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

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ABSTRACT

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

1. Introduction

Chiral β-amino alcohols are important structural elements for the synthesis of a wide range of natural products, chiral ligands, chiral auxiliaries and resolving reagents.[1] It is evident from the biological study that chiral β-amino alcohol motifs are an ideal source for a broad range of drug molecules used for the treatment of numerous diseases such as hypertension, cardiac arrhythmia, angina pectoris and open angle glaucoma.[2] The most common methods for the synthesis of this class of compounds are reduction of optically active α-amino acids[3] and asymmetric ring-opening/aminolytic kinetic resolution of *meso*/racemic epoxides with amines.[4] The kinetic resolution of β-amino alcohols through enzyme-catalyzed acylation or deacylation is also one of the most efficient methods for the synthesis of chiral β-amino alcohols.[5] Non-enzymatic kinetic resolution (NKR) is an alternative for the enzymatic process, which is particularly attractive and versatile. In contrast to the large variety of enzymes and metallic catalysts reported for the kinetic resolution (KR) of racemic amino alcohols over the last decade,[6] non-enzymatic kinetic resolution methods designed for amino alcohols have rarely been reported. In recent years, some effort has therefore been made to design non-enzymatic alternatives and substantial progress has been made.[7]

Recently, we reported the NKR of racemic *trans*-β-amino alcohols by halogenation of the hydroxyl group using chiral BINAP [(−)-2,2′-bis(diphenylphosphino]-1′1-binaphthyl) and *N*-chlorosuccinimide (NCS) as the chlorinating agent.[8] In this kinetic resolution, the reaction produces racemic chloride with *trans* stereochemistry through an aziridinium ion intermediate (through double S_N2 reactions; Scheme 1). As part of our ongoing research towards finding a suitable method for the halogenative kinetic resolution of racemic amino alcohols to produce optically active β-amino chloride, we found that having a strong electron-withdrawing group on the amine will provide *cis*-chloride with inversion of configuration.[9] Herein, we report the enantioselective non-enzymatic kinetic resolution of amido alcohols through S_N2 displacement of the hydroxy group by halides with halogenating agents in the presence of commercially available chiral diphosphine BINAP and NCS which produces both optically active recovered *trans*-amido alcohols and *cis*-chlorides with an inversion of configuration (Scheme 2).

2. Results and discussion

First, we chose the racemic *trans*-*N*-(2-hydroxycyclohexyl)-4-methylbenzenesulfonamide (±)-*trans*-**1**, as a model substrate and subjected it to kinetic resolution with NCS and (*S*)-BINAP in CH_2Cl_2 at 60 °C (Scheme 3). After 4 h, 23% of optically active *trans*-β-amido alcohol (30% ee) and 38% of optically active *cis*-β-amido chloride (10% ee) were isolated. The selectivity factor *s* ($k_{(fast)}/k_{(slow)}$)[10] is 1.5 at 75% conversion. In the reaction, the slow reacting enantiomer (1*R*,2*R*)-*trans*-**1** was recovered with 30% ee.[11] In this NKR, the hydroxy group of the (*S*,*S*)-enantiomer of the racemic amido alcohol was selectively replaced by a chloride ion through S_N2 reaction to produce optically active *cis*-β-amido chloride, (1*R*,2*S*)-*cis*-**2**. The *cis*-stereochemistry of the β-amido chloride (1*R*,2*S*)-*cis*-**2** was confirmed by comparing its ^1H and ^{13}C NMR values with the literature reports.[9,12] The *trans*-chloride was not observed in the reaction. The strong electron-withdrawing nature of sulfonamide group prevented the neighbouring group participation ability of the amino group which resulted in an optically active *cis*-chloride with an inversion of stereochemistry. During the reaction and work-up procedure, the (*S*)-BINAP was converted to the corresponding (*S*)-BINAPO and was recovered in 94% yield without any racemization[13] which could be reused after reduction.[14]

