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Quinine-catalyzed enantioselective desymmetrization of *meso*-aziridines with benzenethiols

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Abstract—Ring opening of *meso*-aziridines with benzenethiols utilizing quinine as an organocatalyst has been developed. The reaction proceeded smoothly in the presence of 10 mol % of quinine in $CHCl_3$ to afford β-amino sulfides in high yields and with moderate to good enantioselectivities.

1. Introduction

Aziridines represent one of the most valuable three membered ring systems in modern synthetic chemistry because of its widely recognized versatility as a significant building block for chemical bond elaborations and functional group transformations. Its powerful synthetic utility has been extensively demonstrated in the literature for aziridine preparation, and its broad applications to other syntheses.[1–5] Compared to the desymmetrization of *meso*-epoxides, there are less examples for the desymmetrization of *meso*-aziridines with nucleophiles, which is considered as a formidable challenge due to both the low reactivity of aziridines and the general difficulty in the differentiation of enantiotopic centers.[6,7] The biggest problem, in general, is that the efficiencies of the catalysts have been found to be substrate-dependent, since varied reaction conditions were needed for various aziridines and nucleophiles because of the different reactivity of the substrates and reagents, as well as the complexity of the structure of aziridines. Although several examples using a chiral Lewis acid catalyst have appeared in the literature,[6] most of them suffered from high catalyst loading, substrate scope limitation, prolonged reaction times, excess amount of reagents, and the need for expensive and/or heavy metal salts to be employed. Recently, Hou[7a] reported that desymmetrization of *meso*-*N*-sulfonylaziridines with thiols was realized using cinchonine-derived chiral quaternary ammonium salts as the catalyst, which gave rise to the corresponding chiral β-amino sulfides in moderate to good enantioselectivities (40–73% ee). Subsequently, the enantioselective ring-opening of *meso*-aziridines with azide nucleophiles was described in the presence of a catalytic amount of a chiral phosphoric acid catalyst.[7b] The products were generated in excellent yield and enantioselectivity. Herein, we report another example using an organocatalyst for the desymmetrization of *meso*-aziridines.

The interest in this field of organocatalysis has increased greatly over the last few years.[8] A tertiary amine as an organocatalyst is an example of a 'privileged catalyst' class. It is able to mediate a wide variety of transformations.[9] For instance, DABCO (1,4-diaza-bicyclo[2.2.2]octane) and its analogues show high efficiency in Morita–Baylis–Hillman reactions[9b] as well as the cyanation of ketones.[10] Recently, we also found that it was efficient as a catalyst in the ring-opening reactions of aziridines[11] or epoxides[12] with various nucleophiles, such as amines or thiols. In this reaction process, tertiary amines act as nucleophilic triggers.[11] We conceive that enantiomeric products may be generated if the chiral tertiary amine could be employed in the desymmetric reactions of *meso*-azidirines with nucleophiles. Thus, we started to investigate the possibility of desymmetrization of *meso*-aziridines with nucleophiles, such as thiols. To the best of our knowledge, only two such examples have been reported in the literature. Oguni[6b,c] reported that chiral zinc complexes [prepared from diethylzinc and dialkyl L-(+)-tartrate] could promote the asymmetric ring opening reactions of *N*-acylaziridines with thiols. However, a large excess amount of zinc complexes was necessary in the

