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Application of sulfonyl chlorides and chiral amines in the efficient synthesis of nonracemic sulfinamides

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ABSTRACT

A simple protocol that allows the preparation of separable epimeric sulfinamides from chiral amines and sulfonyl chlorides reduced in situ with triphenylphosphine in the presence of KOH is described. Using this method, tosyl chloride and nosyl chloride were successfully reacted with α-substituted primary amines to give five diastereomeric pairs, in certain cases accompanied by a small amount of the corresponding sulfonamide. Enantiopure products were isolated by column chromatography. The obtained enantiomerically pure sulfinamides were tested as organocatalysts in the asymmetric epoxide ring opening.

1. Introduction

Sulfinamides play an important role in asymmetric synthesis as efficient chiral auxiliaries and catalysts in stereoselective transformations.[1–4] They have been used for the preparation of enantiopure sulfinimines, valuable precursors of structurally diverse chiral nitrogen-containing molecules, including α-branched amines, α- and β-amino acids, 1,2- and 1,3-aminoalcohols, aziridines, aminooxetanes and α- and β-aminophosphonates.[1,5,6] In addition, sulfinamides can be used as masked amines for their easily removable *N*-sulfinyl protecting group.[6]

Despite the importance of sulfinamides in organic synthesis, only a few methods have been developed for their synthesis from sulfinates,[7] thiosulfinates,[8] sulfinic acids[9] or other sulfinamides.[1,10] Recently, Han et al. introduced aryl *N*-sulfonyl-1,2,3-oxathiazolidine-2-oxide derivatives as chiral sulfinyl-transfer agents, which provide access to a range of enantiopure sulfinamides.[11]

Essentially, sulfinamides can also be obtained directly from sulfinyl chlorides. However, this strategy remains relatively underexplored due to the low stability of these air- and moisture-sensitive compounds.[12] As a consequence, they are typically generated in situ. In 1999, Toru et al. discovered that triphenylphosphine selectively reduced sulfonyl chlorides to the corresponding sulfinyl chlorides, which in the presence of alcohols gave the corresponding sulfinate esters.[13] Following this observation, in 2007 Harmata et al. developed the synthesis of racemic sulfinamides. They reacted primary or secondary amines with admixed triethylamine with sulfinyl chlorides generated from the respective sulfonyl chlorides and triphenylphosphine.[14] However, significant amounts of the corresponding sulfonamides were often isolated from this reaction. In 2011, Chakravarti et al. described the application of magnesium oxide nanoparticles immobilized over mesoporous carbon as a catalyst for sulfinamide synthesis from various amines, sulfonyl chlorides and PPh_3. According to this report, no sulfonamide formation was observed when aniline derivatives were used as substrates.[15]

Since we were interested in the simple access to modular chiral catalysts, we decided to apply a modified Harmata's procedure for the transformation of enantiomeric amines into sulfinamides with newly generated stereogenic centers. Separation of the obtained diastereomers offers a simple methodology for the preparation of various interesting enantiopure sulfonamides, useful as chiral catalysts and synthetic intermediates.

2. Results and discussion

Over the course of our studies on the catalytic applications of chiral bicyclic amines, 2-azabicyclo[2.2.1]heptane (2-azanorbornane) and 2-azabicyclo[3.2.1]octane (bridged azepane), we were interested in the preparation of various compounds bearing both nitrogen and sulfur functionalities.[16–18] The enantiopure amine **1** based on a bridged azepane scaffold is available via a stereoselective route by utilizing ring expansion upon nucleophilic substitution of 2-azanorbornan-3-yl methanol.[17] In order to introduce a Brønsted acidity center, we reacted **1** with tosyl chloride and obtained the sulfonamide **2** in high yield (80%) (Fig. 1). In a quest for other chiral derivatives, we turned our attention to

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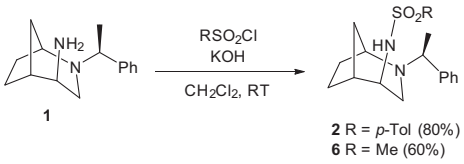


Figure 1. Synthesis of sulfonamides.

sulfonamides, since their formation would result in the introduction of an additional stereogenic center.

We decided to treat **1** with tosyl chloride, triphenylphosphine and triethylamine as described by Harmata.[14] Under these conditions we obtained a mixture of sulfinamides **3a** and **3b** (30%), and sulfonamide **2** (10%). However, when amine **1** was reacted with 1 equivalent of tosyl chloride in the presence of triphenylphosphine (1 equiv), followed by powdered KOH (1.8 equiv), a mixture of epimers **3a** and **3b** (56%) and side-product **2** (15%) were formed (Fig. 2). Sulfinamides **3a** and **3b** were produced in 1:1.4 ratio (S_S):(R_S) within 2 hours. Contrary to Harmata's results,[14] our reaction run under slow reagents addition (syringe pump) resulted in a lower yield. The proposed sequence for the addition of reactants (solution of amine and phosphine + sulfonyl chloride + KOH) was found to be optimal. The preliminary mixing of $TolSO_2Cl$ and PPh_3 led to the generation of excessive amounts of unstable sulfinyl chloride, part of which decomposes before the reaction with the added amine.

