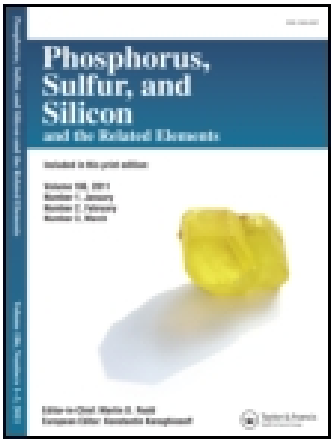

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Ring-Opening of NH-Aziridines with Thiols in Ionic Liquids: Application to the Synthesis of Aminosulfide Catalysts for Asymmetric Epoxidation of Aldehydes

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RING-OPENING OF NH-AZIRIDINES WITH THIOLS IN IONIC LIQUIDS: APPLICATION TO THE SYNTHESIS OF AMINOSULFIDE CATALYSTS FOR ASYMMETRIC EPOXIDATION OF ALDEHYDES

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The ring opening of NH-aziridines with thiols was found to proceed in good yield at room temperature in the presence of an ionic liquid—1-butyl-3-methylimidazolium chloride (BMIM chloride). This mild methodology was applied to the synthesis of a camphor-derived chiral aminosulfide. The sulfide was used to generate a sulfur ylide, which effected an asymmetric epoxidation of benzaldehyde (e.r. 85:15, trans:cis 90:10, 87% yield). The amino group enabled easy recovery of the sulfide (98% yield) after the reaction by a simple acid/base extraction.

Keywords Aziridine ring-opening; asymmetric epoxidation; ionic liquids; sulfide; sulfur ylide; thiols

INTRODUCTION

Asymmetric epoxidation of aldehydes using chiral sulfur ylides was first attempted over 40 years ago,[1] but the complete lack of enantioselectivity with a seemingly optimally differentiated system (the groups on sulfur were adamantyl, ethyl, and methyl) was far from encouraging. This area of research therefore remained in the doldrums until Furukawa et al. showed in 1989 that moderate enantioselectivity could be achieved in reactions of chiral phenyl-stabilized ylides (Scheme 1).[2] This article spawned considerable interest in the field, and since then other groups have made significant contributions in improving all aspects of the reaction.[3,4] However, despite the successes achieved, the application of sulfur ylides in AE reactions is not commonly used by the organic chemistry community in contrast to methodologies for asymmetric alkene epoxidations.[5] One drawback of the existing methodologies is the ease with which the sulfides can be obtained (in both enantiomeric

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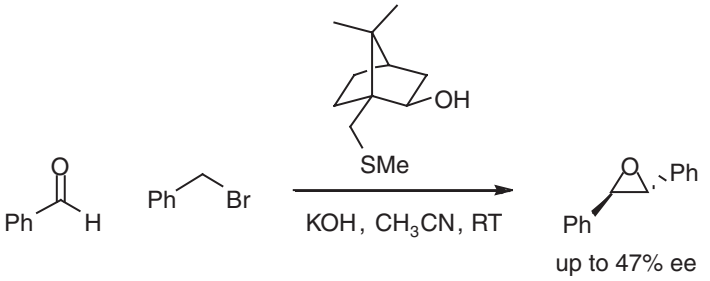
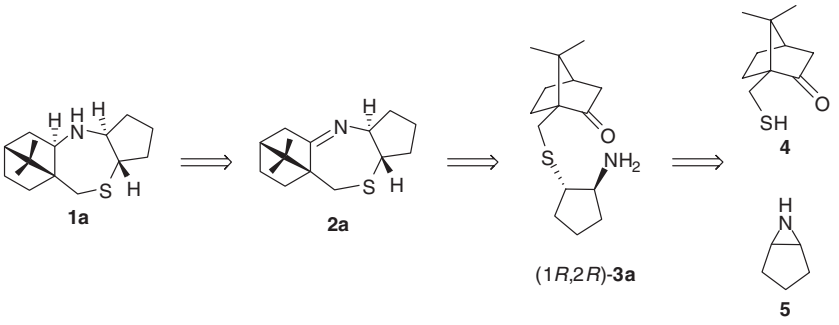
Address correspondence to Prof. V. K. Aggarwal and Dr. E. M. McGarrigle, School of Chemistry, Cantock's Close, Bristol BS8 1TS, UK. E-mail: V.Aggarwal@bristol.ac.uk and eoghan.mcgarrigle@bristol.ac.uk



Scheme 1 Furukawa's asymmetric epoxidation of benzaldehyde.

forms). In addition, after the epoxidation reaction, the separation of the sulfide from the product requires column chromatography, which is undesirable, especially on a large scale. Therefore, the development of an easily synthesized and easily recyclable catalyst that displayed high selectivities in AE is desirable. In this article, we describe efforts towards the synthesis of a sulfide **1a** that we thought would satisfy these criteria. In the course of this work, it was found that existing methods for achieving the ring-opening of an NH-aziridine with a thiol did not always give satisfactory results. Therefore, new conditions to achieve this transformation were developed and are described.

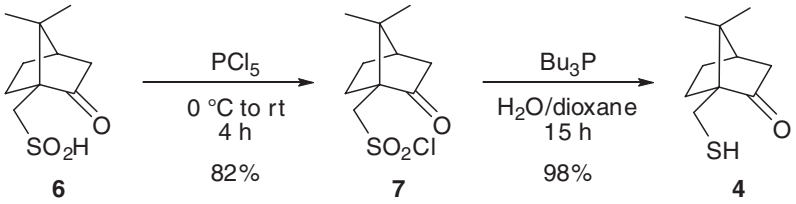
The camphor-derived aminosulfide **1a** was targeted. It was thought that this structure would lead to a conformationally constrained sulfide that would give control over lone-pair alkylation, ylide conformation, and facial selectivity in the aldehyde approach to the ylide—important factors in obtaining highly enantioselective epoxidations.[3e] In addition, the steric bulk of **1a** was similar to previous sulfides, and so it was expected that the *anti*-betaine formation would be nonreversible, making the betaine formation step enantio-determining; on the other hand, under appropriate reaction conditions, the *syn*-betaine formation would be reversible, leading to high diastereoselectivities. The incorporation of an amino group in the sulfide structure would allow the chiral sulfide to be recovered from the reaction mixture by a simple acid/base extraction.[4j] Our retrosynthetic analysis is shown in Scheme 2. It was envisioned that the aminosulfide **1a** could be synthesized by reductive amination of **3a**. In turn, the aminoketone **3a** could be synthesized from the ring-opening of readily available aziridine **5** by the literature known thiol **4**.



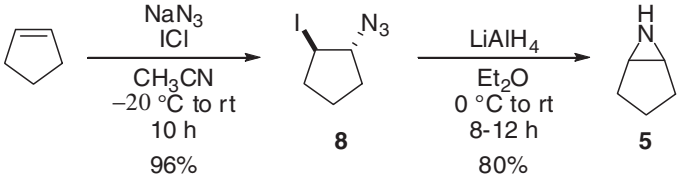
Scheme 2 Retrosynthesis of aminosulfide **1a**.

RESULTS AND DISCUSSION

Thiol **4** was synthesized in two steps and 80% yield using conditions described in the literature (Scheme 3).[6,7] The synthesis of iodoazide **8** was achieved in excellent yield using conditions described in the literature (Scheme 4),[8] but its conversion to the aziridine **5** proved slightly more problematic. It was found that the aziridine was highly volatile and great care had to be taken during workup and, in particular, it was found that it was necessary to remove the Et_2O solvent on a rotary evaporator with the flask immersed in an ice-water bath to avoid loss of the product **5**. After optimization, the aziridine could be obtained in up to 80% yield.



Scheme 3 Synthesis of thiol **4**.