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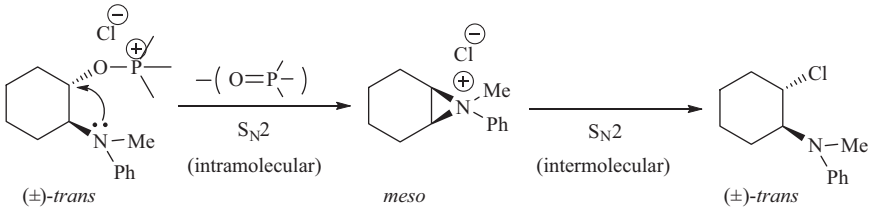
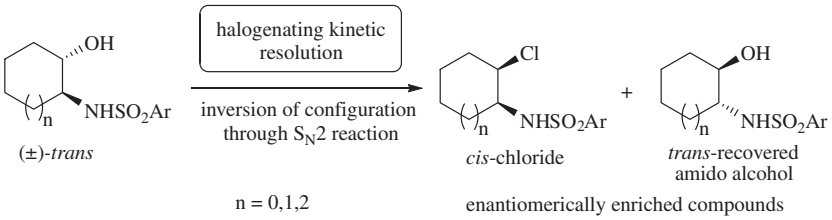
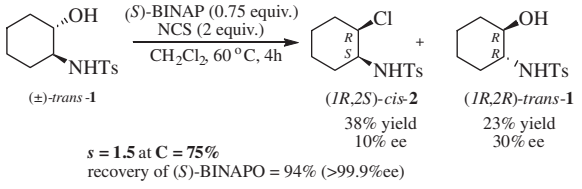


Scheme 1. Halogenative kinetic resolution of (±)-β-amino alcohols with retention of configuration.



Scheme 2. Halogenative kinetic resolution of (±)-*N*-arylsulfonyl-substituted cyclic β-amino alcohols with an inversion of configuration.

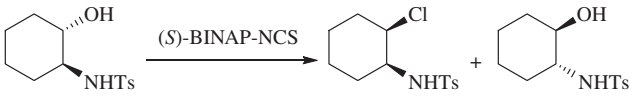


Scheme 3.

In order to improve the selectivity (*s*) of the kinetic resolution, the reaction was screened with different solvents, temperature and different ratios of (*S*)-BINAP and NCS and 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 $s = 8.2$ at $C = 58.5\%$ (entry 4). Lowering the reaction temperature from 60 °C to room temperature caused the selectivity to decrease to 3.2 (entry 5). When the NKR was carried out with other commercially available C_2-symmetric diphosphine ligands such as (−)-DIOP, the selectivity dropped to 4.3 (entry 9). Next, we studied the effect of the ratio of chiral BINAP and NCS in the NKR of racemic *trans*-β-amido alcohol and we observed that the selectivity and conversion were highly dependent on the amount of BINAP and NCS used. Better selectivity was obtained when 0.75 equiv of (*S*)-BINAP and 2 equiv of NCS were used (entry 4).

Using the optimized reaction conditions, a wide range of *trans*-β-*N*-arylsulfonyl-substituted cyclic alcohols was resolved and the results are summarized in Table 2. *trans*-β-*N*-Arylsulfonyl-substituted cyclohexanols with electron-releasing groups (entries 2 and 3) and electron-withdrawing groups (entries 4–6) on the phenyl group were resolved with moderate selectivities. Reducing the ring size to a five-membered-alcohol or increasing the size to a seven-membered (±)-*trans*-β-amido alcohol decreased the selectivity to 2.8 (entries 8 and 9). Racemic unsaturated cyclohexenol was also resolved with $s = 4.4$ at $C = 69.8\%$ (60% ee for the recovered *trans*-alcohol and 26% ee for the *cis*-chloride). In all of the reactions, the halogenative kinetic resolution provided optically active *cis*-chloride (inversion of configuration) through an S$_N$2 substitution

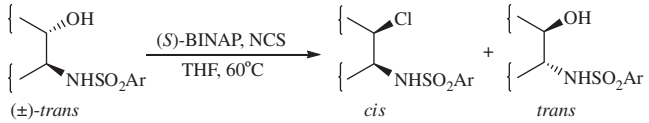
Table 1
Optimization study of NKR of *N*-(2-hydroxycyclohexyl)-4-methylbenzenesulfonamide (±)-*trans*-**1**

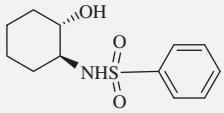
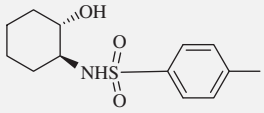
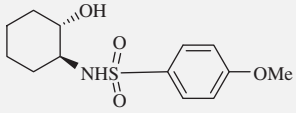
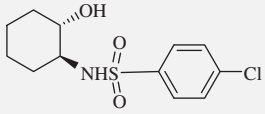
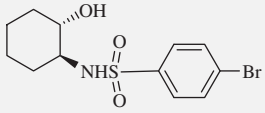
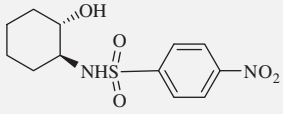
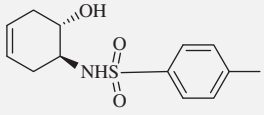
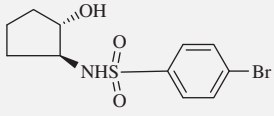
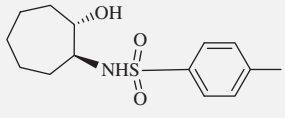