Additional experiments showed that the in situ reduction of sulfonyl chloride with PPh_3 is a key step for the effective formation of sulfinamides. After addition of phosphine to tosyl chloride dissolved in chloroform-*d*, we observed an appearance of new signals in the upfield region of ^{1}H NMR spectrum, attributed to methyl groups of the formed reduction products which however could not be isolated. The formation of sulfonamide by-product **2** in our synthesis results from the competition between two processes: amine **1** can react with both generated sulfinyl chloride and non-reduced sulfonyl chloride. As expected, compound **2** remained unchanged when subjected to the reaction with phosphine and KOH, both in the presence and in the absence of tosyl chloride. The addition of an extra base (potassium hydroxide) to the reaction mixture is essential since our diamine **1** was recovered, when it was mixed solely with tosyl chloride and PPh_3.

Amine **1** was also reacted with other sulfonyl chlorides reduced by PPh_3. Nosyl (*p*-nitrobenzenesulfonyl) chloride performed well, yielding a mixture of sulfinamides **4a** (23%) and **4b** (25%; *dr* = 1:1.1), accompanied by sulfonamide **5** (20%; Fig. 2). On the other hand, mesyl chloride led to a complete recovery of amine **1**. When the reaction of **1** with CH_3SO_2Cl was conducted in the absence of phosphine, sulfonamide **6** was produced in 60% yield (Fig. 1). The failure of our attempt to generate the respective sulfinamides must be thus connected with the particular instability of methanesulfinyl chloride[12] which decomposes before reaction with the amine **1**.

Epimeric sulfinamides **3a**, **3b** and sulfonamide **2**, as well as compounds **4a**, **4b** and **5**, were successfully separated by column chromatography followed by recrystallization from petroleum ether. All new derivatives were fully characterized by ^{1}H NMR, ^{13}C NMR, IR and HRMS techniques. The configuration of the sulfinyl stereocenter in the sulfinamides was determined by the X-ray diffraction study of **3a** and **4b** (Fig. 3). Since four of the five stereocenters have defined configurations (identical to those in starting amine **1**), the determination of the remaining one as (*S*) in **3a** and (*R*) in **4b** was straightforward. In both structures, two independent molecules are present in the cell exhibiting slight differences of bond angles and torsion angles; oxygen atoms of sulfinyl groups are engaged in intermolecular hydrogen bonds with sulfinamide NH.

We also examined our successful procedure with commercially available chiral amines: (*S*)-1-phenylethylamine **7** and (*R*)-1-(2-naphthyl)ethylamine **8** (Fig. 4). Both reactions proceeded

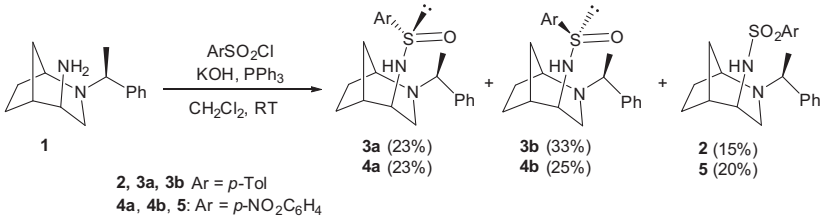


Figure 2. Conversion of amine **1** into sulfinamides.

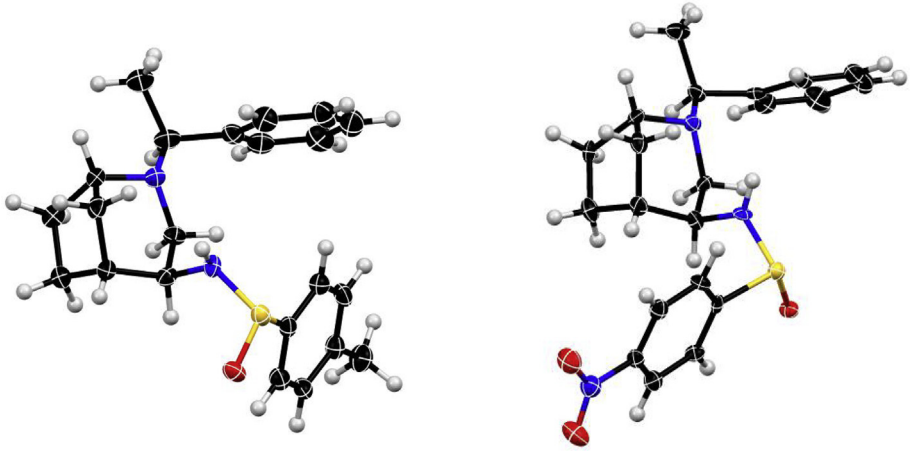


Figure 3. Crystal structure of **3a** (left) and **4b** (in each case one of two independent molecules is shown).

smoothly, resulting in the corresponding sulfinamides in 57% and 68% overall yield, respectively. The diastereoselectivity was modest (**9a**:**9b** 1:1.4; **10a**:**10b** 1:1.3). Moreover, in both cases, the formation of sulfonamides was not observed.

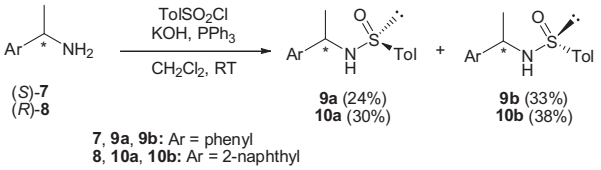


Figure 4. Preparation of diastereomeric sulfinamides.