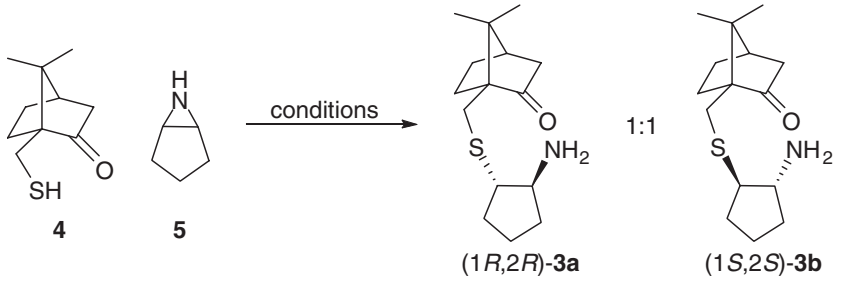


Scheme 4 Synthesis of aziridine **5**.

The ring-opening of aziridine **5** with thiol **4** was then investigated (Table I).[9] Initially the reaction was attempted in refluxing MeOH as reported by Ekegren et al.[10a] and Petra et al.[10b] for similar substrates. However these conditions led to very poor yield and low recovery of organic mass, presumably due to loss of the volatile **5** (carrying out the reaction at room temperature led to low conversions). The use of a catalytic amount of ammonium salts in iPrOH[11] was also investigated but only gave low yields. Therefore reaction conditions that would allow the reaction to take place at lower temperature were sought. The use of a Lewis acid catalyst at room temperature[12] gave moderate yields, but reaction times were still long. The use of ionic liquids to aid the reaction was investigated next, as it was thought the formation of a reactive ion pair (protonated aziridine and thiolate) would be favored in the ionic liquid environment, and that this should facilitate ring-opening.[13–15] Indeed, it was found that stirring the thiol and aziridine in 1-butyl-3-methylimidazolium (BMIM) bromide gave the ring-opened product in 60% yield, while use of BMIM chloride gave the desired product in 94% yield after 2 days. The ring-opening did not exhibit appreciable diastereoselectivity under any conditions (~1:1 ratio was obtained), and the diastereomers **3a** and **3b** were inseparable by chromatography.

To test the generality of this new procedure, a series of thiols was screened in the ring-opening of cyclopentyl and cyclohexyl aziridines **5** and **10** (Table II). Aziridine **10** was

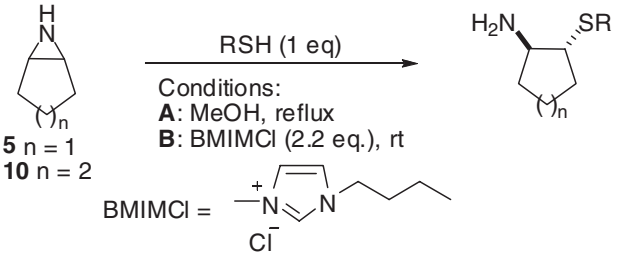
Table I Ring-opening of aziridine **5** with thiol **4** using various conditions



Entry	Conditions	Time (h)	Yield (%)[a]
1	MeOH, reflux	6	3
2	NH_4Cl, iPrOH	24	39
3	$BF_3.Et_2O$	48	60
4	$BMIM^+ Br^-$	72	60
5	$BMIM^+ Cl^-$	24	94

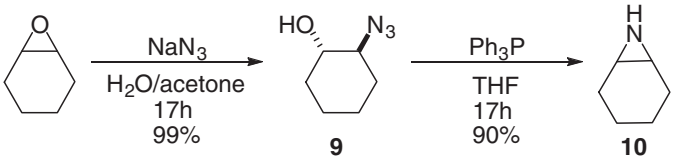
BMIM = 1-butyl-3-methylimidazolium.
[a]Isolated yield.

Table II Ring-opening of NH-aziridines with thiols



Entry	Aziridine	Thiol (RSH)	Conditions	Yield (%)[a]
1	**5**	**4**	**B** 36 h	94[b]
2	**5**	PhSH	**B** 36 h	61
3	**5**	$PhCH_2SH$	**B** 36 h	67
4	**5**	$C_{12}H_{25}SH$	**B** 36 h	30[c]
5	**10**	**4**	**B** 36 h	91[b]
6	**10**	**4**	**A** 15 h	86[b]
7	**10**	PhSH	**B** 24 h	78
8	**10**	$PhCH_2SH$	**B** 24 h	69
9	**10**	$C_{12}H_{25}SH$	**B** 36 h	40[d]
10	**10**	PhSH	**A** 7 h	75
11	**10**	$PhCH_2SH$	**A** 8 h	76
12	**10**	$C_{12}H_{25}SH$	**A** 15 h	67

[a]Isolated yield of aminosulfide.
[b]dr 1:1.
[c]60% unreacted thiol was isolated.
[d]50% unreacted thiol was isolated.



Scheme 5 Synthesis of aziridine **10**.

synthesized in excellent yield using procedures described in the literature (Scheme 5).[16] Moderate-to-good yields were obtained using these simple conditions using thiophenol, benzylmercaptan, and camphor-derived thiol **4**. In the case of dodecanethiol, low yields were obtained. The unreacted thiol was recovered in significant quantities after the reaction. The low conversion was attributed to the poor miscibility of the thiol with the ionic liquid. Results using **10** with literature conditions of refluxing MeOH were similar to the ionic liquid conditions, and in the case of dodecanethiol were better (no miscibility problems were encountered in MeOH). It would appear that the volatility of the cyclopentene aziridine was the major problem in the other cases.

Having established a viable route for the ring-opening of **5** with **4**, the intramolecular reductive amination of **3** was investigated next (Scheme 6). Imine formation was achieved in good yield using Dean–Stark conditions. At the planning stage, it had been expected that the imine reduction with borohydride reagents would exhibit a high degree of selectivity.[17] However in practice, the diastereoselectivity was only moderate. All four possible diastereomers of the reduced product **1** were isolated after column chromatography. The identities of two of the diastereomers (**1a** and **1b**) were confirmed by X-ray crystallography of the sulfonium salts derived from them (see Figure 2 below). The stereochemistry of the diastereomers **1c** and **1d** was assigned based on 2D NMR and NOE studies (Figure 1). Surprisingly, the stereoselectivity of the reduction was not determined by the stereochemistry

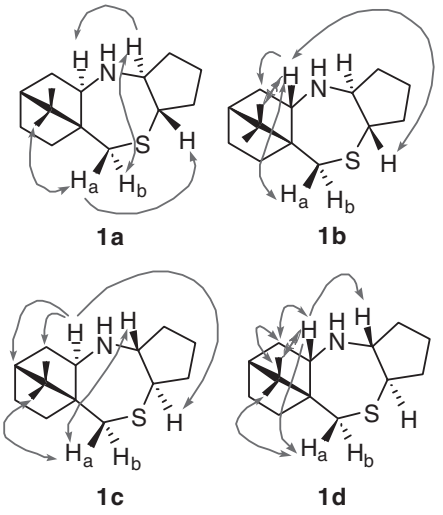
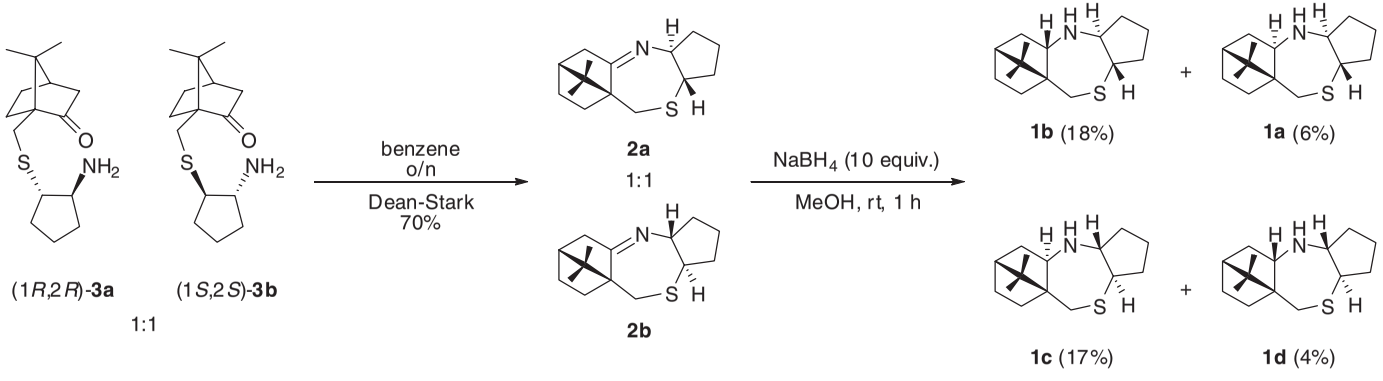
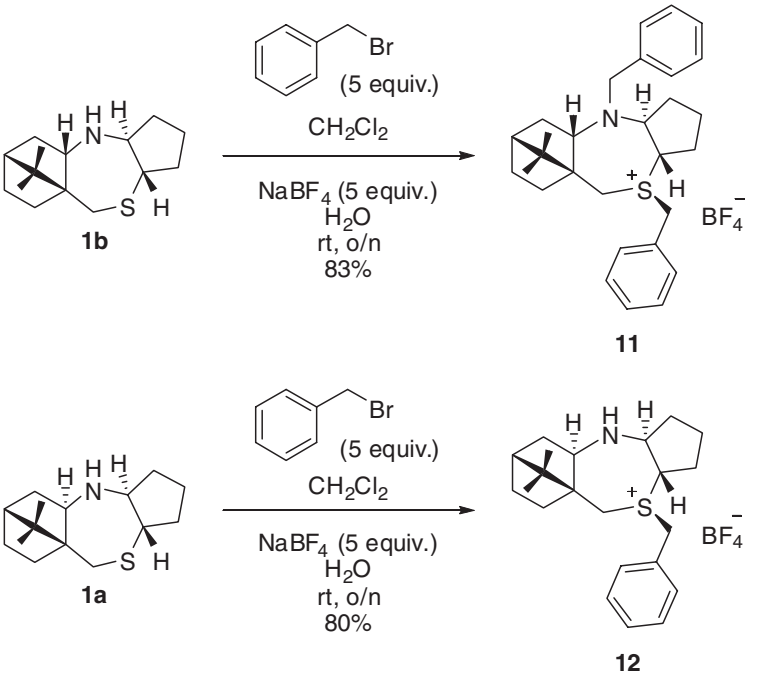