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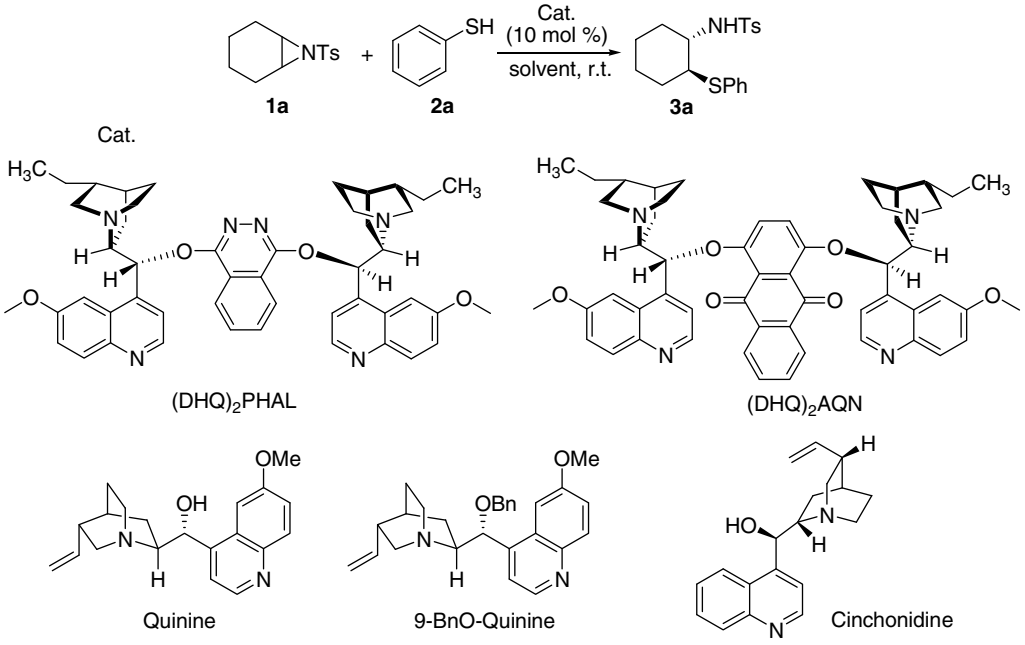
reaction. Another example was presented by Hou[7a] as described above. On the other hand, Deng and other authors[9] discovered that natural cinchona alkaloids may be utilizing both the tertiary amine and the hydroxyl group to activate and orientate both the nucleophile and electrophile, respectively, thus achieving optimum asymmetric catalysis. Prompted by these results and our efforts for aziridine transformations,[13] we hypothesized that a natural cinchona alkaloid such as quinine, upon interaction with both a nucleophile (chiral Lewis-base catalysis) and an electrophile (nucleophilic catalysis) through the suitable atoms of the catalyst, might also be able to form a rigid pocket around the activated nucleophile or electrophile, thereby allowing them to function as efficient chiral Lewis-base or nucleophilic organic catalysts.

2. Results and discussion

To verify the hypothesis, a set of experiments were carried out using *N*-tosylaziridine **1a** with benzenethiol **2a** as model substrates. This preliminary survey, carried out in the presence of quinine as the catalyst at 25 °C, allowed us to evaluate and optimize the catalytic system. In an initial experiment, the desired β-amino sulfide **3a** could be afforded in 51% ee with 36% yield when the reaction was performed in the presence of quinine (10 mol %) using toluene as the solvent (Table 1, entry 1). Changing the amount of quinine catalyst did not improve the result. For instance, 40% ee of product **3a** was obtained when 5 mol % of quinine was employed in the reaction (Table 1, entry 2). When the amount of quinine did increase to

Table 1. Condition screening for desymmetrization of *N*-tosylaziridine **1a** with benzenethiol **2a**



Entry	Catalyst	Solvent	Yield[a] (%)	ee[b] (%)
1	Quinine (10 mol %)	Toluene	36	51
2	Quinine (5 mol %)	Toluene	35	40
3	Quinine (100 mol %)	Toluene	78	49
4	Quinine (10 mol %)	EtOH	99	5
5	Quinine (10 mol %)	CH_2Cl_2	55	42
6	Quinine (10 mol %)	$CHCl_3$	85	72
7	Quinine (10 mol %)	CCl_4	57	34
8	Quinine (10 mol %)	THF	34	3
9	Quinine (10 mol %)	MeCN	86	5
10	Quinine (10 mol %)	Et_2O	31	17
11	Quinine (10 mol %)	*n*-Hexane	98	42
12	Quinine (10 mol %)	$(CH_2Cl)_2$	35	46
13	Quinine (10 mol %)	Xylene	49	49
14	$(DHQ)_2$PHAL (10 mol %)	$CHCl_3$	39	4
15	$(DHQ)_2$AQN (10 mol %)	$CHCl_3$	57	3
16	9-BnO-Quinine (10 mol %)	$CHCl_3$	13	41
17	Cinchonidine (10 mol %)	$CHCl_3$	73	45