Sulfinamides **9a** and **9b** could be separated by a simple crystallization from petroleum ether. Their identity was confirmed by the comparison of their spectroscopic characteristics with the literature data of products of two-step reaction from enantiomerically pure sulfinate.[19] In the case of naphthyl derivatives, pure diastereomer **10b** was isolated by crystallization, and its (R,R_S)-configuration was established by X-ray studies (Fig. 5). When amine **7** was replaced with benzylamine, we were unable to detect the desired sulfinylated products. Apparently, the steric hindrance introduced by the α-methyl group seemed to be a key factor for the efficient sulfinamidation.

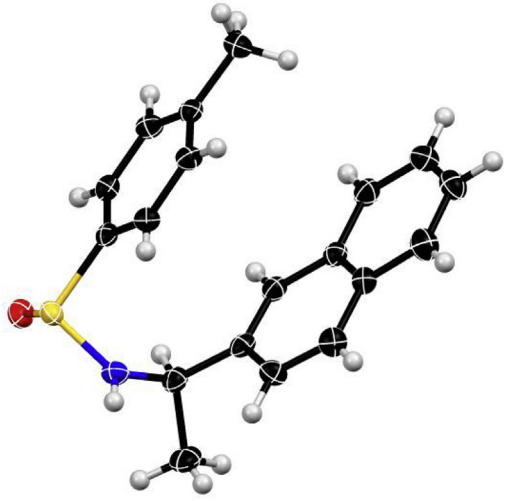


Figure 5. X-ray structure of sulfoxide **10b**.

Cinchona alkaloids offer privileged chiral moieties for a range of organocatalysts and ligands.[20] For this reason, we also submitted enantiopure 9-amino-*epi*-quinine **11** to the sulfinamidation reaction (Fig. 6). The reaction led to a mixture of diastereomeric sulfinamides **12a** and **12b** in excellent yield (87%; *dr* = 1:1.2), accompanied with trace amounts of the corresponding sulfonamide **13**. Chromatographic separation allowed for the isolation of fractions containing particular epimers **12a** (major, less polar, contained 15% of sulfonamide **13**) and **12b**, which differed in the sign of the specific rotation and the signs of the respective Cotton effects in their CD spectra (Supporting Information, Fig. S1). On this base we tentatively assign an (S)-configuration for the sulfur stereocenter **12a** and an (R)-configuration for **12b**. Their NMR spectra measured in chloroform-*d* at 300 K showed complicated patterns, which could be explained by the presence of rotamers (atropisomers). It is known that certain modifications of *Cinchona* alkaloids lead to the formation of such atropisomers.[21,22] Here, the ^{1}H NMR spectrum of epimer **12b** shows two sets of signals in a 2:1 intensity ratio, and the NOESY spectrum clearly reveals EXSY peaks due to the chemical exchange between the two forms (Supporting Information, Fig. S8).

Sulfonamide **13**, which could be obtained via the reaction of amine **11** with tosyl chloride and KOH, was identified by comparison with the literature data.[23]

Under the conditions used, (1*R*,2*R*)-diaminocyclohexane, (*S*)-(pyrrolidin-2-yl)methanol, and bicyclic [(1*S*,3*R*,4*R*)-2-azanorbornan-3-yl)]methanol were found to be unreactive.

For the sake of comparison, alkyl sulfinamide based on a bicyclic backbone was also prepared. Enantiomerically pure *tert*-butane sulfinamide bearing the 2-azabicyclo[2.2.1]heptane skeleton **15** was obtained using a different synthetic route. The reaction of aldehyde **14** and Ellmann's reagent [(*R*)-*tert*-butane sulfonamide] in the presence of $Ti(OEt)_4$ followed by reduction with $NaBH_4$ gave compound **15** in 59% overall yield (Fig. 7).[3] Due to both enantiopure reactants being used, this procedure leads to a particular stereoisomer, although chromatographic purification is still necessary. It is noteworthy that since this method based on achiral sulfonyl chlorides and chiral amines provides a much simpler one-step preparation of two easily separable epimers.

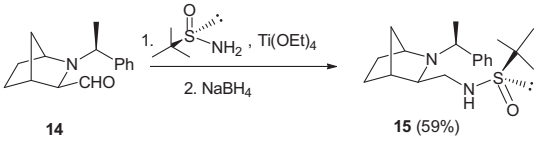


Figure 7. Synthesis of sulfinamide **15**.

Our preliminary catalytic experiments showed that the application of the isolated enantiopure sulfinamides (20 mol %) in the ring opening of cyclohexene oxide with aniline[24] resulted in an enantiomerically enriched product in low yield (up to 30%) (Fig. 8). Both sulfonamides and compound **15** gave only trace amounts of the desired product. Further catalytic tests are currently underway in our laboratory.

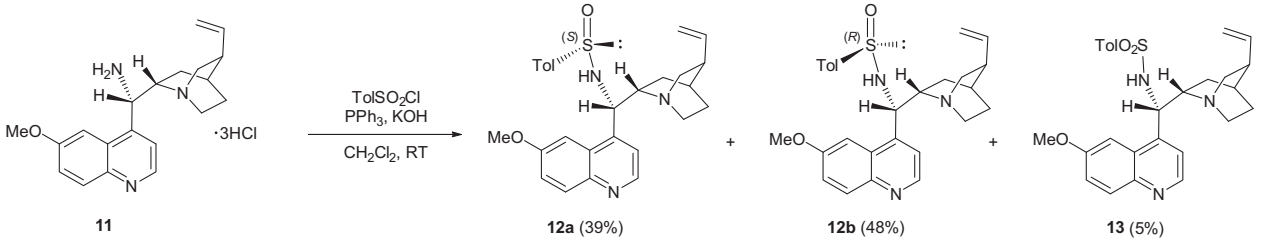
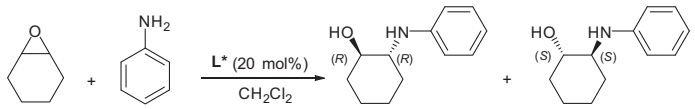


Figure 6. Synthesis of sulfinamides derived from quinine.