Entry	Solvent	Molar ratio of alcohol/BINAP/NCS	Temperature (°C)	Time (h)	*C* (%)	Yield[a] (%)		% ee[b]		*s*
						Alcohol	Chloride	Alcohol	Chloride	
1	DCM	1:0.75:2	60	4	75.0	23	38	30	10	1.5
2	1,4-Dioxane	1:0.75:2	60	9	57.1	35	47	44	33	3.0
3	$CHCl_3$	1:0.75:2	60	2	92.0	07	82	46	04	1.5
4	THF	1:0.75:2	60	5	58.5	30	58	79	56	8.2
5	THF	1:0.75:2	rt	3	66.7	20	65	60	36	3.2
6	THF	1:0.5:1	60	16	39.0	56	22	34	52	4.5
7	THF	1:0.4:0.9	60	14	25.0	70	15	18	52	4.0
8	THF	1:0.4:0.9	rt	48	24.6	72	12	19	58	4.5
9	THF	1:0.75:0.9	60	60	70.6	24	62	78	33	4.3[c]

[a] Isolated yield.
[b] Determined by HPLC analysis using chiral columns.
[c] (−)-DIOP was used instead of (*S*)-BINAP.

Table 2
NKR of various (±)-*trans*-*N*-arylsulfonyl cyclic β-amino alcohols with (*S*)-BINAP and NCS[a]



Entry	Substrate	Time (h)	*C* (%)	Yield[b] (%)		% ee[c]		*s*
				Alcohol	Chloride	Alcohol	Chloride	
1		3	55.4	43	31	46	36	3.3
2		5	58.5	30	58	79	56	8.2
3		4	70.0	29	35	63	27	4.5
4		10	27.0	71	23	20	54	4.1
5		10	27.3	69	23	21	56	4.3
6		2	54.1	45	32	38	32	2.8
7		2	69.8	29	35	60	26	4.4
8		4	63.0	36	52	29	17	2.8
9		2	56.8	36	50	42	32	2.8

[a] Molar ratio of alcohol/BINAP/NCS = 1.0:0.75:2.
[b] Isolated yield.
[c] Determined by HPLC analysis using chiral columns.

reaction and in none of the cases *trans*-chloride (retention of configuration) was isolated.

3. Conclusion

In conclusion, we have demonstrated the enantioselective non-enzymatic kinetic resolution of racemic *trans*-β-amido alcohols using commercially available chiral BINAP and NCS. Using this NKR, a wide range of *trans*-β-*N*-arylsulfonyl-substituted cyclic amino alcohols was resolved including five-membered and seven-membered *trans*-β-amino alcohol. By substituting a strong electron-withdrawing group such as a sulfonyl group on the amine, we were able to successfully prevent neighbouring group participation ability of the amino group to produce optically active *cis*-chlorides.

4. Experimental

4.1. General information

All reactions were carried out in reaction tubes under a nitrogen atmosphere. All the solvents used in the experiments 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 carried out by silica gel (100–200 mesh) column chromatography using hexanes and ethyl acetate mixture as eluent. (*S*)-BINAP, (−)-DIOP and NCS were obtained from the Sigma–Aldrich company. Racemic amido alcohols were synthesized using the literature procedures.[15] 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 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 amido alcohols

trans-*N*-(2-Hydroxycyclohexyl)-4-methylbenzenesulfonamide (±)-*trans*-**1** (67.3 mg, 0.25 mmol), *N*-chlorosuccinimide (66.8, 0.5 mmol) and (*S*)-BINAP (116.8 mg, 0.1875 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 refluxed at 60 °C until 50–60% completion of the reaction had taken place (monitored by TLC). The reaction mixture was then allowed to cool to room temperature and the solvent was evaporated by rotary evaporator. The crude residue was purified by silica gel column chromatography to provide the corresponding *cis*-chloride (41.7 mg, 58%) and recovered *trans*-alcohol (20.2 mg, 30%). The enantiopurity of the product and the recovered amido alcohols were measured by HPLC using chiral column.