Figure 1 Summary of relationships observed in NOE NMR studies of **1a**–**1d**.



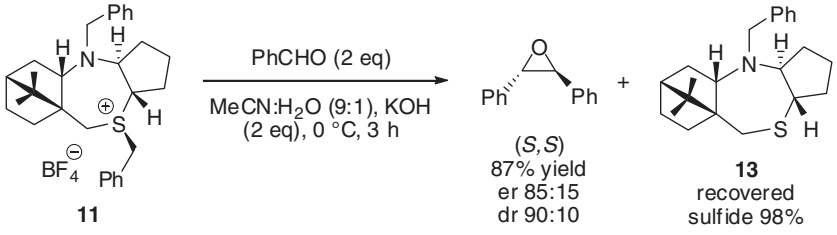
Scheme 6 Reductive amination of **3**.

of the camphor unit but by the cyclopentane stereocenters (e.g., the major diastereomer arising from **2a** was **1b**, whereas the major diastereomer arising from **2b** was **1c**). The reaction of **2a** favors formation of **1b**, and from examination of molecular models, it appears that the pathway to **1b** requires minimal rearrangement through a chair-like transition state and so is favored. The reaction of **2b** gave **1c** as the major diastereomer as would be predicted from literature precedent.[17]



Scheme 7 Synthesis of sulfonium salts **11** and **12**.

The alkylations of the diastereomers **1a** and **1b** were achieved in good yields using standard conditions (Scheme 7).[4j] In the case of **1b**, both the sulfur and the nitrogen atoms were alkylated, whereas with **1a** only the sulfur atom was alkylated. Crystals suitable for X-ray crystallography were obtained for both salts (see Figure 2), which enabled the determination of the stereochemistry at the cyclopentane junctions and at sulfur.



Scheme 8 Asymmetric epoxidation of aldehydes with **11**.

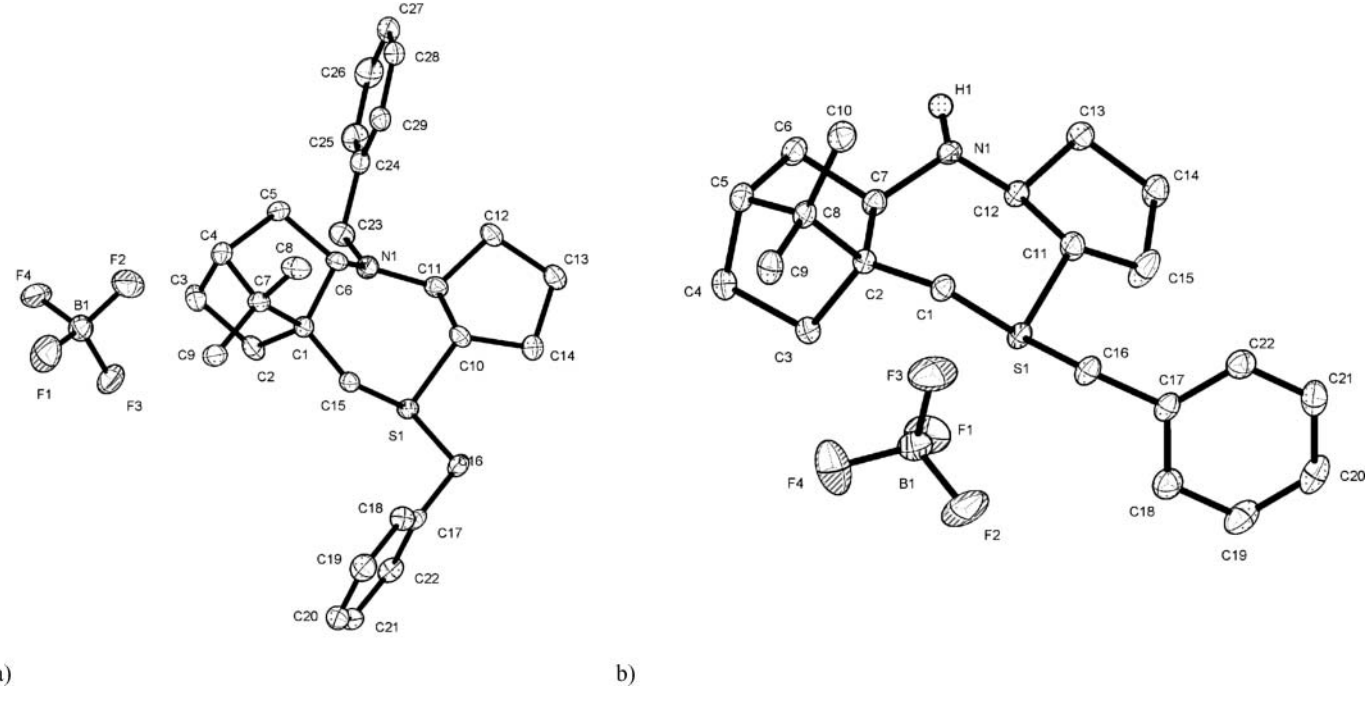


Figure 2 Solid-state structures of a) **11** and b) **12**. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms have been omitted for clarity.

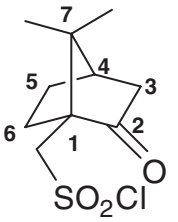
We tested the reactivity of **11** in the asymmetric epoxidation of benzaldehyde (Scheme 8). Stilbene oxide was obtained in good yield, diastereoselectivity (*trans*:*cis* 90:10), and, in comparison to the best chiral sulfides, moderate enantioselectivity (e.r. 85:15). The sulfide **13** was recovered in excellent yield (98%) by a simple acid/base wash, thus validating the idea of incorporating the amino group to aid easy recycling of the sulfide. Ultimately, given the unexpected difficulties and lack of selectivity in the reductive amination step, it was decided that the aminosulfides were not sufficiently accessible to be worthy of further investigation.