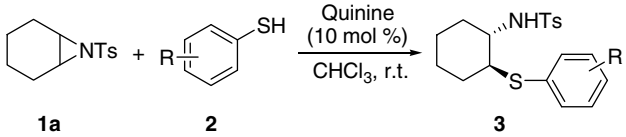
[a] Isolated yield based on aziridine **1a**.
[b] Ee value was determined by chiral HPLC.

100 mol %, similar enantioselectivity was observed, although the yield did increase to 78% (Table 1, entry 3). After preliminary screening of solvents and cinchona alkaloids, we found that this result could be dramatically improved upon when the reaction took place in $CHCl_3$ (Table 1, entry 4; 72% ee, 85% yield). The absolute configuration of the ring opening product **3a** was assigned as (*S*,*S*) via comparison with a previous report.[7a] Inferior results were displayed when other solvents were utilized in the reaction. For example, moderate enantioselectivities (42–49% ee) were obtained when several non-polar solvents (CH_2Cl_2, CCl_4, $ClCH_2CH_2Cl$, *n*-hexane, xylene) were employed in the reaction (Table 1, entries 5, 7, and 11–13). However, only 5% ee was generated when EtOH was used in the reaction (Table 1, entry 4). Similar results were also observed when the solvent was replaced as THF (3% ee), CH_3CN (5% ee), or Et_2O (17% ee) (Table 1, entries 8–10). The heteroatom (O or N) in the solvents may deactivate the hydroxyl group in the quinine via a hydrogen bond. Further investigation revealed that the protection of hydroxyl group in quinine retarded the reaction and decreased the enantioselectivity, which demonstrated the critical role of the hydroxyl group in the reaction process (Table 1, entries 14–16). For instance, only 4% ee with 39% yield was generated when $(DHQ)_2PHAL$ was employed in the reaction as a replacement for the quinine catalyst (Table 1, entry 14). Cinchonidine was also used in the reaction and the desired product **3a** was afforded in 45% ee with 73% yield (Table 1, entry 17). Changing the temperature did not improve the result (data not shown in Table 1). We also synthesized a series of chiral thiourea catalysts,[14] and applied them in the same reaction as shown in Table 1, however, no better results were generated.

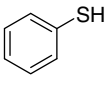
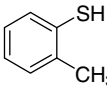
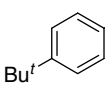
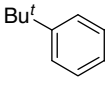
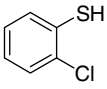
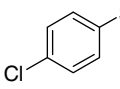
We next investigated the reaction scope of this quinine catalytic system under the optimized conditions [quinine (10 mol %), $CHCl_3$, 25 °C] (Tables 2 and 3). For reactions of *N*-tosylaziridine **1a** with various benzenethiols (Table 2), the corresponding products were generated in moderate ee. For example, *N*-tosylaziridine **1a** reacted with 2-methylbenzenethiol **2b** to give the desired product **3b** in 52% yield with 50% ee (Table 2, entry 2). When 2-methyl-5-*tert*-butylbenzenethiol **2d** was utilized in the reaction the expected product **3d** was obtained in 63% ee (Table 2, entry 4). 2-Chlorobenzenethiol **2e** or 4-chlorobenzenethiol **2f** was also employed in the reaction with *N*-tosylaziridine **1a**, with 56% or 42% ee being observed, respectively (Table 2, entries 5 and 6).