L*: **3a**: (*R*,*R*):(*S*,*S*) = 20:80
3b: (*R*,*R*):(*S*,*S*) = 85:15
4a: (*R*,*R*):(*S*,*S*) = 20:80
4b: (*R*,*R*):(*S*,*S*) = 52:48
9a: (*R*,*R*):(*S*,*S*) = 22:78
9b: (*R*,*R*):(*S*,*S*) = 50:50
12b: (*R*,*R*):(*S*,*S*) = 43:57

Figure 8. Catalytic ring opening of cyclohexene oxide with aniline (1.1 equiv) in dichloromethane with the prepared sulfinamides (20 mol %). The results were determined by chiral HPLC of a crude reaction mixture obtained after 3 days at room temperature (Chiralpak OD column, mobile phase: hexane/*i*-PrOH 90/10).

3. Conclusion

In conclusion, a simple procedure for the synthesis of enantiomerically pure sulfinamides from chiral amines under mild conditions has been developed. Due to in situ generation of sulfinyl chlorides, handling and purification of these troublesome reagents is avoided.[12] The described method offers the possibility of preparing both epimeric products. In our hands, the obtained separable sulfinyl derivatives appeared both chemically and configurationally stable and can be further applied as chiral catalysts or building blocks in asymmetric synthesis. Preliminary experiments have already demonstrated their usefulness in the catalytic epoxide ring opening.

4. Experimental section

4.1. General

CD spectra were recorded for CH_3CN solutions at 25 °C in 0.1 or 0.2 cm cells with 100 nm/min scan speed at 0.1 nm step and 1.00 nm bandwidth. IR spectra were recorded on a 2000 FTIR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were measured on a 500 MHz spectrometer using solvent residual peak (chloroform-*d*, $\delta(^1H) = 7.28$ ppm, $\delta(^{13}C) = 77.0$ ppm as a reference. The reported *J* values are those observed from the splitting patterns in the spectrum and may not reflect the true coupling constant values. High resolution mass spectra were recorded utilizing electrospray ionization mode. Chromatographic separations were performed on silica gel 60 (70–230 mesh). Thin layer chromatography was carried out using silica gel 60 precoated plates. HPLC analyses were performed on Chiracel OD-H or Chiralpak AD-H chiral columns (flow rate of 1.0 mL/min).

4.2. X-ray crystallography

Single crystal data for **3a**, **4b** and **10b** were collected using Xcalibur Ruby diffractometer equipped with a two-dimensional CCD Sapphire area detector. The graphite monochromatized MoKα radiation ($\lambda = 0.71073$ Å) was used. Data collection and reduction, along with absorption correction, were performed using CrysAlis software package.[25] The structure was solved by direct methods using SHELXT2014 revealing the positions of almost all non-hydrogen atoms. The remaining atoms were located from subsequent difference Fourier syntheses. The structure was refined using SHELXL2014 with the anisotropic thermal displacement parameters.[26] Aromatic C-bonded H and CH_2, CH atoms were generated in their calculated positions and a riding model was used with $U_{eq} = 1.2$ or 1.5 U_{eq}(parent C atom). The H atom of NH group was found from difference maps and constrained with N–H = 0.90 (1) Å and $U_{iso}(H) = 1.5U_{eq}(N)$. CCDC−1492186, CCDC−1530091 and CCDC-1530090 contain the supplementary crystallographic data. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Tel: +44 1223 336408; fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk).

4.3. Preparation of compounds

The bicyclic amine, (1*S*,4*S*,5*R*)-2-[(*S*)-1-phenylethyl]-4-amine-2-azabicyclo[3.2.1]octane **1** was prepared as described previously.[16] (9*R*)-Amino-deoxyquinine **11** was obtained from 9-*epi*-quinine as described in the literature.[27] Aldehyde (1*S*,3*R*,4*R*)-2-[(*S*)-1-phenylethyl]-2-azabicyclo[2.2.1]heptan-3-al **14** was synthesized according to the literature.[28,29]

4.3.1. Synthesis of sulfinamides 3, 4, 9, 10, 12 and sulfonamides 2, 5, 6, 13

To a solution of amine **1**, **7**, **8** or **11** (3.0 mmol) and triphenylphosphine (0.81 g, 3.0 mmol, 1.0 equiv) in a dry dichloromethane (10.0 mL), stirred at room temperature, the appropriate sulfonyl chloride (3.0 mmol, 1.0 equiv) and potassium hydroxide (0.30 g, 5.4 mmol, 1.8 equiv) were added in a 5 min gap. The reaction was monitored by TLC for the complete conversion of the sulfonyl chloride. The reaction mixture was then washed several times with water and brine. The organic phase were dried over sodium sulfate, filtered, and evaporated under a reduced pressure. Reaction products were separated by column chromatography.

