entry 2)

Pale yellowish viscous liquid; R_f 0.52 (5% ethyl acetate in hexanes); $[\alpha]_D^{25} = -9.8$ (*c* 1.0, acetone); IR (neat): 1487, 1594, 2864, 2360 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35–1.51 (m, 2H), 1.65–1.93 (m, 4H), 1.99–2.09 (m, 1H), 2.10–2.20 (m, 1H), 4.30–4.35 (m, 1H), 4.37 (td, *J* = 8, 3.2, 3.2 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 22.2, 27.6, 32.1, 60.9, 77.4, 113.9, 118.9, 132.5, 156.7; HRMS (ESI): *m*/*z* calcd for $C_{12}H_{15}BrClO$ [M+H$^+$]: 287.9901; found: 287.9901. The enantiomeric excess (% ee) was determined to be 46% by HPLC using Diacel Chiralcel OJ column (3% *i*-PrOH/hexanes, 0.2 mL/min, 220 nm). Retention time: 37.567 min (minor); 40.333 min (major).

4.2.5. 1-(4-(2-Hydroxycyclohexyloxy)phenyl)ethanone (Table 2, entry 3)

White solid; mp 125–126.5 °C ; R_f 0.32 (30% ethyl acetate in hexanes); IR (neat): 1259, 1597, 2935, 3434 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27–1.49 (m, 4H), 1.73–1.82 (m, 2H), 2.07–2.20 (m, 2H), 2.53 (s, 1H), 2.55 (s, 3H), 3.71–3.79 (m, 1H), 4.08–4.16

(m, 1H), 6.96 (d, J = 8.8 Hz, 2H), 7.91 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.9, 24.0, 26.5, 29.2, 32.3, 73.3, 82.1, 115.5, 130.6, 130.8, 162.1, 196.9; HRMS (ESI): m/z calcd for $C_{14}H_{19}O_3$ [M+H$^+$]: 235.1334; found: 235.1330. The enantiomeric excess (% ee) was determined to be 14% by HPLC using Diacel ChiralPAK AS-H column (25% i-PrOH/hexanes, 1 mL/min, 220 nm). Retention time: 8.100 min (minor); 13.233 min (major).

4.2.6. 1-(4-(2-Chlorocyclohexyloxy)phenyl)ethanone (Table 2, entry 3)

White solid; mp 94.5 °C; R_f 0.48 (30% ethyl acetate in hexanes); IR (neat): 1254, 1601, 1659, 2860, 2942 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38–1.53 (m, 2H), 1.69–1.98 (m, 4H), 2.04–2.24 (m, 2H), 2.55 (s, 3H), 4.32–4.38 (m, 1H), 4.56 (dt, J = 7.6, 2.8, 2.8 Hz, 1H), 6.99 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 22.4, 26.5, 27.7, 32.1, 60.7, 76.7, 115.9, 130.8, 130.9, 161.6, 196.8; HRMS (ESI): m/z calcd for $C_{14}H_{18}O_2Cl$ [M+H$^+$]: 253.0995; found: 253.0999. The enantiomeric excess (% ee) was determined to be 60% by HPLC using Diacel ChiralPAK AS-H (25% i-PrOH/hexanes, 0.5 mL/min, 220 nm). Retention time: 24.142 min (minor); 28.583 min (major).

4.2.7. 2-(4-Methoxyphenoxy)cyclohexanols[6] (Table 2, entry 4)

White solid; mp 78–80 °C; R_f 0.58 (30% ethyl acetate in hexanes); $[\alpha]_D^{25} = -28.4$ (c 1.0, MeOH); IR (neat): 1214, 1503, 2861, 2934, 3414 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23–1.44 (m, 4H), 1.70–1.78 (m, 2H), 2.06–2.13 (m, 2H), 2.30 (br s, 1H), 3.65–3.73 (m, 1H), 3.77 (s, 3H), 3.80–3.88 (m, 1H), 6.82 (d, J = 9.2 Hz, 2H), 6.90 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 24.1, 29.4, 32.2, 55.8, 73.6, 83.8, 114.8, 118.3, 151.9, 154.5; HRMS (ESI): m/z calcd for $C_{13}H_{19}O_3$ [M+H$^+$]: 223.1334; found: 223.1336. The enantiomeric excess (% ee) was determined to be 48% by HPLC using Diacel Chiralcel OD-H column (3% i-PrOH/hexanes, 1 mL/min, 220 nm). Retention time: 15.033 min (minor); 13.350 min (major).