In conclusion, we have described the synthesis of camphor-derived chiral aminosulfides and the application of one of them in asymmetric epoxidation of aldehydes. The incorporation of an amino group enabled the sulfide to be easily recovered by acid/base wash after the reaction. During the course of investigations, novel conditions for the ring-opening of NH-aziridines by thiols in the presence of ionic liquids at room temperature were developed. These are likely to provide a useful alternative to existing methodologies, especially where one of the coupling partners is particularly sensitive or bears groups that are incompatible with other conditions.

EXPERIMENTAL

NMR assignments were made using COSY, HMBC, and HMQC where needed.

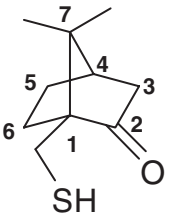
Preparation of (1*S*,4*R*)-1-(Mercaptomethyl)-7,7-dimethylbicyclo[2.2.1] heptan-2-one 4



(1*S*,4*R*)-(+)-10-Camphorsulfonyl chloride[6,7]. Based on the procedure of Vandewalle et al.:[7] (+)-10-Camphorsulfonic acid (1.01 g, 4.35 mmol) was placed in a 50 mL round-bottomed flask with a gas outlet tube leading to a saturated $NaHCO_3$ trap (a positive pressure was maintained using a nitrogen inlet). The flask was cooled in a large ice bath, and solid PCl_5 (1.35 g, 6.48 mmol) was added portionwise. The mixture was agitated manually using a glass rod to initiate the liquefaction of the mixture, before being stirred magnetically. After 1 h, the cooling bath was removed, and the reaction was allowed to warm to r.t. and was stirred for 3 h. The reaction mixture was then slowly poured portionwise into a 100 mL separating funnel that was approximately 50% filled with crushed ice. After addition of each portion, the separating funnel was thoroughly shaken before further material was added. Once addition of the reaction mixture to the separating funnel was complete, CH_2Cl_2 (20 mL) was added, and the separating funnel was shaken. The CH_2Cl_2 was removed, and the aqueous material was further extracted with CH_2Cl_2 (2 × 10 mL). The combined organic fractions were dried with $MgSO_4$

and filtered, and the solvent was removed under reduced pressure to afford an off-white crystalline solid. This solid was then recrystallized from petrol to afford the product as white crystalline flakes (0.89 g, 82%). Mp 66–67°C (hexane) [Lit.[18] 67–68°C (heptane)]; R_f 0.42 (20% EtOAc/petrol); υ_{max} (neat)/cm^{-1} 2980 (C—H), 2850 (C—H) 1750 (C=O), 1055 (S=O); δ_H (400 MHz, $CDCl_3$) 4.31 (1H, d, *J* 14.6, C*H*HS), 3.73 (1H, d, *J* 14.6, CH*H*S), 2.40–2.52 (2H, m, C^3*H*H, C^{6}H*H*), 2.17 (1H, dd, *J* 4.5, 4.5, C^{4}H), 2.05–2.15 (1H, m, C^{6}H*H*), 1.99 (1H, d, *J* 18.6, C^{3}H*H*), 1.78 (1H, ddd, *J* 13.1, 9.5, and 4.0, C^5*H*H), 1.49 (1H, ddd, *J* 13.1, 9.5 and 4.0, C^{5}H*H*), 1.15 (3H, s, CH_3), 0.93 (3H, s, CH_3); δ_C (101 MHz, CDCl3) 212.7 (C=O), 64.2 (SCH_2), 59.6 (C1), 48.1 (C7), 42.7 (C4), 42.3 (C3), 26.8 (C6), 25.2 (C5), 19.7 (CH_3), 19.6 (CH_3). All spectroscopic and physical data were identical to commercially available material.

(1*S*,4*R*)-1-(Mercaptomethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 2.



A solution of (1*S*,4*R*)-(+)-(10)-camphorsulfonyl chloride (17.2 g, 68.6 mmol) in 1,4-dioxane (130 mL) was degassed by bubbling N_2 through it for 10 min. Meanwhile, a mixture of H_2O (40 mL) and 1,4-dioxane (156 mL) in a 500 mL three-necked round-bottomed flask fitted with two heat-resistant septa, a reflux condenser, and a large magnetic stirrer bar was degassed in the same way. After 10 min, tri-*n*-butylphosphine (50.8 mL, 0.206 mol) was added to the H_2O/dioxane mixture via syringe, giving a biphasic solution. This was followed rapidly by addition of the degassed camphorsulfonyl chloride solution via cannula, which resulted in the solution becoming monophasic. The reaction mixture was then stirred and heated to reflux for 15 h. The reaction mixture was then allowed to cool to rt and transferred to a 1 L separating funnel, where it was partitioned between petrol (150 mL) and ice-cold H_2O (150 mL). The aqueous layer was removed and extracted with petrol (3 × 100 mL), the total volume of these organic extracts was then reduced to 100 mL, and the colorless solution was then washed with ice-cold H_2O (3 × 100 mL) and the solvent evaporated to give a white crystalline solid. The initial petrol layer was washed with ice-cold H_2O (3 × 100 mL) and then evaporated to give a yellow crystalline mass. This was then washed with petrol to give a white crystalline solid. The organic washings were then evaporated to dryness and filtered through a short silica plug (eluent 5% EtOAc in petrol), collecting all fractions that stained a $KMnO_4$ plate. After evaporation of the appropriate fractions, the white crystalline solid obtained was combined with the other solids obtained to give the thiol **4** as white crystalline solid (12.4 g, 98%); mp 66–68°C (petrol) [lit.[19] 65–66°C]; R_f 0.41 (10% EtOAc in petrol). υ_{max} (neat)/cm^{-1} 2980 (C—H), 2575 (S—H), 1750 (C=O); δ_H (400 MHz; $CDCl_3$) 2.87 (1H, dd, *J* 14.0, 6.5, C*H*HS), 2.37 (1H, dd, *J* 14.0, 10.0, CH*H*S), 2.36 (1H, ddd, *J* 17.0, 5.0, 2.5, COCH*H*^{eq}), 2.09 (1H, dd, *J* 5.0, 5.0, C^{4}H), 2.04–1.87 (2H, m, C^5*H*H, C^6*H*H), 1.94 (1H, dd, *J* 10.0, 6.5, SH), 1.88 (1H, d, *J* 17.0, COCH*H*^{ax}), 1.75–1.67 (1H, m, C^{5}H*H*), 1.43–1.37 (1H, m, C^{6}H*H*), 1.02 (3H, s, CH_3), 0.91 (3H, s, CH_3). δ_C (101 MHz, $CDCl_3$) 217.9 (C=O), 60.7 (C1), 47.9 (C7), 43.7 (C4), 43.3

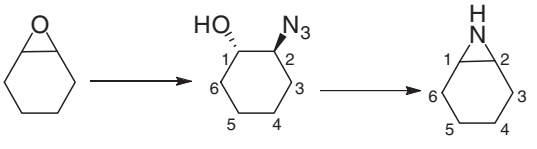
(CH_2SH), 26.7 (C3), 26.6 (C6), 21 (C5), 20.4 (CH_3), 19.9 (CH_3). All spectroscopic and physical data were in agreement with those published.[19,20]

Synthesis of NH-Aziridines: Preparation of 6-Azabicyclo[3.1.0]hexane 5

(±)-*trans*-1-Azido-2-iodocyclopentane 8. The method of da Zhang and Scheffold[21] was used: A solution of ICl (18.3 g, 0.113 mol) in MeCN (20 mL) was added slowly over 20 min to a stirred suspension of NaN_3 (16.3 g, 0.251 mol) in MeCN (100 mL) in a cooling bath (−20°C). After stirring for an additional 10 min, cyclopentene (7.8 g, 0.11 mol) was added, and the mixture was allowed to warm up to rt with stirring for 10 h. The red-brown slurry was poured into H_2O (250 mL) and extracted with Et_2O (3 × 250 mL). The organic phase was washed with 5% $Na_2S_2O_3$ in H_2O (150 mL) and brine (2 × 300 mL), dried ($MgSO_4$), and evaporated to yield **8** (26.1 g, 96%) as an orange oil; υ_{max} (neat)/cm^{-1} 2980 (C—H), 2890 (C—H), 2110 (—N_3), 1255 (C—N); δ_H (400 MHz, $CDCl_3$) 4.17 (1H, dt, *J* 6.6, 4.5, N_3CH), 4.11 (1H, apparent q, *J* 5.4, IC*H*), 2.26–2.39 (1H, m, N_3CCHH), 2.04–2.24 (2H, m, C*H*H, N_3CCHH), 1.74–1.93 (2H, m, C*H*H, ICCH*H*), 1.62–1.72 (1H, m, ICCH*H*) δ_C (101 MHz, $CDCl_3$) 71.6 (N_3CH), 36.7 (CH_2), 29.3 (CH_2), 28.7 (ICH), 22.5 (CH_2). The spectroscopic data were in agreement with those published.[21]