4.2.1. Spectroscopic data for recovered alcohol: *N*-(2-hydroxycyclohexyl)-4-methylbenzenesulfonamide (Table 2, entry 2)

White solid, mp 121–122 °C (lit.[11] 120 °C); R_f 0.14 (in hexanes/ethyl acetate, 80:20 V/V); IR (neat): 3481, 3273, 2934, 2861, 1519, 1450, 1322, 1283, 1156, 1069, 912, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03–1.28 (m, 4H), 1.48–1.57 (m, 1H), 1.58–1.71 (m, 2H), 1.94–2.03 (m, 1H), 2.40 (s, 3H), 2.80–2.89 (m, 1H), 3.01 (br s, 1H), 3.31 (td, J = 9.6, 9.6, 4.4 Hz, 1H), 5.50 (br s, 1H), 7.29 (d, J = 8 Hz, 2H), 7.79 (d, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 23.9, 24.7, 31.7, 33.4, 59.7, 73.2, 127.2, 129.8, 137.7, 143.6; HRMS (ESI): m/z calcd for $C_{13}H_{20}NO_3S$ [M+H$^+$]: 270.1164; found: 270.1172. The enantiomeric excess (% ee) was determined to be 79% by HPLC using Diacel Chiralcel OD-H column (10% *i*-PrOH/hexanes, 0.5 mL/min, 220 nm): retention time (minor, 21.842 min), retention time (major, 25.942 min).

4.2.2. Spectroscopic data for product: *N*-(2-chlorocyclohexyl)-4-methylbenzenesulfonamide (Table 2, entry 2)

White solid, mp 105–107 °C; R_f 0.66 (in hexanes/ethyl acetate, 80:20 V/V); IR (neat): 3273, 2940, 2863, 1150 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19–1.32 (m, 2H), 1.38–1.46 (m, 1H), 1.57–1.60 (m, 1H), 1.60–1.64 (m, 1H), 1.64–1.76 (m, 2H), 1.94–2.03 (m, 1H), 2.43 (s, 3H), 3.38–3.48 (m, 1H), 4.13–4.19 (m, 1H), 4.80 (d, J = 9.2 Hz, 1H), 7.31 (d, J = 8 Hz, 2H), 7.76 (d, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 21.7, 24.5, 28.3, 33.3, 55.1, 64.1, 127.0, 129.9, 138.6, 143.6; HRMS (ESI): m/z calcd for $C_{13}H_{19}NO_2SCl$ [M+H$^+$]: 288.0825; found: 288.0821. The enantiomeric excess (ee) was determined to be 56% by HPLC using Diacel ChiralPAK AS-H column (10% *i*-PrOH/hexanes, 1 mL/min, 220 nm): Retention time (minor, 27.192 min), Retention time (major, 18.567 min).

4.2.3. *N*-(2-Hydroxycyclohexyl)benzenesulfonamide (Table 2, entry 1)

White solid, mp 80–82 °C; R_f 0.26 (in hexanes/ethyl acetate, 70:30 V/V); IR (neat): 3504, 3267, 2934, 2860, 1448, 1321, 1157, 1091, 689, 592 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06–1.30 (m, 4H), 1.52–1.63 (m, 1H), 1.63–1.71 (m, 1H), 1.71–1.82 (m, 1H), 1.85–2.17 (m, 2H), 2.82–2.94 (m, 1H), 3.30 (td, J = 9.6, 9.2, 3.6 Hz, 1H), 4.70 (br s, 1H), 7.50–7.56 (m, 2H), 7.56–7.62 (m, 1H), 7.91 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 24.8, 32.1, 33.6, 59.9, 73.5, 127.3, 129.3, 132.9, 140.6; HRMS (ESI): m/z calcd for $C_{12}H_{18}NO_3S$ [M+H$^+$]: 256.1007; found: 256.1006. The enantiomeric excess (ee) was determined to be 46% by HPLC using Diacel ChiralPAK AS-H column (30% *i*-PrOH/hexanes, 1 mL/min, 220 nm): Retention time (minor, 14.108 min), Retention time (major, 11.950 min).