4.2.8. 1-(2-Chlorocyclohexyloxy)-4-methoxybenzene (Table 2, entry 4)

Pale yellowish liquid; R_f 0.38 (5% ethyl acetate in hexanes); $[\alpha]_D^{25} = -11.5$ (c 1.0, MeOH); IR (neat): 1221, 1501, 2863, 2942 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33–1.51 (m, 2H), 1.66–1.91 (m, 4H), 1.97–2.16 (m, 2H), 3.77 (s, 3H), 4.24 (dt, J = 8.4, 3.2, 3 Hz, 1H), 4.31–4.38 (m, 1H), 6.82 (d, J = 9.2 Hz, 2H), 6.94 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 22.1, 27.7, 32.2, 55.8, 61.2, 78.8, 114.8, 119.1, 151.5, 154.8; HRMS (ESI): m/z calcd for $C_{13}H_{18}O_2Cl$ [M+H$^+$]: 241.0995; found: 241.0996. The enantiomeric excess (% ee) was determined to be 53% by HPLC using Diacel Chiralcel OJ column (3% i-PrOH/hexanes, 0.5 mL/min, 220 nm). Retention time: 30.392 min (minor); 27.533 min (major).

4.2.9. 2-(4-*tert*-Butylphenoxy)cyclohexanols[6] (Table 2, entry 5)

White solid; mp 96–98 °C; R_f 0.20 (5% ethyl acetate in hexanes); $[\alpha]_D^{25} = -13.4$ (c 1.0, acetone); IR (neat): 1244, 2859, 2941, 3302 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23–1.49 (m, 13H), 1.70–1.82 (m, 2H), 2.06–2.23 (m, 2H), 2.30 (br s, 1H), 3.66–3.75 (m, 1H), 3.92–4.01 (m, 1H), 6.89 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1, 24.2, 29.5, 31.6, 32.2, 34.2, 73.7, 82.5, 116.0, 126.5, 144.2, 155.7; HRMS (ESI): m/z calcd for $C_{16}H_{24}O_2Na$ [M+Na$^+$]: 271.1674; found: 271.1669. The enantiomeric excess (% ee) was determined to be 34% by HPLC using Diacel ChiralPAK AS-H column (3% i-PrOH/hexanes, 0.4 mL/min, 220 nm). Retention time: 14.550 min (minor); 17.592 min (major).

4.2.10. 1-*tert*-Butyl-4-(2-chlorocyclohexyloxy)benzene (Table 2, entry 5)

Colorless liquid; R_f 0.64 (5% ethyl acetate in hexanes); $[\alpha]_D^{25} = -27.7$ (c 1.2, acetone); IR (neat): 1238, 1507, 2865, 2949 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 9H), 1.33–1.50 (m, 2H), 1.66–1.92 (m, 4H), 2.00–2.21 (m, 2H), 4.31–4.43 (m, 2H), 6.90 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 22.1, 27.7, 31.7, 32.2, 34.3, 61.2, 77.2, 116.5, 126.4, 144.4, 155.2; HRMS (ESI): m/z calcd for $C_{16}H_{23}OClNa$ [M+Na$^+$]: 289.1335; found: 289.1340. The enantiomeric excess (% ee) was determined to be 50% by HPLC using Diacel Chiralcel OJ column (3% i-PrOH/hexanes, 0.35 mL/min, 220 nm). Retention time: 17.733 min (minor); 25.567 min (major).