In a second set of experiments, the scope of the process with respect to N-substituted aziridines was investigated (Table 3). Most of the expected products were generated in good yields with moderate enantioselectivities under our standard experimental conditions. Aziridine **1b** reacted with benzenethiol **2a** leading to the formation of product **3g** in 54% ee with 80% yield (Table 3, entry 1); while 36% ee of product **3h** was observed when aziridine **1c** was used as a replacement (Table 3, entry 2). When aziridine **1d** was utilized as a substrate in the reaction, the desired product **3i** was afforded in 52% ee (Table 3, entry 3). *N*-Acylaziridines were also examined in the reaction of benzenethiol **2a**. For instance, 45% ee of product **3j** was generated when *N*-3,5-dinitrobenzoyl aziridine **1e** was employed (Table 3, entry 4). However, inferior results were observed when other acyl groups were used; no enantioselectivity was detected when *N*-Boc aziridine **1i** was used (Table 3, entry 8).

Table 2. Desymmetrization of *N*-tosylaziridine **1a** with benzenethiol **2** catalyzed by quinine (10 mol %) in $CHCl_3$ at room temperature



1a **2** **3**

Entry	Thiol **2**	Product **3**	Yield[a] (%)	ee[b] (%)
1	 **2a**	**3a**	85	72
2	 **2b**	**3b**	52	50
3	 **2c**	**3c**	80	32
4	 **2d**	**3d**	53	63
5	 **2e**	**3e**	82	56
6	 **2f**	**3f**	71	42

[a] Isolated yield based on aziridine **1a**.
[b] Ee value was determined by chiral HPLC.

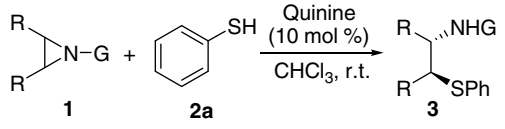
3. Conclusion

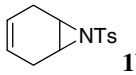
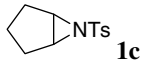
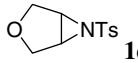
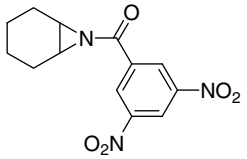
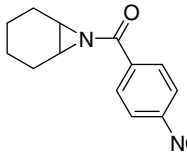
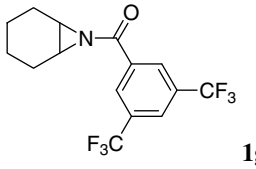
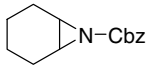
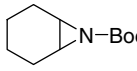
In conclusion, we have described quinine as an efficient organocatalyst for the enantioselective desymmetrization of *meso*-aziridines with benzenethiols, which gives rise to the β-amino sulfides in high yields and with moderate to good enantioselectivities. Efforts to explore other nucleophiles for desymmetrization of *meso*-aziridines using chiral organocatalyst are currently in progress in our laboratory.

4. Experimental

All the reactions were performed in test tubes under a nitrogen atmosphere. Flash column chromatography was performed using silica gel (60 Å pore size, 32–63 μm, standard grade). Analytical thin–layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Solvents were re-distilled prior to use in the reactions. Aziridines **1a–c**,[15] **1d**,[16] **1e–g**,[6g] **1f**,[6c]

Table 3. Desymmetrization of N-substituted aziridine **1** with benzenethiol **2a** catalyzed by quinine (10 mol %) in $CHCl_3$ at room temperature



Entry	Aziridine **1**	Product **3**	Yield[a] (%)	ee[b] (%)
1	 **1b**	**3g**	80	54
2	 **1c**	**3h**	65	36
3	 **1d**	**3i**	72	52
4	 **1e**	**3j**	87	45
5	 **1f**	**3k**	74	42
6	 **1g**	**3l**	85	24
7	 **1h**	**3m**	30	19
8	 **1i**	**3n**	45	0

[a] Isolated yield based on aziridine **1a**.
[b] Ee value was determined by chiral HPLC.