4.2.4. *N*-(2-Chlorocyclohexyl)benzenesulfonamide (Table 2, entry 1)

White solid, mp 110–111 °C; R_f 0.59 (in hexanes/ethyl acetate, 80:20 V/V); IR (neat): 3259, 3061, 2941, 2862, 1445, 1326, 1159, 1091, 688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17–1.31 (m, 1H), 1.37–1.46 (m, 1H), 1.48–1.76 (m, 5H), 1.93–2.02 (m, 1H), 3.40–3.51 (m, 1H), 4.12–4.21 (m, 1H), 4.96 (br s, 1H), 7.48–7.54 (m, 2H), 7.55–7.61 (m, 1H), 7.87–7.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 24.4, 28.2, 33.2, 55.2, 64.1, 126.9, 129.3, 132.8, 141.6; HRMS (ESI): m/z calcd for $C_{12}H_{17}NO_2SCl$ [M+H$^+$]: 274.0669; found: 274.0668. The enantiomeric excess (ee) was determined to be 36% by HPLC using Diacel ChiralPAK AS-H column (30% *i*-PrOH/hexanes, 0.5 mL/min, 220 nm): Retention time (minor, 20.008 min), Retention time (major, 17.083 min).

4.2.5. *N*-(2-Hydroxycyclohexyl)-4-methoxybenzenesulfonamide (Table 2, entry 3)

Colourless viscous liquid; R_f 0.48 (50% ethyl acetate in hexane); IR (neat): 3488, 3273, 2929, 2858, 1596, 1498, 1258, 1150, 834, 669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06–1.29 (m, 4H), 1.53–1.61 (m, 1H), 1.62–1.69 (m, 1H), 1.71–1.80 (m, 1H), 1.97–2.03 (m, 1H), 2.28 (s, 1H), 2.78–2.88 (m, 1H), 3.25–3.34 (m, 1H), 3.87 (s, 3H), 4.90 (s, 1H), 6.95–7.01 (m, 2H), 7.81–7.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 24.8, 32.1, 33.6, 55.7, 59.8, 73.5, 114.5, 129.4, 132.1, 163.1; HRMS (ESI): m/z calcd for $C_{13}H_{20}NO_4S$ [M+H$^+$]: 286.1113; found: 286.1109. The enantiomeric excess (ee) was determined to be 63% by HPLC using Diacel Chiralcel OJ column (30% *i*-PrOH/hexanes, 1 mL/min, 220 nm): Retention time (minor, 35.708 min), Retention time (major, 29.533 min).

4.2.6. *N*-(2-Chlorocyclohexyl)-4-methoxybenzenesulfonamide (Table 2, entry 3)

White solid, mp 99–100 °C; R_f 0.53 (in hexanes/ethyl acetate, 80:20 V/V); IR (neat): 3273, 2940, 2863, 1596, 1498, 1150 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18–1.31 (m, 1H), 1.38–1.46 (m, 1H), 1.50–1.75 (m, 5H), 1.94–2.02 (m, 1H), 3.37–3.45 (m, 1H), 3.87 (s, 3H), 4.15–4.19 (m, 1H), 4.81 (d, J = 8.8 Hz, 1H), 6.96–7.00 (m, 2H), 7.80–7.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 24.5, 28.3, 33.3, 55.1, 55.8, 64.1, 114.5, 129.2, 133.2, 163.1; HRMS (ESI): m/z calcd for $C_{13}H_{19}NO_3SCl$ [M+H$^+$]: 304.0774; found: 304.0776. The enantiomeric excess (ee) was determined to be 27% by HPLC using Diacel ChiralPAK AS-H column (30% *i*-PrOH/hexanes, 0.5 mL/min, 220 nm): Retention time (minor, 24.358 min), Retention time (major, 19.308 min).

4.2.7. 4-Chloro-*N*-(2-hydroxycyclohexyl)benzenesulfonamide (Table 2, entry 4)

White solid, mp 138–140 °C; R_f 0.54 (in hexanes/ethyl acetate, 70:30 V/V); IR (neat): 3511, 3274, 2936, 2863, 1585, 1519, 1450,

1159, 1085, 912, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.07–1.32 (m, 4H), 1.53–1.79 (m, 3H), 1.96–2.05 (m, 1H), 2.69 (s, 1H), 2.83–2.96 (m, 1H), 3.27–3.38 (m, 1H), 5.41 (br s, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 24.7, 31.9, 33.7, 59.9, 73.2, 128.7, 129.5, 139.2, 139.4; HRMS (ESI): m/z calcd for $C_{12}H_{17}NO_3SCl$ [M+H$^+$]: 290.0618; found: 290.0616. The enantiomeric excess (ee) was determined to be 20% by HPLC using Diacel ChiralPAK AS-H column (30% *i*-PrOH/hexanes, 1 mL/min, 220 nm): Retention time (minor, 12.583 min), Retention time (major, 15.108 min).