6-Azabicyclo[3.1.0]hexane 5. A mixture of anhydrous diethyl ether (90 mL) and $LiAlH_4$ (2.32 g, 61.1 mmol) in a 250-mL, three-neck flask fitted with a reflux condenser and an additional funnel was cooled in an ice bath. A solution of (±)-*trans*-1-azido-2-iodocyclopentane **8** (7.87 g, 33.2 mmol) in a minimal amount of ether (∼20 mL) was added slowly to the stirred slurry (***Caution!*** The β-iodo azide should be added slowly over a period of 20–30 min to avoid vigorous delayed frothing.) Once the addition was complete, the mixture was allowed to warm to rt and to stir for 8–12 h. Workup was accomplished by the slow addition of 20% sodium hydroxide (10 mL) followed by 30–45 min of vigorous stirring. The white, granular salts were filtered through a medium porosity sintered-glass funnel and washed well with ether. The filtrate was dried ($MgSO_4$) and concentrated (***with care!!!***) under reduced pressure in a water/ice bath to afford 6-azabicyclo[3.1.0]hexane **5** (2.21 g, 80%) as a volatile colorless liquid, stored under argon in the freezer; υ_{max} (neat)/cm^{-1} 3044 (N—H), 2980 (C—H), 1215 (C—N) δ_H (400 MHz, $CDCl_3$) 2.50 (1H, s, NH), 2.43 (2H, s, 2 × HNC*H*), 1.84 (2H, dd, *J* 12.8, 7.7, C*H*H, CH*H*), 1.67–1.49 (3H, m, C*H*H, CH*H*, C*H*H), 1.36–1.24 (1H, m, CH*H*), δ_C (101 MHz, $CDCl_3$) 35.8 (2 × NCH), 27.2 (2 × CH_2), 18.1 (CH_2). The spectral data were in agreement to those published.[21]

Preparation of 7-Azabicyclo[4.1.0]heptane 10



(±)-9 **10**

(±)-*trans*-2-Azidocyclohexanol 9. Following the procedure by Krasnova and Yudin,[16] a mixture of cyclohexene oxide (15.5 mL, 153 mmol) and NaN_3 (25.2 g, 387 mmol) in H_2O–acetone (1:1, 160 mL) was heated at reflux for 17 h (the temperature of

the oil bath was 75°C). Acetone was removed under reduced pressure, and the residue was extracted with Et_2O (3 × 80 mL). The combined extracts were washed with H_2O (2 × 20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield the azido alcohol (±)-*trans*-**9** (22.1 g, 99%) as a yellow oil, which was used in the next step without further purification. R_f 0.60 (petrol:EtOAc, 9:1); υ_{max} (neat)/cm^{-1} 3360 (O—H, br), 2985 (C—H), 2100 (—N_3), 1250 (C—N); δ_H (400 MHz; $CDCl_3$); 3.53 (1H, br s, OH), 3.31–3.23 (1H, m, OCH), 3.11–3.02 (1H, m, N_3CH), 1.94–1.85 (2H, m, C^6HH, C^3HH), 1.61–1.58 (2H, m, C^6HH, C^3HH), 1.23–1.14 (4H, m, C^5H_2, C^4H_2); δ_C (101 MHz, $CDCl_3$) 73.4 (OCH), 66.9 (N_3CH), 33.3 (C6), 29.9 (C3), 24.2 (C5), 23.9 (C4). The spectral data are consistent with literature values.[16]

7-Azabicyclo[4.1.0]heptane 10. Following the procedure by Krasnova and Yudin,[16] triphenylphosphine (38.6 g, 148 mmol) was added over 30 min to a solution of (±)-*trans*-2-azidocyclohexanol **9** (20.9 g, 148 mmol) in THF (125 mL) while N_2 evolved from the reaction mixture. The reaction mixture was then refluxed for 17 h. Pentane (~500 mL) was added to precipitate Ph_3PO; the white precipitate was filtered off, and the solvent was removed on a rotary evaporator (water bath 30–45°C). The solvent was removed in vacuo to give aziridine **10** as a colorless oil (13.0 g, 90%), which was used without further purification. The oil solidified upon cooling at −5°C. Storage: over KOH in the freezer; R_f 0.25 (CH_2Cl_2:MeOH 9:1); υ_{max} (neat)/cm^{-1} 3044 (N—H), 2980 (C—H), 1215 (C—N); δ_H (400 MHz; $CDCl_3$) 2.05 (2H, br s, 2 × NHC*H*), 1.74–1.61 (4H, m, C^6H_2, C^3H_2), 1.31–1.19 (2H, m, C^5HH, C^4HH), 1.17–1.03 (2H, m, C^5HH, C^4HH), 0.36 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 29.1 (2 × NCH), 24.3 (C6 and C3), 19.8 (C5 and C4). The spectral data are consistent with literature values.[16]

General Procedure A: Ring-Opening of Aziridines Using MeOH as Solvent: Synthesis of Aminosulfides 3a and 3b

Following the procedure by Ekegren et al.:[10a] To a solution of thiol **4** (0.99 g, 5.4 mmol) in MeOH (6 mL), aziridine **5** (300 mg, 3.61 mmol) was added via syringe at rt, and the mixture was degassed for 10 min using freeze/thaw cycles, then refluxed for 6 h under argon. The solvent was then evaporated in vacuo. EtOAc (10 mL) was added to residue, and the resulting solution was washed with 1N HCl (3 × 7 mL). The aqueous layer was basified with saturated $NaHCO_3$ to pH ~8 and then extracted with CH_2Cl_2 (3 × 7 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford amino sulfide **3a:3b** as a yellow oil (29 mg, 3%) in a 51:49 ratio of diastereoisomers. The poor yield was attributed to the loss of aziridine under these conditions due to its volatility and to formation of a product tentatively assigned as a disulfide formed from dimerization of thiol **4**. The spectroscopic data were in agreement with those obtained using method **B**.

Synthesis of (1*S*,4*R*)-1-(((1*S*,2*S*)-2-Aminocyclohexylthio)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 14a and (1*S*,4*R*)-1-(((1*R*,2*R*)-2-Aminocyclohexylthio)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 14b Using General Procedure A

Following general procedure **A**, aziridine **10** (1.00 mL, 10.4 mmol) and thiol **4** (2.30 g, 12.5 mmol) were refluxed in MeOH (14 mL) for 15 h. Workup afforded amino sulfides **14a** and **14b** as a yellow oil (2.50 g, 86%) in a 53:47 ratio of diastereoisomers. The spectral data were consistent with those obtained using method **B**.

Synthesis of (±)-*trans*-2-Benzylsulfanylcyclohexylamine 15 Using General Procedure A

Following general procedure **A**, aziridine **10** (1.00 mL, 10.4 mmol) and benzyl mercaptan (1.61 mL, 12.5 mmol) were refluxed in MeOH (14 mL) for 8 h. The solvent was then evaporated in vacuo, and flash chromatography of the residue (silica gel; CH_2Cl_2:MeOH, 9:1) afforded amino sulfide **15** as a colorless oil (1.75 g, 76%). The spectral data were consistent with those obtained using method **B**.