1h–**i**[6c,17] were prepared according to the literature procedures. Other commercial reagents were used as received. High-performance liquid chromatography was carried out using the following apparatus: SHIMADZU LC-20AT (liquid chromatograph), SHIMADZU SPD-20A (UV detector), column, Daicel Chiralpak AD-H, AS-H, or Daicel Chiralcel OD-H.

4.1. General procedure for desymmetrization of aziridine 1 with benzenethiol 2

To a solution of quinine (3.3 mg, 0.01 mmol) and aziridine **1** (0.1 mmol) in $CHCl_3$ (1.0 mL) was added benzenethiol **2** (0.11 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature. After completion of the reaction as indicated by TLC, the solvent was removed and the residue purified on a flash chromatography column to afford the desired compound **3**.

4.2. 4-Methyl-*N*-((1*S*,2*S*)-2-(phenylthio)cyclohexyl)-benzenesulfonamide 3a[11]

^{1}H NMR (400 MHz, $CDCl_3$) (ppm) 1.25–1.39 (m, 4H), 1.54–1.61 (m, 2H), 2.00–2.03 (m, 1H), 2.28–2.30 (m, 1H), 2.44 (s, 3H), 2.89–2.96 (m, 2H), 5.18 (s, 1H), 7.21–7.17 (m, 5H), 7.30 (d, $J = 8.3$ Hz, 2H), 7.75 (d, $J = 8.3$ Hz, 2H). HPLC analysis: Daicel Chiralcel OD-H (hexane/^{i}PrOH = 96/4, 1.0 mL/min, 230 nm), $t_{r\text{-}(R,R)}$ 15.38 min, $t_{r\text{-}(S,S)}$ 18.31 min.

4.3. 4-Methyl-*N*-((1*S*,2*S*)-2-(*o*-tolylthio)cyclohexyl)-benzenesulfonamide 3b[7a]

^{1}H NMR (400 MHz, $CDCl_3$) (ppm) 1.23–1.46 (m, 4H), 1.56–1.63 (m, 2H), 1.96–2.00 (m, 1H), 2.24–2.27 (m, 1H), 2.32 (s, 3H), 2.42 (s, 3H), 2.98–3.00 (m, 1H), 3.05–3.08 (m, 1H), 5.19 (s, 1H), 7.16–7.21 (m, 4H), 7.27 (d, $J = 8.1$ Hz, 2H), 7.72 (d, $J = 7.8$ Hz, 2H). HPLC analysis: Daicel Chiralpak AD-H (hexane/^{i}PrOH = 85/15, 1.0 mL/min, 214 nm), $t_{r\text{-}(R,R)}$ 7.36 min, $t_{r\text{-}(S,S)}$ 9.62 min.

4.4. *N*-((1*S*,2*S*)-2-(4-*tert*-Butylphenylthio)cyclohexyl)-4-methylbenzenesulfonamide 3c[7a]

^{1}H NMR (400 MHz, $CDCl_3$) (ppm) 1.23–1.38 (m, 13H), 1.58–1.63 (m, 2H), 1.99–2.03 (m, 1H), 2.30–2.32 (m, 1H), 2.43 (s, 3H), 2.83–2.86 (m, 1H), 2.93–2.95 (m, 1H), 5.34 (s, 1H), 7.17 (d, $J = 8.2$ Hz, 2H), 7.24–7.26 (m, 2H), 7.30 (d, $J = 7.8$ Hz, 2H), 7.76 (d, $J = 8.3$ Hz, 2H). HPLC analysis: Daicel Chiralpak AD-H (hexane/^{i}PrOH = 90/10, 1.0 mL/min, 214 nm), $t_{r\text{-}(R,R)}$ 8.84 min, $t_{r\text{-}(S,S)}$ 14.00 min.