Sulfonamides **2, 6** were prepared in an analogous manner from amine **1** and tosyl chloride or mesyl chloride, respectively, but triphenylphosphine was not added to the reaction mixture. Similarly, sulfonamide **13** was obtained from amine **11** and tosyl chloride in the presence of KOH.

4.3.1.1. 4-Methyl-*N*-((1*S*,4*S*,5*R*)-2-((*S*)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)benzenesulfonamide 2. Yellow solidifying oil. Yield 0.92 g (80%) $[\alpha]_D^{20} = -32.2$ (*c* 0.51, CH_2Cl_2) R_f 0.4 (silica, $CHCl_3/CH_3OH$ 95/5 v/v). ^1H NMR (500 MHz, $CDCl_3$): δ 1.19–1.35 (m, 3H), 1.22 (d, 3H, $J = 6.6$ Hz), 1.57–1.62 (m, 2H), 1.81–1.85 (m, 2H), 1.96–1.99 (part of ABX system, 1H, $J_1 = 12.6$ Hz, $J_2 = 3.6$ Hz), 2.26 (q, 1H, $J = 4.8$ Hz), 2.33 (s, 3H), 2.97–2.99 (m, 1H), 3.19 (q, 1H, $J = 6.6$ Hz), 3.51 (t, 1H, $J = 4.8$ Hz), 4.98 (d, 1H, $J = 8.8$ Hz, NH), 7.06 (d, 2H, $J = 8.0$ Hz, ArH), 7.14–7.17 (m, 2H, ArH), 7.23–7.28 (m, 3H, ArH), 7.50 (d, 2H, $J = 8.2$ Hz, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.2, 21.5, 21.7, 27.1, 34.3, 39.9, 49.0, 52.6, 55.6, 62.2, 126.7, 126.9, 127.1, 128.4, 129.6, 137.7, 142.8, 145.2. IR (KBr): 3287, 2951, 2862, 2802, 1448, 1323, 1162, 1091, 703, 545 cm^{-1}. HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd for $[C_{22}H_{29}N_2O_2S]^+$ 385.1950; found 385.1953.

4.3.1.2. 4-Methyl-*N*-((1*S*,4*S*,5*R*)-2-((*S*)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)benzene-(*S*)-sulfinamide 3a. White solid, Mp 155–156 °C Yield 0.24 g (23%). $[\alpha]_D^{20} = +33.7$ (*c* 0.36, CH_2Cl_2) R_f 0.24 (silica, $CHCl_3/CH_3OH$ 95/5 v/v). ^1H NMR

(500 MHz, $CDCl_3$): δ 1.25–1.35 (m, 3H), 1.28 (d, 3H, J = 6.6 Hz), 1.58–1.67 (m, 2H), 1.97 (d, 1H, *J* = 11.7 Hz), 2.19–2.21 (m, 2H), 2.37 (s, 3H), 2.44–2.46 (m, 1H), 3.04–3.06 (m, 1H), 3.30 (q, 1H, *J* = 6.6 Hz), 3.50 (t, 1H, *J* = 4.7 Hz), 4.61 (d, 1H, *J* = 7.9 Hz), 7.18–7.30 (m, 7H, ArH), 7.48 (d, 2H, *J* = 8.2 Hz, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.9, 21.3, 22.0, 27.5, 34.4, 41.1, 50.4, 52.5, 56.1, 62.4, 125.9, 126.9, 127.4, 128.3, 129.5, 140.9, 141.7, 145.1. IR (KBr): 3435, 3240, 2966, 2929, 1491, 1453, 1091, 1046, 812, 700 cm^{-1}. HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd for $[C_{22}H_{29}N_2OS]^+$ 369.2001; found 369.1996.

4.3.1.3. 4-Methyl-*N*-((1*S*,4*S*,5*R*)-2-((*S*)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)benzene-(*R*)-sulfinamide 3b. Pale yellow solidifying oil. Yield 0.34 g (33%). $[\alpha]_D^{20}$ = −147.5 (*c* 0.97, CH_2Cl_2) R_f 0.33 (silica, $CHCl_3/CH_3OH$ 95/5 v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.21–1.33 (m, 3H), 1.28 (d, 3H, J = 6.7 Hz), 1.51–1.60 (m, 2H), 1.92 (d, 1H, *J* = 11.7 Hz), 1.98–2.01 (m, 1H); 2.35 and 2.53 (ABX system, 2H, J_1 = 12.4 Hz, J_2 = 3.6 Hz), 2.41 (s, 3H), 3.09–3.13 (m, 1H), 3.40 (q, 1H, *J* = 6.7 Hz), 3.48 (t, 1H, *J* = 4.7 Hz), 4.65 (d, 1H, *J* = 7.9 Hz), 7.28–7.31 (m, 7H, ArH), 7.55 (d, 2H, *J* = 8.2 Hz, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.8, 21.4, 22.2, 27.5, 34.4, 40.8, 50.8, 51.9, 56.1, 62.4, 126.2, 126.9, 127.3, 128.3, 129.4, 140.9, 142.2, 145.0. IR (KBr): 3435, 3255, 2932, 1491, 1452, 1088, 1066, 811, 701 cm^{-1}. HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd for $[C_{22}H_{29}N_2OS]^+$ 369.2001; found 369.1999.