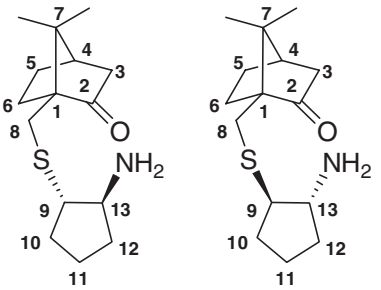
(±)-*trans*-2-Phenylsulfanylcyclohexylamine 16 Using General Procedure A

Using general procedure **A,** aziridine **10** (1.01 g, 10.4 mmol) and thiophenol (1.29 mL, 12.5 mmol) were refluxed in MeOH (14 mL) for 7 h. The crude material was purified via flash chromatography (CH_2Cl_2:MeOH 95:5) to afford amino sulfide (±)-**16** as a colorless oil (1.63 g, 75%). R_f 0.12 (CH_2Cl_2:MeOH 9:1). The spectral data were consistent with those reported for method **B**.

(±)-*trans*-2-(Dodecylthio)cyclohexylamine 17 Using General Procedure A

Using general procedure **A,** aziridine **10** (1.01 g, 10.4 mmol) and 1-dodecanethiol (2.99 mL, 12.5 mmol) were refluxed in MeOH (14 mL) for 15 h. The crude material was purified via flash chromatography (CH_2Cl_2:MeOH 95:5) to afford amino sulfide (±)-*trans*-**17** as a colorless oil (2.09 g, 67%); R_f 0.33 (CH_2Cl_2:MeOH 9:1). The spectral data were consistent with those reported for method **B**.

General Procedure B: Ring-Opening of Aziridines Using Ionic Liquid—Synthesis of Aminosulfides 3a and 3b

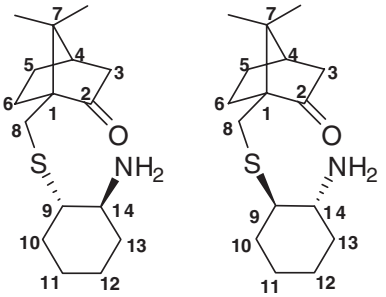


(1*R*,2*R*)-**30a** (1*S*,2*S*)-**30b**

To thiol **4** (69 mg, 0.37 mmol) and aziridine **5** (62 mg, 0.74 mmol), ionic liquid 1-butyl-3-methylimidazolium chloride (143 mg, 0.82 mmol) was added under argon. The reaction mixture was degassed using freeze/thaw cycles for about 10 min and then allowed to stir at rt for 2 days. Water (20 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL); the organic layers were combined and washed with 1N HCl (60 mL). The aqueous layer was basified with saturated $NaHCO_3$ to pH ~8 then extracted with CH_2Cl_2 (3 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford amines **3a:3b** as a light brown oil (93 mg, 94%) in a 51:49 ratio of diastereoisomers. R_f

0.35 (dichloromethane:methanol, 9:1); υ_{max} (neat)/cm^{-1} 3380 (N−H), 3350 (N−H), 2890 (C−H), 1750 (C=O), 1597 (NH_2), 1055 (C−N); δ_H (400 MHz; $CDCl_3$); 2.95–2.87 (1H, m, NCH), 2.91 (1H, m, NCH), 2.71 (1H, d, *J* 9.7, SC*H*H), 2.68 (1H, d, *J* 9.7, SCH*H*), 2.48 (2H, $q_{(app)}$, *J* 7.8, 2 × SCH), 2.43 (1H, d, *J* 9.5, SC*H*H), 2.39 (1H, d, *J* 9.5, SCH*H*), 2.37 (2H, br s, NH_2), 2.19 (2H, br s, NH_2), 1.19–1.59 (6H, m, 2 × COC*H*H^{eq}, 2 × C^5*H*H, 2 × C^6*H*H), 1.59–1.41 (2H, m, 2 × C^{12}*H*H), 1.53 (2H, d, *J* 18.3, 2 × COCH*H*^{ax}), 1.41–1.22 (10H, m, 2 × C^{5}H*H*, 2 × C^{10}*H*H, 2 × C^{11}*H*H, 2 × C^{11}H*H*, 2 × C^{4}H), 1.22–1.10 (2H, m, 2 × C^{6}H*H*), 1.10–0.89 (4H, m, 2 × C^{12}H*H*, 2 × C^{10}H*H*), 0.73 (6H, s, 2 × CH_3), 0.58 (6H, s, 2 × CH_3); δ_C (101 MHz, $CDCl_3$) 216.6 (C=O), 216.5 (C=O), 77.8 (C1), 76.2 (C1), 58.7 (NH_2CH), 58.5 (NH_2CH), 55.1 (SCH), 54.9 (SCH), 47.4 (C7), 47.5 (C7), 43.9 (C4), 43.3 (C4), 42.8 (CO*C*H_2), 42.9 (CO*C*H_2), 33.8 (2 × C10), 33.6 (C12), 32.8 (C12), 32.0 (SCH_2), 31.9 (SCH_2), 30.2 (C6), 27.6 (C6), 27.5 (C5), 27.4 (C5), 26.7 (C11), 26.5 (C11), 20.1 (CH_3), 20.0 (CH_3), 19.9 (CH_3), 19.8 (CH_3); *m/z* (EI$^+$) 267.2 (20%, M$^+$), 249.1 (27%, M$^+$−H_2O), 182.1 (23%), 141.1 (39%), 116.1 (84%), 100.0 (28%), 83.1 (67%), 67.0 (67%), 56.0 (100%); HRMS (EI$^+$) $C_{15}H_{25}NOS$ requires 267.1657; found 267.1647.

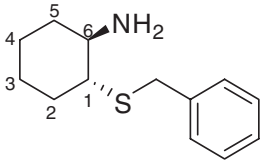
Synthesis of (1*S*,4*R*)-1-(((1*S*,2*S*)-2-Aminocyclohexylthio)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 14a and (1*S*,4*R*)-1-(((1*R*,2*R*)-2-Aminocyclohexylthio)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 14b Using General Procedure B



Using general procedure **B**, BMIM chloride (3.99 g, 22.9 mmol), thiol **4** (2.30 g, 12.5 mmol), and aziridine **10** (1.01 g, 10.4 mmol) were stirred under argon at rt for 36 h. Workup afforded a mixture of amino sulfides **14a** and **14b** as a yellow oil (2.65 g, 91%) in a 51:49 ratio of diastereoisomers (based on signals due to SCHH). R_f 0.35 (CH_2Cl_2:MeOH, 9:1). υ_{max} (neat)/cm^{-1} 3380 (N−H), 3350 (N−H), 2890 (C−H), 1750 (C=O), 1597 (NH_2), 1055 (C−N); δ_H (400 MHz; $CDCl_3$); 3.19 (4H, br s, 2 × NH_2), 2.77 (1H, d, *J* 9.8, SC*H*H, minor), 2.74 (1H, d, *J* 9.8, SCH*H*), 2.60–2.50 (2H, m, 2 × NCH), 2.52 (1H, d, *J*, 12.8, SC*H*H), 2.48 (1H, d, *J* 12.8, SCH*H*, major), 2.33–2.21 (4H, m, 2 × SCH, 2 × COC*H*H^{eq}), 2.08–1.84 (10H, m, 2 × C^{4}H, 2 × C^5*H*H, 2 × C^6*H*H, 2 × C^{10}*H*H, 2 × C^{13}*H*H), 1.78 (2H, d, *J* 18.3, 2 × COCH*H*^{ax}), 1.71–1.57 (4H, m, 2 × C^{11}*H*H, 2 × C^{12}*H*H), 1.49–1.11 (12H, m, 2 × C^{5}H*H*, 2 × C^{6}H*H*, 2 × C^{10}H*H*, 2 × C^{11}H*H*, 2 × C^{12}H*H*, 2 × C^{13}H*H*), 0.96 (6H, s, 2 × CH_3), 0.82 (6H, s, 2 × CH_3); δ_C (101 MHz, $CDCl_3$) 217.6 (C=O), 217.5 (C=O), 60.5 (C1), 60.4 (C1), 50.0 (2 × NCH), 53.9 (SCH), 53.5 (SCH), 47.7 (C7), 47.6 (C7), 43.3 (C4), 43.2 (C4), 42.9 (2 × $COCH_2$), 34.5 (2 × C10), 33.1 (C13), 33.0 (C13), 26.7 (2 × SCH_2), 26.6 (C6), 26.5 (C6), 26.3 (C5), 26.2 (C5), 26.1 (2 × C11), 24.7 (2 × C12), 20.1 (2 × CH_3), 20.0 (2 × CH_3); *m/z* (%) (EI) 281.1 (18, M$^+$), 182.0 (38), 139.0 (36), 130.0 (70),

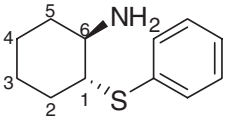
113.0 (50), 98.1 (64), 81.0 (66), 69.0 (50), 56.0 (100); HRMS (EI) $C_{16}H_{27}NOS$ requires: 281.1813; found: 281.1805.