4.2.8. 4-Chloro-*N*-(2-chlorocyclohexyl)benzenesulfonamide (Table 2, entry 4)

White solid, mp 100–102 °C; R_f 0.56 (in hexanes/ethyl acetate, 80:20 V/V); IR (neat): 3278, 2939, 2864, 1330, 1160, 1083, 827, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.12–1.26 (m, 1H), 1.32–1.41 (m, 1H), 1.43–1.71 (m, 5H), 1.89–1.97 (m, 1H), 3.34–3.43 (m, 1H), 4.15–4.23 (m, 1H), 4.98 (s, 1H), 7.39–7.44 (m, 2H), 7.73–7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 24.4, 28.3, 33.2, 55.3, 63.9, 128.4, 129.6, 139.3, 140.1; HRMS (ESI): m/z calcd for $C_{12}H_{16}NO_2SCl_2$ [M+H$^+$]: 308.0279; found: 308.0276. The enantiomeric excess (ee) was determined to be 54% by HPLC using Diacel ChiralPAK AS-H column (30% *i*-PrOH/hexanes, 0.5 mL/min, 220 nm): Retention time (minor, 18.658 min), Retention time (major, 15.150 min).

4.2.9. 4-Bromo-*N*-(2-hydroxycyclohexyl)benzenesulfonamide (Table 2, entry 5)

White solid, mp 126–128 °C; R_f = 0.48 (in hexanes/ethyl acetate, 70:30 V/V); IR (neat): 3502, 3272, 2935, 2860, 1575, 1324, 1159, 1068, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.08–1.35 (m, 4H), 1.56–1.65 (m, 1H), 1.65–1.73 (m, 1H), 1.77–1.86 (m, 1H), 1.97–2.09 (m, 1H), 2.37 (s, 1H), 2.84–2.98 (m, 1H), 3.34 (td, J = 9.9, 9.8, 4.4 Hz, 1H), 5.18 (s, 1H), 7.66–7.70 (m, 2H), 7.78–7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 24.7, 32.1, 33.8, 60.0, 73.4, 127.9, 128.8, 132.6, 139.8; HRMS (ESI): m/z calcd for $C_{12}H_{17}NO_3SBr$ [M+H$^+$]: 334.0113; found: 334.0115. The enantiomeric excess (ee) was determined to be 21% by HPLC using Diacel ChiralPAK AS-H column (30% *i*-PrOH/hexanes, 1 mL/min, 220 nm): Retention time (minor, 13.033 min), Retention time (major, 15.958 min).

4.2.10. 4-Bromo-*N*-(2-chlorocyclohexyl)benzenesulfonamide (Table 2, entry 5)

White solid, mp 120–122 °C; R_f = 0.79 (in hexanes/ethyl acetate, 80:20 V/V); IR (neat): 3286, 2936, 2860, 1446, 1331, 1161, 1091, 826, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.27–1.32 (m, 1H), 1.40–1.48 (m, 1H), 1.50–1.77 (m, 5H), 1.96–2.07 (m, 1H), 3.40–3.50 (m, 1H), 4.16–4.22 (m, 1H), 4.92 (d, J = 9.2 Hz, 1H), 7.63–7.67 (m, 2H), 7.73–7.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 24.4, 28.3, 33.2, 55.3, 64.0, 127.8, 128.5, 132.6, 140.7; HRMS (ESI): m/z calcd for $C_{12}H_{16}NO_2SClBr$ [M+H$^+$]: 351.9774; found: 351.9777. The enantiomeric excess (ee) was determined to be 56% by HPLC using Diacel ChiralPAK AS-H column (30% *i*-PrOH/hexanes, 0.5 mL/min, 220 nm): Retention time (minor, 19.250 min), Retention time (major, 15.658 min).

4.2.11. *N*-(2-Hydroxycyclohexyl)-4-nitrobenzenesulfonamide (Table 2, entry 6)

White solid, mp 162–163 °C; R_f = 0.57 (in hexanes/ethyl acetate, 50:50 V/V); IR (neat): 3523, 3288, 3105, 2934, 2863, 1528, 1350, 1162, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.14–1.31 (m, 4H), 1.62–1.66 (m, 1H), 1.66–1.73 (m, 1H), 1.87–1.94 (m, 1H), 1.98–2.06 (m, 1H), 2.09 (s, 1H), 2.90–3.00 (m, 1H), 3.28–3.38 (m, 1H), 5.02 (d, J = 5.2 Hz, 1H), 8.08–8.13 (m, 2H), 8.34–8.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 24.6, 32.4, 34.1, 60.2, 73.4, 124.5, 128.6, 146.7, 150.2; HRMS (ESI): m/z calcd for $C_{12}H_{16}N_2O_5SNa$ [M+Na$^+$]: 323.0678; found: 323.0676. The enantiomeric excess (ee) was determined to be 38% by HPLC using Diacel ChiralPAK AS-H column (30% *i*-PrOH/hexanes, 0.7 mL/min, 220 nm): Retention time (minor, 21.325 min), Retention time (major, 23.258 min).