4.3.1.4. 4-Nitro-*N*-((1*S*,4*S*,5*R*)-2-((*S*)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)benzene-(*S*)-sulfinamide 4a. White solid. Mp 155–156 °C Yield 0.28 g (23%). $[\alpha]_D^{20}$ = +81 (*c* 0.06, CH_2Cl_2) R_f 0.15 (silica, $CHCl_3/CH_3OH$ 95/5 v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18–1.38 (m, 3H), 1.28 (d, 3H, J = 6.1 Hz), 1.61–1.75 (m, 2H), 1.92–1.95 (m, 1H); 2.05 and 2.12 (ABX system, 2H, J_1 = 12.5 Hz, J_2 = 3.5 Hz), 2.41–2.44 (m, 1H), 2.98–3.01 (m, 1H), 3.26 (q, 1H, *J* = 6.0 Hz), 3.56 (s, 1H), 4.84 (bs, 1H), 7.22–7.32 (m, 5H, ArH), 7.74 (d, 2H, *J* = 8.8 Hz, ArH), 8.18 (d, 2H, *J* = 8.8 Hz, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.0, 21.7, 27.5, 34.3, 41.1, 50.4, 52.4, 56.0, 62.4, 123.9, 127.1, 127.3, 127.4, 128.4, 145.0, 149.3, 151.5. IR (KBr): 3435, 2924, 1632, 1526, 1070, 722 cm^{-1}. HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd for $[C_{21}H_{26}N_3O_3S]^+$ 400.1695; found 400.1696.

4.3.1.5. 4-Nitro-*N*-((1*S*,4*S*,5*R*)-2-((*S*)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)benzene-(*R*)-sulfinamide 4b. White solid, Mp 159–160 °C. Yield 0.30 g (25%). $[\alpha]_D^{20}$ = −106.3 (*c* 0.32, CH_2Cl_2) R_f 0.18 (silica, $CHCl_3/CH_3OH$ 95/5 v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16–1.35 (m, 3H), 1.32 (d, 3H, *J* = 6.7 Hz), 1.50–1.62 (m, 2H), 1.88–1.92 (m, 2H), 2.37 and 2.50 (ABX system, 2H, J_1 = 12.4 Hz, J_2 = 3.6 Hz), 3.06–3.08 (m, 1H), 3.40 (q, 1H, *J* = 6.7 Hz), 3.51 (t, 1H, *J* = 4.7 Hz), 4.88 (d, 1H, *J* = 8.2 Hz), 7.21–7.31 (m, 5H, ArH), 7.86 (d, 2H, *J* = 8.8 Hz, ArH), 8.32 (d, 2H, *J* = 8.8 Hz, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.7, 22.1, 27.3, 34.3, 40.7, 50.8, 52.0, 56.1, 62.4, 123.8, 127.1, 127.3, 127.6, 128.4, 144.8, 149.5, 152.2. IR (KBr): 3435, 3297, 2970, 2932, 1606, 1521, 1342, 1087, 1070, 1056, 854 cm^{-1}. HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd for $[C_{21}H_{26}N_3O_3S]^+$ 400.1695; found 400.1698.

4.3.1.6. 4-Nitro-*N*-((1*S*,4*S*,5*R*)-2-((*S*)-1-phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)benzenesulfonamide 5. White solid, Mp 163–165 °C. Yield 0.25 g (20%). $[\alpha]_D^{20}$ = +39.0 (*c* 0.26, CH_2Cl_2) R_f 0.22 (silica, $CHCl_3/CH_3OH$ 95/5 v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22 (d, 3H, J = 6.6 Hz), 1.25–1.36 (m, 3H), 1.63–1.71 (m, 3H), 1.83 (d, 1H, *J* = 12.1 Hz), 2.04 (dd, 1H, J_1 = 12.7 Hz, J_2 = 3.7 Hz), 2.28–2.29 (m, 1H), 3.09 (bs, 1H), 3.12 (q, 1H, *J* = 6.6 Hz), 3.55–3.56 (m, 1H), 5.14 (bs, 1H, NH), 7.11–7.13 (m, 2H, ArH), 7.21–7.22 (m, 3H, ArH), 7.78 (d, 2H, *J* = 8.9 Hz, ArH), 8.09 (d, 2H, *J* = 8.8 Hz, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.2, 21.4, 27.2, 34.2, 40.0, 49.2, 52.9, 55.4, 62.2, 124.3, 127.0, 127.1, 127.8, 128.5, 145.0, 146.7, 149.6. IR (KBr): 3426, 3326, 2969, 1608, 1532, 1349, 1170, 740, 731 cm^{-1}. HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd for $[C_{21}H_{26}N_3O_4S]^+$ 416.1644; found 416.1632.

4.3.1.7. *N*-((1*S*,4*S*,5*R*)-2-((*S*)-1-Phenylethyl)-2-azabicyclo[3.2.1]octan-4-yl)methanesulfonamide 6. White solid, Mp 139–140 °C. Yield 0.34 g (60%). $[\alpha]_D^{20}$ = −90.7 (*c* 0.13, CH_2Cl_2) R_f 0.22 (silica, $CHCl_3/CH_3OH$ 95/5 v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25–1.41 (m, 4H), 1.31 (d, 3H, J = 6.6 Hz), 1.67–1.74 (m, 2H), 1.87 (d, 1H, *J* = 12.0 Hz), 2.33 (d, 2H, *J* = 2.7 Hz), 2.39 (q, 1H, *J* = 4.6 Hz), 2.74 (s, 3H), 3.21 (bs, 1H), 3.33 (q, 1H, *J* = 6.6 Hz), 3.58 (t, 1H, *J* = 4.6 Hz), 4.86 (d, 1H, *J* = 6.8 Hz), 7.20–7.23 (m, 1H, ArH), 7.25–7.31 (m, 4H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.1, 21.8, 27.3, 34.3, 40.0, 41.7, 49.8, 52.9, 55.9, 62.3, 127.1, 127.3, 128.5, 145.1. IR (KBr): 3436, 3277, 2988, 2967, 2937, 2807, 1452, 1425, 1309, 1155, 1134, 772 cm^{-1}. HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd for $[C_{16}H_{25}N_2O_2S]^+$ 309.1637; found 309.1638.