Synthesis of (±)-*trans*-2-Benzylsulfanylcyclohexylamine 15 Using General Procedure B



Using general procedure **B**, a degassed mixture of BMIM chloride (3.99 g, 22.9 mmol), benzyl thiol (1.61 mL, 12.5 mmol), and aziridine **10** (1.01 g, 10.4 mmol) was warmed gently to liquefy the remaining solid ionic liquid. The reaction mixture was then allowed to stir at rt for 24 h. The reaction mixture was treated with ethyl acetate (4 × 20 mL) followed by filtration to afford the ionic liquid as a solid in quantitative yield. The filtrate was washed once with water (40 mL) and then brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified via flash chromatography (CH_2Cl_2:MeOH, 95:5) to afford amino sulfide (±)-**15** as a colorless oil (1.58 g, 69%). R_f 0.08 (CH_2Cl_2:MeOH, 9:1). υ_{max} (neat)/cm^{-1} 3380 (N—H), 3030 (N—H), 2930 (C—H), 2355 (C—H), 1605 (C=C), 1450 (C=C); δ_H (400 MHz; $CDCl_3$) 7.25–7.17 (4H, m, ArCH), 7.15–7.10 (1H, m, ArCH), 3.69 (1H, d, *J* 12.9, SC*H*HPh), 3.65 (1H, d, *J* 12.9, SCH*H*Ph), 2.41 (1H, ddd, *J* 10.4, 10.4, 4.0 NCH), 2.12 (1H, ddd, *J* 11.9, 10.4, 4.0, SCH), 1.98–1.93 (1H, m, C^2HH), 1.88–1.82 (1H, m, C^5HH), 1.64–1.57 (2H, m, C^4HH, C^3HH), 1.49 (2H, br s, NH_2), 1.34 (1H, ddd, *J* 15.5, 12.7, 3.5, C^2HH), 1.24–0.95 (2H, m, C^4HH, C^3HH), 0.99 (1H, ddd, *J* 16.2, 12.7, 3.5, C^5HH); δ_C (101 MHz, $CDCl_3$) 138.4 (C), 128.5 (2 × CH), 128.2 (2 × CH), 126.6 (CH), 53.5 (C6), 53.4 (C1), 35.2 (C5), 34.3 (SCH_2), 33.1 (C2), 26.1 (C4 or C3), 24.7 (C3 or C4); *m/z* (%) (EI) 221.1 (14, M^+), 204.1 (13.9), 130.1 (69), 123.0 (30), 113.0 (53), 99.1 (31), 91.0 (68), 86.0 (66), 83.9 (100), 79.0 (27), 65.0 (17), 56.0 (38); HRMS (EI) $C_{13}H_{19}NS$ requires: 221.1238; found 221.1236. The spectra data were consistent with those published.[10a]

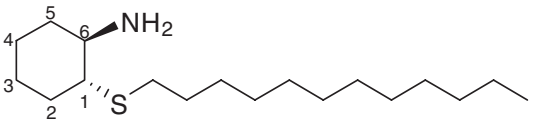
Synthesis of (±)-*trans*-2-Phenylsulfanylcyclohexylamine 16 Using General Procedure B



General procedure **B** was followed as reported above for the synthesis of **15**. Aziridine **10** (1.01 g, 10.4 mmol), thiophenol (1.29 mL, 12.5 mmol), and BMIM chloride (3.99 g, 22.9 mmol) were stirred at rt for 24 h. The ionic liquid was recovered in quantitative yield. The crude material was purified via flash chromatography (CH_2Cl_2:MeOH, 95:5) to afford amino sulfide (±)-**16** as a colorless oil (1.68 g, 78%). R_f 0.12 (CH_2Cl_2:MeOH 9:1); υ_{max} (neat)/cm^{-1} 3380 (N—H), 3030 (N—H), 2930 (C—H), 2355 (C—H), 1605 (C=C), 1450

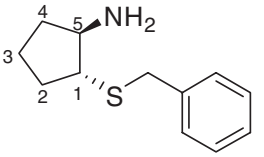
(C=C); δ_H (400 MHz; $CDCl_3$) 7.39–7.32 (2H, m, 2 × ArCH), 7.22–7.11 (3H, m, 3 × ArCH), 2.59 (1H, ddd, *J* 11.6, 10.1, 4.0, SCH), 2.48 (1H, ddd, *J* 10.1, 10.1, 4.0, NCH), 2.01–1.96 (1H, m, C^2HH), 1.92–1.86 (1H, m, C^5HH), 1.67 (2H, br s, NH_2), 1.64–1.54 (2H, m, C^4HH, C^3HH), 1.33–1.19 (1H, m, C^2HH), 1.19–1.03 (3H, m, C^3HH, C^4HH, C^5HH); δ_C (101 MHz, $CDCl_3$) 133.7 (C), 132.9 (CH), 128.6 (CH), 127.0 (CH), 56.8 (C1), 53.7 (C6), 35.4 (C5), 33.2 (C2), 26.2 (C4 or C3), 24.7 (C3 or C4); *m/z* (%) (EI) 207.1 (63, M^+), 135.0 (6), 109.0 (14), 98.1 (88), 83.9 (66), 81.0 (23), 69.1 (25), 56.0 (100); HRMS (EI) $C_{12}H_{17}NS$ requires: 207.1082; found: 207.1076. The spectra data were consistent with those published.[10a]

Synthesis of (±)-*trans*-2-(Dodecylthio)cyclohexylamine 17 Using General Procedure B



General procedure **B** was followed as reported above for the synthesis of **15**. Aziridine **10** (1.01 g, 10.4 mmol), 1-dodecanethiol (2.99 mL, 12.5 mmol), and BMIM chloride (3.99 g, 22.9 mmol) were stirred for 36 h at rt. The ionic liquid was recovered in quantitative yield. The crude material was purified via flash chromatography (CH_2Cl_2:MeOH, 95:5) to afford amino sulfide (±)-**17** as a colorless oil (1.25 g, 40%) as well as the starting material 1-dodecanethiol (1.27 g, 50%). (±)-**17**: R_f 0.33 (CH_2Cl_2:MeOH 9:1). υ_{max} (neat)/cm^{-1} 3379 (N—H), 3033 (N—H), 2930 (C—H), 2355 (C—H); δ_H (400 MHz; $CDCl_3$) 2.49 (2H, t, *J* 7.5, SCH_2), 2.47 (1H, ddd, *J* 10.3, 10.3, 4.0, NCH), 2.16 (1H, ddd, *J* 11.8, 10.3, 3.9, SCH), 2.05–1.99 (1H, m, C^5HH), 1.95–1.89 (1H, m, C^2HH), 1.71–1.59 (4H, m, C^4HH, C^3HH, NH_2), 1.55–1.46 (2H, m, C^2HH, C^5HH), 1.42–1.03 (22H, m, C^3HH, C^4HH, 10 × CH_2), 0.82 (3H, t, *J* 7.1, CH_3); δ_C (101 MHz, $CDCl_3$) 53.9 (C6), 53.7 (C1), 35.4 (C5), 33.6 (C2), 31.7 (SCH_2), 30.1 (CH_2), 29.9 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 26.5 (C4 or C3), 24.9 (C3 or C4), 22.5 (CH_2-Me), 13.9 (CH_3); *m/z* (%) (EI) 299.2 (18, M^+), 282.2 (6), 215.2 (4), 201.2 (29), 130.1 (40), 113.0 (27), 99.1 (80), 84.0 (44), 69.1 (44.5), 56.0 (100); HRMS (EI) $C_{18}H_{37}NS$ requires: 299.2647; found 299.2648.