4.2.11. 2-(*m*-Tolyloxy)cyclohexanol[6] (Table 2, entry 6)

White solid; mp 69–70 °C; R_f 0.21 (5% ethyl acetate in hexanes); $[\alpha]_D^{25} = -10.4$ (c 1.0, acetone); IR (neat): 1256, 1488, 1584, 1861, 3403, 2934 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22–1.47 (m, 4H), 1.70–1.82 (m, 2H), 2.05–2.20 (m, 2H), 2.32 (s, 3H), 2.61 (s, 1H), 3.65–3.75 (m, 1H), 3.91–4.04 (m, 1H), 6.72–6.81 (m, 3H), 7.15 (t, J = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 24.1, 24.2, 29.4, 32.2, 73.6, 82.3, 113.4, 117.4, 122.3, 129.4, 139.8, 158.1; HRMS (ESI): m/z calcd for $C_{13}H_{18}O_2Na$ [M+Na$^+$]: 229.1204; found: 229.1200. The enantiomeric excess (% ee) was determined to be 19% by HPLC using Diacel Chiralcel OD-H column (3% i-PrOH/hexanes, 1 mL/min, 220 nm). Retention time: 11.800 min (minor); 8.383 min (major).

4.2.12. 1-(2-Chlorocyclohexyloxy)-3-methylbenzene (Table 2, entry 6)

Colorless liquid; R_f 0.61 (5% ethyl acetate in hexanes); $[\alpha]_D^{25} = -7.4$ (c 0.5, MeOH); IR (neat): 690, 770, 1059, 1154, 1256, 1447, 1487, 1583, 1601, 2861, 2940 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25–1.42 (m, 2H), 1.57–1.84 (m, 4H), 1.92–2.12 (m, 2H), 2.24 (s, 3H), 4.24–4.28 (m, 1H), 4.31 (dt, J = 8, 2.8, 2.8 Hz, 1H), 6.66–6.74 (m, 3H), 7.07 (t, J = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 21.9, 22.1, 27.6, 32.1, 61.2, 76.9, 113.7, 118.0, 122.5, 129.3, 139.7, 157.5; HRMS (ESI): m/z calcd for $C_{13}H_{18}OCl$ [M+H$^+$]: 225.1046; found: 225.1042. The enantiomeric excess (% ee) was determined to be 62% by HPLC using Diacel Chiralcel OJ column (3% i-PrOH/hexanes, 0.25 mL/min, 220 nm). Retention time: 28.942 min (minor); 26.775 min (major).

4.2.13. 2-(3-Methoxyphenoxy)cyclohexanol[6] (Table 2, entry 7)

White solid; mp 77–79 °C; R_f 0.32 (5% ethyl acetate in hexanes); $[\alpha]_D^{25} = -11.6$ (c 1.2, MeOH); IR (neat): 1148, 1593, 2862, 2935, 3419 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22–1.46 (m, 4H), 1.70–1.81 (m, 2H), 2.06–2.21 (m, 2H), 2.58 (d, J = 1.2 Hz, 1H), 3.66–3.75 (m, 1H), 3.79 (s, 3H), 3.93–4.04 (m, 1H), 6.51 (s, 1H), 6.52–6.57 (m, 2H), 7.17 (t, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1, 24.1, 29.4, 32.2, 55.4, 73.6, 82.4, 103.0, 106.9, 108.6, 130.1, 159.3, 161.1; HRMS (ESI): m/z calcd for $C_{13}H_{18}O_3Na$ [M+Na$^+$]: 245.1154; found: 245.1151. The enantiomeric excess (% ee) was determined to be 17% by HPLC using Diacel ChiralPAK AS-H column (3% i-PrOH/hexanes, 1 mL/min, 220 nm). Retention time: 13.217 min (minor); 14.442 min (major).