4.2.12. *N*-(2-Chlorocyclohexyl)-4-nitrobenzenesulfonamide (Table 2, entry 6)

White solid, mp 135–136 °C; R_f 0.73 (in hexanes/ethyl acetate, 80:20 V/V); IR (neat): 3297, 2942, 2866, 1529, 1349, 1165, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.22–1.35 (m, 1H), 1.41–1.49 (m, 1H), 1.50–1.62 (m, 2H), 1.66–1.77 (m, 3H), 1.97–2.06 (m, 1H), 3.49–3.59 (m, 1H), 4.18–4.24 (m, 1H), 5.13 (d, J = 8.8 Hz, 1H), 8.06–8.11 (m, 2H), 8.34–8.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 24.3, 28.4, 33.2, 55.6, 63.8, 124.6, 128.2, 147.4, 150.2; HRMS (ESI): m/z calcd for $C_{12}H_{15}N_2O_4SClNa$ [M+Na$^+$]: 341.0339; found: 341.0334. The enantiomeric excess (ee) was determined to be 32% by HPLC using Diacel ChiralPAK AS-H column (30% *i*-PrOH/hexanes, 1 mL/min, 220 nm): Retention time (minor, 11.483 min), Retention time (major, 9.758 min).

4.2.13. *N*-(6-Hydroxycyclohex-3-enyl)-4-methylbenzenesulfonamide (Table 2, entry 7)

Colourless viscous liquid; R_f 0.31 (30% ethyl acetate in hexane); IR (neat): 3490, 3263, 3033, 2922, 1598, 1438, 1321, 1157, 1093, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.86–1.97 (m, 1H), 1.99–2.09 (m, 1H), 2.30–2.40 (m, 1H), 2.44 (s, 3H), 2.45–2.54 (m, 1H), 3.16–3.27 (m, 1H), 3.69 (td, J = 9.0, 8.8, 5.6 Hz, 1H), 4.75 (d, J = 6 Hz, 1H), 5.42–5.48 (m, 1H), 5.51–5.57 (m, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 31.9, 33.4, 55.5, 69.4, 124.1, 124.7, 127.3, 130.0, 137.5, 143.9; HRMS (ESI): m/z calcd for $C_{13}H_{18}NO_3S$ [M+H$^+$]: 268.1007; found: 268.1002. The enantiomeric excess (ee) was determined to be 60% by HPLC using Diacel ChiralPAK AS-H column (30% *i*-PrOH/hexanes, 1 mL/min, 220 nm): Retention time (minor, 9.883 min), Retention time (major, 11.775 min).

4.2.14. *N*-(6-Chlorocyclohex-3-enyl)-4-methyl-benzenesulfonamide (Table 2, entry 7)

White solid, mp 100–101 °C; R_f 0.59 (in hexanes/ethyl acetate, 80:20 V/V); IR (neat): 3272, 3036, 2927, 1710, 1599, 1530, 1431, 1327, 1158, 1090, 913, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.06–2.24 (m, 2H), 2.43 (s, 3H), 2.45–2.51 (m, 1H), 2.58–2.70 (m, 1H), 3.60–3.70 (m, 1H), 4.17–4.24 (m, 1H), 4.89 (d, J = 9.2 Hz, 1H), 5.46–5.53 (m, 1H), 5.53–5.61 (m, 1H), 7.31 (d, J = 8 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 28.8, 34.3, 52.3, 60.2, 122.4, 124.6, 127.1, 130.0, 138.4, 143.8; HRMS (ESI): m/z calcd for $C_{13}H_{16}NO_2SClNa$ [M+Na$^+$]: 308.0488; found: 308.0492. The enantiomeric excess (ee) was determined to be 26% by HPLC using Diacel ChiralPAK AS-H column (30% *i*-PrOH/hexanes, 1 mL/min, 220 nm): Retention time (minor, 9.883 min), Retention time (major, 11.775 min).