4.5. *N*-((1*S*,2*S*)-2-(5-*tert*-Butyl-2-methylphenylthio)-cyclohexyl)-4-methylbenzenesulfonamide 3d

^{1}H NMR (400 MHz, $CDCl_3$) (ppm) 1.21–1.38 (m, 13H), 1.57–1.62 (m, 2H), 1.96–1.99 (m, 1H), 2.27–2.30 (m, 1H), 2.33 (s, 3H), 2.42 (s, 3H), 2.91–2.93 (m, 1H), 3.03–3.05 (m, 1H), 5.16 (d, $J = 4.6$ Hz, 1H), 7.12–7.21 (m, 2H), 7.24–7.26 (m, 2H), 7.37 (d, $J = 1.8$ Hz, 1H), 7.70 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) (ppm) 20.3, 21.5, 23.2, 24.3, 31.2, 34.3, 46.1, 50.9, 55.6, 124.7, 127.2, 129.5, 130.1, 130.2, 133.1, 137.1, 137.4, 143.2, 149.5. MS (ESI): m/z 432.0 (M^++1). Anal. Calcd for $C_{24}H_{33}NO_2S_2$: C, 66.78; H, 7.71, N, 3.24. Found: C, 66.69; H, 7.57, N, 3.42. HPLC analysis: Daicel Chiralpak AD-H (hexane/^{i}PrOH = 95/5, 1.0 mL/min, 214 nm), $t_{r\text{-}(R,R)}$ 8.27 min, $t_{r\text{-}(S,S)}$ 9.68 min.

4.6. *N*-((1*S*,2*S*)-2-(2-Chlorophenylthio)cyclohexyl)-4-methylbenzenesulfonamide 3e

^{1}H NMR (400 MHz, $CDCl_3$) (ppm) 1.25–1.61 (m, 6H), 2.00–2.04 (m, 1H), 2.24–2.27 (m, 1H), 2.32 (s, 3H), 2.42 (s, 3H), 3.08 (s, 2H), 5.22 (s, 1H), 7.17–7.21 (m, 2H), 7.27 (d, $J = 8.2$ Hz, 2H), 7.33–7.40 (m, 2H), 7.74 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) (ppm) 21.6, 23.2, 24.2, 31.3, 32.5, 50.2, 55.3, 127.3, 127.4, 128.4,

129.7, 130.1, 133.2, 136.4, 137.1, 143.5. MS (ESI): *m/z* 396.0 (M^++1). Anal. Calcd for $C_{19}H_{22}ClNO_2S_2$: C, 57.63; H, 5.60, N, 3.54. Found: C, 57.38; H, 5.57, N, 3.42. HPLC analysis: Daicel Chiralpak AD-H (hexane/^{i}PrOH = 85/15, 1.0 mL/min, 214 nm), $t_{r\text{-}(R,R)}$ 8.50 min, $t_{r\text{-}(S,S)}$ 11.13 min.

4.7. *N*-((1*S*,2*S*)-2-(4-Chlorophenylthio)cyclohexyl)-4-methylbenzenesulfonamide 3f[11]

^{1}H NMR (400 MHz, $CDCl_3$) (ppm) 1.25–1.43 (m, 4H), 1.56–1.60 (m, 2H), 1.97–2.01 (m, 1H), 2.19–2.25 (m, 1H), 2.43 (s, 3H), 2.91–3.00 (m, 2H), 5.34 (s, 1H), 7.20–7.26 (m, 4H), 7.28 (d, J = 7.8 Hz, 2H), 7.73 (d, J = 8.2 Hz, 2H). HPLC analysis: Daicel Chiralpak AS-H (hexane/^{i}PrOH = 50/50, 1.0 mL/min, 214 nm), $t_{r\text{-}(R,R)}$ 10.92 min, $t_{r\text{-}(S,S)}$ 25.53 min.