4.2.14. 1-(2-Chlorocyclohexyloxy)-3-methoxybenzene (Table 2, entry 7)

Colorless liquid; $[\alpha]_D^{25} = -12.8$ (c 1.0, MeOH); R_f 0.38 (5% ethyl acetate in hexanes); IR (neat): 1148, 1593, 2862, 2941 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35–1.51 (m, 2H), 1.68–1.93 (m, 4H), 2.01–2.21 (m, 2H), 3.79 (s, 3H), 4.35–4.43 (m, 2H), 6.51–6.58 (m, 3H), 7.15–7.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 22.1, 27.6, 32.2, 55.4, 61.1, 77.1, 103.5, 107.3, 108.9, 130.0, 158.8, 161.0; HRMS (ESI): m/z calcd for $C_{13}H_{18}O_2Cl$ [M+H$^+$]: 241.0995; found: 241.0996. The enantiomeric excess (% ee) was determined to be 70% by HPLC using Diacel Chiralcel AD-H column (3% i-PrOH/hexanes, 0.35 mL/min, 220 nm). Retention time: 15.083 min (minor); 15.975 min (major).

4.2.15. 1-(3-(2-Hydroxycyclohexyloxy)phenyl)ethanone (Table 2, entry 8)

Pale orange solid; mp 99.5–101.5 °C; R_f 0.38 (30% ethyl acetate in hexanes); IR (neat): 1678, 1268, 2862, 2934, 3436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.25–1.49 (m, 4H), 1.72–1.81 (m, 2H), 2.07–2.19 (m, 2H), 2.59 (s, 3H), 2.62 (s, 1H), 3.70–3.79 (m, 1H), 4.03–4.13 (m, 1H), 7.12–7.17 (m, 1H), 7.36 (t, J = 8 Hz, 1H), 7.50–7.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 24.0, 26.8, 29.2, 32.3, 73.5, 82.5, 115.3, 121.5, 121.6, 129.8, 138.8, 158.3, 198.0; HRMS (ESI): m/z calcd for $C_{14}H_{19}O_3$ [M+H$^+$]: 235.1334; found: 235.1336. The enantiomeric excess (% ee) was determined to be 21% by HPLC using Diacel ChiralPAK AS-H column (25% i-PrOH/hexanes, 1 mL/min, 220 nm). Retention time: 5.750 min (minor); 6.942 min (major).

4.2.16. 1-(3-(2-Chlorocyclohexyloxy)phenyl)ethanone (Table 2, entry 8)

Colorless liquid; R_f 0.35 (5% ethyl acetate in hexanes); IR (neat): 1272, 1586, 1684, 2942 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.36–1.54 (m, 2H), 1.69–1.97 (m, 4H), 2.02–2.23 (s, 2H), 2.59 (s, 1H), 4.32–4.38 (m, 1H), 4.51 (dt, J = 8, 2.8, 2.8 Hz, 1H), 7.16–7.21 (m, 1H), 7.35–7.43 (m, 1H), 7.52–7.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 22.2, 26.9, 27.7, 32.2, 60.9, 77.2, 115.5, 122.0, 122.3, 129.9, 138.8, 157.9, 198.0; HRMS (ESI): m/z calcd for $C_{14}H_{17}O_2NaCl$ [M+Na$^+$]: 275.0815; found: 275.0812. The enantiomeric excess (% ee) was determined to be 50% by HPLC using Diacel ChiralPAK AS-H (25% i-PrOH/hexanes, 0.5 mL/min, 220 nm). Retention time: 16.408 min (minor); 15.367 min (major).

Acknowledgments

We thank DST (Project No.: SR/S1/OC-06/2008) and CSIR, New Delhi, for the financial support. E.A.J. and I.K. thank CSIR, New Delhi, for the fellowship. We thank DST, New Delhi, for the funding toward the 400 MHz NMR machine to the Department of Chemistry, IIT-Madras, under the IRPHA scheme and ESI-MS facility under the FIST programme.

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