4.2.15. 4-Bromo-*N*-(2-hydroxycyclopentyl)benzenesulfonamide (Table 2, entry 8)

Pale grey solid, mp 83–84 °C; R_f 0.33 (in hexanes/ethyl acetate, 70:30 V/V); IR (neat): 3490, 3263, 2957, 1575, 1470, 1324, 1154, 1090, 1068, 738, 608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.29–1.42 (m, 1H), 1.49–1.73 (m, 3H), 1.86–2.05 (m, 2H), 2.39 (s, 1H), 3.21–3.30 (m, 1H), 4.04 (q, J = 6.8 Hz, 1H), 5.01 (s, 1H), 7.64–7.69 (m, 2H), 7.74–7.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1, 30.1, 31.7, 62.1, 78.5, 128.0, 128.9, 132.6, 139.1; HRMS (ESI): m/z calcd for $C_{11}H_{15}NO_3SBr$ [M+H$^+$]: 319.9956; found: 319.9959. The enantiomeric excess (ee) was determined to be 29% by HPLC using Diacel ChiralPAK AS-H column (10% *i*-PrOH/hexanes, 0.4 mL/min, 220 nm): Retention time (minor, 63.800 min), Retention time (major, 59.858 min).

4.2.16. 4-Bromo-*N*-(2-chlorocyclopentyl)benzenesulfonamide (Table 2, entry 8)

White solid, mp 82–83 °C; R_f 0.62 (in hexanes/ethyl acetate, 80:20 V/V); IR (neat): 3274, 2956, 1574, 1343, 1323, 1160, 1091, 900, 822, 734, 608, 556 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.59–1.68 (m, 2H), 1.82–1.96 (m, 2H), 1.98–2.04 (m, 2H), 3.72–3.82 (m, 1H), 4.07–4.12 (m, 1H), 4.94 (d, J = 9.2 Hz, 1H), 7.64–7.68 (m, 2H), 7.74–7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 28.5, 33.4, 58.1, 64.8, 127.9, 128.7, 132.5, 140.1; HRMS (ESI): m/z calcd for $C_{11}H_{14}NO_2SBrCl$ [M+H$^+$]: 337.9617; found: 337.9624. The enantiomeric excess (ee) was determined to be 17% by HPLC using Diacel ChiralPAK AS-H column (30% *i*-PrOH/hexanes, 0.5 mL/min, 220 nm): Retention time (minor, 19.967 min), Retention time (major, 17.117 min).

4.2.17. *N*-(2-Hydroxycycloheptyl)-4-methyl-benzenesulfonamide (Table 2, entry 9)

White solid, mp 79–81 °C; R_f 0.45 (in hexanes/ethyl acetate, 70:30 V/V); IR (neat): 3526, 3262, 2929, 2861, 1598, 1445, 1321, 1153, 1092, 729, 662 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.19–1.65 (m, 9H), 1.75–1.85 (m, 1H), 2.40 (s, 3H), 2.91 (br s, 1H), 2.96–3.05 (m, 1H), 3.48 (td, J = 8.4, 8.3, 3.2 Hz, 1H), 5.47 (d, J = 6.8 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 22.1, 23.7, 27.3, 31.1, 32.9, 62.3, 76.2, 127.3, 129.9, 137.4, 143.6; HRMS (ESI): m/z calcd for $C_{14}H_{22}NO_3S$ [M+H$^+$]: 284.1320; found: 284.1318. The enantiomeric excess (ee) was determined to be 42% by HPLC using Diacel Chiralcel OD-H column (30% *i*-PrOH/hexanes, 1 mL/min, 220 nm): Retention time (minor, 4.942 min), Retention time (major, 5.592 min).

4.2.18. *N*-(2-Chlorocycloheptyl)-4-methylbenzenesulfonamide (Table 2, entry 9)

White solid, mp 98–99 °C; R_f 0.30 (in hexanes/ethyl acetate, 90:10 V/V); IR (neat): 3268, 2933, 2864, 1428, 1330, 1275, 1159, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.33–1.43 (m, 1H), 1.46–1.67 (m, 5H), 1.68–1.99 (m, 4H), 2.42 (s, 3H), 3.47–3.55 (m, 1H), 4.24–4.29 (m, 1H), 4.97 (d, J = 8.85 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 22.1, 23.8, 26.3, 31.1, 33.8, 58.7, 67.5, 127.0, 129.9, 138.2, 143.6; HRMS (ESI): m/z calcd for $C_{14}H_{21}NO_2SCl$ [M+H$^+$]: 302.0982; found: 302.0980. The enantiomeric excess (ee) was determined to be 32% by HPLC using Diacel ChiralPAK AS-H column (30% *i*-PrOH/hexanes, 1 mL/min, 220 nm): Retention time (minor, 9.808 min), Retention time (major, 8.550 min).

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