4.8. 4-Methyl-*N*-((1*S*,6*S*)-6-(phenylthio)cyclohex-3-enyl)benzenesulfonamide 3g[7a]

^{1}H NMR (400 MHz, $CDCl_3$) (ppm) 1.83–1.87 (m, 1H), 2.13–2.18 (m, 1H), 2.43 (s, 3H), 2.57–2.74 (m, 2H), 3.37–3.40 (m, 2H), 5.03 (d, J = 5.5 Hz, 1H), 5.53 (d, J = 10.1 Hz, 1H), 5.63 (d, J = 10.5 Hz, 1H), 7.26–7.28 (m, 7H), 7.68 (d, J = 8.2 Hz, 2H). HPLC analysis: Daicel Chiralpak AS-H (hexane/^{i}PrOH = 60/40, 1.0 mL/min, 214 nm), $t_{r\text{-}(R,R)}$ 13.13 min, $t_{r\text{-}(S,S)}$ 35.24 min.

4.9. 4-Methyl-*N*-((1*S*,2*S*)-2-(phenylthio)cyclopentyl)-benzenesulfonamide 3h[7a]

^{1}H NMR (400 MHz, $CDCl_3$) (ppm) 1.47–1.60 (m, 4H), 1.65–1.71 (m, 2H), 2.43 (s, 3H), 3.27–3.34 (m, 2H), 4.80 (d, J = 4.2 Hz, 1H), 7.25–7.28 (m, 7H), 7.66 (d, J = 8.1 Hz, 2H). HPLC analysis: Daicel Chiralcel OD-H (hexane/^{i}PrOH = 95/5, 1.0 mL/min, 214 nm), $t_{r\text{-}(R,R)}$ 17.59 min, $t_{r\text{-}(S,S)}$ 20.11 min.

4.10. 4-Methyl-*N*-((3*S*,4*R*)-4-(phenylthio)-tetrahydrofuran-3-yl)benzenesulfonamide 3i[7a]

^{1}H NMR (400 MHz, $CDCl_3$) (ppm) 2.43 (s, 3H), 3.59–3.70 (m, 4H), 3.97 (dd, J = 9.6, 4.6 Hz, 1H), 4.20–4.25 (m, 1H), 7.26–7.29 (m, 7H), 7.59 (d, J = 8.2 Hz, 2H). HPLC analysis: Daicel Chiralpak AD-H (hexane/^{i}PrOH = 80/20, 1.0 mL/min, 214 nm), $t_{r\text{-}(R,R)}$ 11.32 min, $t_{r\text{-}(S,S)}$ 33.86 min.

4.11. 3,5-Dinitro-*N*-((1*S*,2*S*)-2-(phenylthio)cyclohexyl)-benzamide 3j

^{1}H NMR (400 MHz, $CDCl_3$) (ppm) 1.36–1.52 (m, 4H), 1.79–1.83 (m, 2H), 2.21–2.30 (m, 2H), 3.13–3.16 (m, 1H), 3.99–4.02 (m, 1H), 6.26 (d, J = 7.8 Hz, 1H), 7.20–7.26 (m, 3H), 7.40 (d, J = 7.8 Hz, 2H), 8.75 (d, J = 1.4 Hz, 2H), 9.13 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) (ppm) 24.6, 25.9, 33.0, 33.6, 51.5, 55.1, 120.9, 127.1, 127.3, 129.0, 132.4, 133.7, 137.9, 148.4, 162.0. MS (ESI): *m/z* 402.0 (M^++1). Anal. Calcd for $C_{19}H_{19}N_3O_5S$: C, 56.85; H, 4.77, N, 10.47. Found: C, 56.68; H, 4.57, N, 10.42. HPLC analysis: Daicel Chiralpak AD-H (hexane/^{i}PrOH = 88/12, 1.0 mL/min, 214 nm), $t_{r\text{-}(R,R)}$ 10.85 min, $t_{r\text{-}(S,S)}$ 15.82 min.