4.3.1.8. (*R*,*S*$_S$)-*N*-α-Methylbenzyl-*p*-tolylsulfinamide 9a. White solid. Yield 0.19 g (24%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 (d, 3H, *J* = 6.8 Hz); 2.41 (s, 3H); 4.13 (d, 1H, *J* = 4.6 Hz); 4.65–4.71 (m, 1H); 7.28–7.45 (m, 7H, ArH), 7.60 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.4, 24.7, 53.6, 125.5, 127.0, 127.7, 128.7, 129.5, 141.4, 142.5, 143.3. Physicochemical characteristics is in agreement with literature data.[11]

4.3.1.9. (*R*,*R*$_S$)-*N*-α-Methylbenzyl-*p*-tolylsulfinamide 9b. White solid. Yield 0.26 g (33%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.63 (d, 3H, *J* = 6.6 Hz); 2.38 (s, 3H); 4.21 (d, 1H, *J* = 4.4 Hz); 4.54–4.59 (m, 1H); 7.19–7.28 (m, 7H, ArH), 7.56 (d, 2H, *J* = 8.3 Hz, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.3, 23.7, 52.4, 125.8, 126.4, 127.5, 128.5, 129.4, 141.3, 141.5, 143.7. Physicochemical characteristics is in agreement with literature data for (*S*, *S*$_S$)-enantiomer.[19]

4.3.1.10. 4-Methyl-*N*-(1-(naphthalen-2-yl)ethyl)benzenesulfinamides 10a and 10b (mixture of epimers). Pale yellow solid. Yield 0.63 g (68%); *dr* = 1:1.3. (*R*,*R*$_S$)-*N*-4-Methyl-*N*-(1-(naphthalen-2-yl)ethyl)benzenesulfinamide **10b.** Mp 135–136 °C. Yield 0.35 g (38%). $[\alpha]_D^{20}$ = +50.0 (*c* 0.32, CH_2Cl_2) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.70 (d, 3H, *J* = 6.6 Hz), 2.29 (s, 3H), 4.34 (d, 1H, *J* = 4.5 Hz), 4.71–4.76 (m, 1H), 7.16 (d, 2H, *J* = 8.0 Hz), 7.34 (dd, 1H, J_1 = 8.5 Hz, J_2 = 1.8 Hz), 7.42–7.47 (m, 2H), 7.54–7.56 (m, 3H), 7.72–7.79 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.2, 23.7, 52.1, 124.6, 125.2, 125.8, 125.9, 126.2, 127.6, 127.9, 128.4, 129.4, 132.7, 133.2, 141.0, 141.27, 141.31. HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd for $[C_{19}H_{20}NOS]^+$ 310.1266; found 310.1255.

4.3.1.11. (9*R*)-*N*-Quinyl-*p*-tolylsulfinamide 12b. Colorless oil. Yield 0.66 g (48%). $[\alpha]_D^{20}$ = +89.2 (*c* 0.90, CH_2Cl_2) R_f 0.53 (silica, $CHCl_3/CH_3OH$ 95/5 v/v). ^{1}H NMR (500 MHz, $CDCl_3$), major atropisomer δ 0.78–0.82 (m, 1H), 1.21–1–25 (m, 1H), 1.60–1.67 (m, 2H), 1.89 (s, 3H), 2.29–2.31 (m, 1H), 2.70–2.78 (m, 2H), 2.97–2.99 (m, 1H), 3.37–3.44 (m, 2H), 3.99 (s, 3H), 4.91–4.88 (m, 2H), 5.20 (d, 1H, *J* = 10.8 Hz), 5.65–5.72 (m, 1H), 6.30 (s, 1H, NH), 6.37 (d, 2H, *J* = 8.0 Hz), 7.01 (d, 2H, *J* = 8.0 Hz), 7.17 (d, 1H, *J* = 2.4 Hz), 7.24–7.30 (m, 2H), 7.77 (d, 1H, *J* = 9.2 Hz), 8.50 (d, 1H, *J* = 4.6 Hz); minor atropisomer δ 0.83–0.87 (m, 1H), 1.27–1.32 (m, 1H), 1.60–1.67 (m, 2H), 2.01 (s, 3H), 2.29–2.31 (m, 1H), 2.70–2.78 (m, 2H), 3.27–3.44 (m, 3H), 3.97 (s, 3H), 4.64 (d, 1H, *J* = 10.9 Hz), 4.84–4.91 (m, 2H), 5.55–5.62 (m, 1H), 6.42 (d, 2H, *J* = 8.0 Hz), 6.45 (s, 1H, NH), 6.70 (d, 1H, *J* = 4.3 Hz), 6.99 (d, 2H, *J* = 8.0 Hz), 7.25–7.28 (m, 1H), 7.73 (d, 1H, *J* = 2.5 Hz), 7.82 (d, 1H, *J* = 9.2 Hz), 8.24 (d, 1H, *J* = 4.3 Hz); ^{13}C NMR (2:1 mixture of atropisomers): δ 20.8, 20.9, 25.4, 26.8, 27.6, 27.7, 27.8, 39.5, 39.8, 40.2, 45.2, 55.0, 55.7, 55.9, 56.1, 56.7,