4.12. 4-Nitro-*N*-((1*S*,2*S*)-2-(phenylthio)cyclohexyl)-benzamide 3k[6c]

^{1}H NMR (400 MHz, $CDCl_3$) (ppm) 1.26–1.48 (m, 4H), 1.74–1.81 (m, 2H), 2.16–2.35 (m, 2H), 3.06–3.11 (m, 1H), 3.91–3.94 (m, 1H), 6.22 (s, 1H), 7.26–7.41(m, 5H), 7.75 (d, J = 8.7 Hz, 2H), 8.22 (d, J = 9.1 Hz, 2H). HPLC analysis: Daicel Chiralpak AD-H (hexane/^{i}PrOH = 85/15, 1.0 mL/min, 214 nm), $t_{r\text{-}(R,R)}$ 13.24 min, $t_{r\text{-}(S,S)}$ 23.49 min.

4.13. *N*-((1*S*,2*S*)-2-(Phenylthio)cyclohexyl)-3,5-bis(trifluoromethyl)benzamide 3l

^{1}H NMR (400 MHz, $CDCl_3$) (ppm) 1.31–1.51 (m, 4H), 1.75–1.81 (m, 2H), 2.19–2.26 (m, 2H), 3.12–3.15 (m, 1H), 3.98–4.01 (m, 1H), 6.35 (d, J = 7.8 Hz, 1H), 7.16–7.25 (m, 3H), 7.39–7.41 (m, 2H), 7.95 (s, 1H), 8.04 (s, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) (ppm) 24.5, 25.9, 33.1, 33.6, 51.7, 54.8, 121.5, 124.2, 124.8, 127.1, 127.4, 129.0, 131.4, 131.7, 132.1, 132.4, 132.6, 133.8, 136.6, 163.9. MS (ESI): *m/z* 448.0 (M^++1). Anal. Calcd for $C_{21}H_{19}F_6NOS$: C, 56.37; H, 4.28, N, 3.13. Found: C, 56.48; H, 4.57, N, 3.32. HPLC analysis: Daicel Chiralcel OD-H (hexane/^{i}PrOH = 95/5, 1.0 mL/min, 214 nm), $t_{r\text{-}(R,R)}$ 5.76 min, $t_{r\text{-}(S,S)}$ 10.12 min.

4.14. Benzyl (1*S*,2*S*)-2-(phenylthio)cyclohexylcarbamate 3m[18]

^{1}H NMR (400 MHz, $CDCl_3$) (ppm) 1.20–1.45 (m, 4H), 1.63–1.71 (m, 2H), 2.05–2.21 (m, 2H), 2.88–2.92 (m, 1H), 3.46–3.48 (m, 1H), 4.92, (s, 1H), 5.10 (s, 2H), 7.23–7.25 (m, 3H), 7.31–7.36 (m, 5H), 7.40–7.43 (m, 2H). HPLC analysis: Daicel Chiralcel OD-H (hexane/^{i}PrOH = 95/5, 1.0 mL/min, 214 nm), $t_{r\text{-}(R,R)}$ 10.64 min, $t_{r\text{-}(S,S)}$ 16.51 min.

4.15. *tert*-Butyl (1*S*,2*S*)-2-(phenylthio)cyclohexylcarbamate 3n[19]

^{1}H NMR (400 MHz, $CDCl_3$) (ppm) 1.20–1.41 (m, 4H), 1.45 (s, 9H), 1.63–1.70 (m, 2H), 2.05–2.19 (m, 2H), 2.84–2.88 (m, 1H), 3.37–3.40 (m, 1H), 4.66, (s, 1H), 7.21–7.29 (m, 3H), 7.44 (d, J = 7.8 Hz, 2H). HPLC analysis: Daicel Chiralpak AD-H (hexane/^{i}PrOH = 98/2, 1.0 mL/min, 214 nm), $t_{r\text{-}(R,R)}$ 12.77 min, $t_{r\text{-}(S,S)}$ 14.20 min.

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