61.2, 101.3, 104.1, 114.7, 120.8, 121.0, 121.3, 123.7, 125.2, 125.7, 127.1, 127.6, 128.0, 131.2, 131.5, 138.4, 138.8, 140.4, 140.8, 141.1, 141.3, 141.9, 143.9, 144.7, 145.8, 146.4, 147.0, 156.7, 157.3. IR (film): 3206, 2932, 2240, 1621, 1508, 1475, 1241, 1093, 1063, 855, 733 cm^{-1}. HRMS (ESI-TOF): m/z $[M+H]^+$ calcd for $[C_{27}H_{32}N_3O_2S]^+$ 462.2215; found 462.2208.

4.3.1.12. (9*R*)-*N*-Quinyl-*p*-tolylsulfonamide 13. Yield 1.03 g (72%). HRMS (ESI-TOF): m/z $[M+H]^+$ calcd for $[C_{27}H_{32}N_3O_3S]^+$ 478.2164; found 478.2152. Physicochemical characteristics in agreement with the literature data.[23]

4.3.2. Synthesis of sulfinamide 15

Compound **15** was prepared according to the procedure reported by Brun et al.[3] A round-bottomed flask equipped with a magnetic stirring bar was charged with (*R*)-2-methyl-2-propanesulfinamide (0.31 g, 1.4 mmol) under argon atmosphere. $Ti(OEt)_4$ (0.28 g, 1.2 mmol) in anhydrous THF (10 mL) was then added, and the solution was stirred for 10 min at room temperature. (1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethyl]-2-azabicyclo[2.2.1]heptan-3-al **14** (0.15 g, 1.2 mmol) was then added and the crude reaction mixture was heated at reflux. The progress of the reaction was followed by TLC. After completion of the reaction, a suspension of $NaBH_4$ (0.095 g, 2.5 mmol) in anhydrous THF (2 mL) was added to the crude reaction mixture previously cooled to 0 °C. The mixture was then allowed to warm to room temperature. After 1 hour, methanol (10 mL) was added dropwise with vigorous stirring. The resulting mixture was poured over brine and extracted with dichloromethane. The reaction mixture was then filtered through the Celite®, washed with dichloromethane, and evaporated under vacuum. The resulting product was purified by column chromatography.

4.3.2.1. (*R*)-2-Methyl-*N*-(((1*S*,3*R*,4*R*)-2-((*S*)-1-phenylethyl)-2-azabicyclo[2.2.1]heptan-3-yl)methyl)propane-2-sulfinamide 15. White solid. Mp 99–100 °C. Yield 0.24 g (59%) $[\alpha]_D^{20} = -56.0$ (*c* 0.50, CH_2Cl_2) R_f 0,39 (silica, $CHCl_3/CH_3OH$ 95/5 v/v). ^1H NMR (500 MHz, $CDCl_3$): δ 1.06 (s, 9H); 1.22–1.41 (m, 3H); 1.31 (d, 3H, $J = 6.5$ Hz), 1.60–1.67 (m, 1H); 1.70–1.75 (m, 3H); 1.94–2.00 (m, 1H); 2.07–2.18 (m, 3H); 2.32–2.38 (m, 1H); 2.74–2.79 (m, 1H); 3.46 (q, 1H, $J = 6.5$ Hz); 3.60 (s, 1H); 7.22–7.35 (m, 5H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.1, 22.5, 22.6, 28.9, 35.1, 40.2, 50.2, 55.6, 58.8, 61.0, 70.0, 127.5, 128.2, 128.4, 146.0. IR (KBr): 3488, 3158, 2964, 2871, 1637, 1453, 1394, 1304, 1162, 1024, 751 cm^{-1}. HRMS (ESI-TOF): m/z $[M+H]^+$ calcd for $[C_{19}H_{31}N_2OS]^+$ 335.2157; found 335.2161.

4.4. Typical procedure for the epoxide ring opening

To a 5 mL round bottom flask fitted with stopper and equipped with a magnetic stirring bar, a chiral organocatalyst (0.04 mmol, 20 mol %) dissolved in dry dichloromethane (0.8 mL) and cyclohexene oxide (0.2 mmol) were introduced. After 10 min, aniline (0.22 mmol, 1.1 equiv) was added and the reaction mixture was stirred for 3 days at room temperature. The progress of the reaction was checked on TLC using hexane/ethyl acetate (90/10) as mobile phase. The crude reaction mixture was evaporated and the enantiomeric excess was determined by HPLC (Chiralpak OD column, mobile phase: hexane/*i*-PrOH 90/10; flow rate 0.8 mL/min, retention times: (1*S*,2*S*): 13.07 min, (1*R*,2*R*): 14.94 min).[24]

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A. Supplementary data

Supplementary data (CD and NOESY spectra of quinine-derived sulfinamides, copies of ^1H and ^{13}C NMR spectra, X-ray data for **3a**, **4b**, and **10b**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2017.03.00.

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