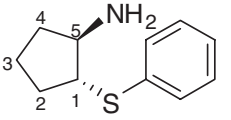
Synthesis of (±)-*trans*-2-(Benzylthio)cyclopentanamine 18 Using General Procedure B



General procedure **B** was followed as reported above for the synthesis of **15**. BMIM chloride (4.69 g, 26.8 mmol), benzyl mercaptan (1.57 mL, 12.2 mmol), and aziridine **5**

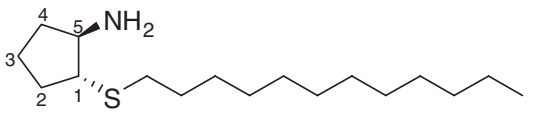
(1.01 g, 12.2 mmol) were stirred at rt for 36 h. Ethyl acetate (40 mL) was added to the reaction mixture, but the ionic liquid was not recovered because it oiled out. Instead, water (40 mL) was added to the biphasic mixture, and then the mixture was extracted with more ethyl acetate (3 × 20 mL); the combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified via flash chromatography (silica gel; petrol:EtOAc, 9:1, 2.5% NEt_3) to afford amino sulfide (±)-**18** as a colorless oil (1.70 g, 67%). R_f 0.07 (petrol:EtOAc, 9:1, 2.5% NEt_3). υ_{max} (neat)/cm^{-1} 3383 (N—H), 3035 (N—H), 2930 (C—H), 2355 (C—H), 1605 (C=C), 1450 (C=C); δ_H (400 MHz; $CDCl_3$) 7.26–7.17 (4H, m, ArCH), 7.15–7.11 (1H, m, ArCH), 3.69 (1H, d, *J* 13.2, SCH*H*Ph), 3.56 (1H, d, *J* 13.2, SC*H*HPh), 2.94 (1H, ddd, *J* 7.5, 7.5, 7.5, NCH), 2.42 (1H, ddd, *J* 7.5, 7.5, 7.5, SCH), 2.03–1.95 (1H, m, C^4HH), 1.94–1.84 (1H, m, C^2HH), 1.61–1.52 (2H, m, C^3H_2), 1.51–1.43 (1H, m, C^4HH), 1.32–1.16 (3H, m, C^2HH, NH_2); δ_C (101 MHz, $CDCl_3$) 138.5 (C), 128.5 (CH), 128.2 (CH), 126.6 (CH), 58.6 (C5), 52.8 (C1), 35.7 (SCH_2Ph), 33.8 (C2), 32.2 (C4), 21.6 (C3); *m/z* (%) (EI) 207.1 (6, M^+), 190.1 (9), 170 (6), 123.0 (12), 116.0 (51), 99.0 (29), 91.0 (59), 85.0 (52), 83.9 (80), 82.1 (19), 73.0 (7), 65.0 (17), 56.0 (100); HRMS (EI) $C_{12}H_{17}NS$ requires: 207.1082; found 207.1080. The spectra data were consistent with those published.[10a]

Synthesis of (±)-*trans*-2-(Phenylthio)cyclopentanamine 19[22] Using General Procedure B



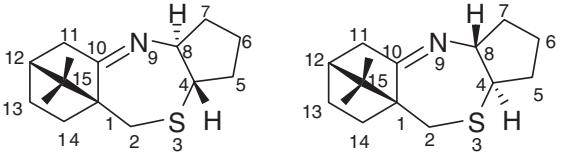
General procedure **B** was followed as reported for **18**. Aziridine **5** (1.01 g, 12.2 mmol), thiophenol (1.30 mL, 12.2 mmol), and BMIM chloride (4.69 g, 26.8 mmol) were stirred for 36 h at rt. The crude material was purified via flash chromatography (silica gel; petrol:EtOAc, 9:1, 2.5% NEt_3) to afford amino sulfide (±)-**19** as a colorless oil (1.44 g, 61%); R_f 0.08 (petrol:EtOAc, 9:1, 2.5% NEt_3). υ_{max} (neat)/cm^{-1} 3364 (N—H), 3056 (N—H), 2933 (C—H), 2351 (C—H), 1608 (C=C), 1450 (C=C); δ_H (400 MHz; $CDCl_3$) 7.34–7.29 (2H, m, ArCH), 7.22–7.15 (2H, m, ArCH), 7.13–7.08 (1H, m, ArCH), 3.09–2.94 (2H, m, NCH, SCH), 2.19–2.06 (1H, m, C^4HH), 2.00–1.90 (1H, m, C^2HH), 1.71–1.50 (3H, m, C^3H_2, C^4HH), 1.44–1.23 (3H, m, C^2HH, NH_2); δ_C (101 MHz, $CDCl_3$) 135.6 (C), 130.8 (CH), 128.6 (CH), 126.2 (CH), 58.6 (C5), 55.5 (C1), 33.7 (C2), 32.1 (C4), 21.5 (C3); *m/z* (%) (EI) 193.1 (43, M^+), 135.0 (7), 116.0 (5), 109.0 (14), 93.0 (6), 87.9 (10), 85.9 (67), 83.9 (100), 82.1 (56), 67.0 (30), 63.0 (23), 56.0 (86); HRMS (EI) $C_{11}H_{15}NS$ requires: 193.0925; found 193.0932.

Synthesis of (±)-*trans*-2-(Dodecylthio)cyclopentanamine 20 Using General Procedure B



General procedure **B** was followed as reported for **18**. Aziridine **5** (1.01 g, 12.2 mmol), 1-dodecanethiol (2.90 mL, 12.2 mmol), and BMIM chloride (4.69 g, 26.8 mmol) were stirred for 36 h at rt. The crude material was purified via flash chromatography (silica gel; petrol:EtOAc, 9:1, 2.5% NEt_3) to afford amino sulfide (±)-**20** as a yellow oil (1.05 g, 30%) as well as recovered starting material 1-dodecanethiol (1.48 g, 60%). Amino sulfide (±)-**20**; R_f 0.12 (petrol:EtOAc, 9:1, 2.5% NEt_3). υ_{max} (neat)/cm^{-1} 3364 (N—H), 3056 (N—H), 2933 (C—H), 2351 (C—H); δ_H (400 MHz; $CDCl_3$) 3.31–3.27 (1H, m, NH_2CH), 3.15–3.07 (1H, m, SCH), 2.61–2.46 (2H, m, SCH_2), 2.27–2.17 (1H, m, C^2HH), 2.13–2.05 (1H, m, C^4HH), 1.90 (2H, br s, NH_2), 1.83–1.61 (3H, m, C^3H_2, C^2HH), 1.60–1.41 (3H, m, C^4HH, CH_2), 1.21–0.99 (18H, br s, 9 × CH_2), 0.77 (3H, t, *J* 7.1, CH_3); δ_C (101 MHz, $CDCl_3$) 58.0 (C5), 48.9 (C1), 32.1 (C2), 31.9 (SCH_2), 31.7 (C4), 30.2 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 23.5 (CH_2), 22.7 (CH_2), 22.2 (C3), 14.1 (CH_3); *m/z* (%) (EI) 285.2 (17, M^+), 201.1 (10, $C_{12}H_{25}S^+$), 116.0 (73), 99.0 (19), 85.1 (52), 83.1 (84), 82.1 (71), 69.1 (16), 67.0 (34), 56.0 (100); HRMS (EI) $C_{17}H_{35}NS$ requires: 285.2490; Found 285.2484.

Synthesis of Imines 2a and 2b



Benzene (30 mL) was added to a mixture of amino ketone **3a:3b** (1.00 g, 3.74 mmol) in a round bottom flask equipped with a Dean–Stark apparatus. The reaction mixture was refluxed overnight. The reaction was allowed to cool to rt, and the benzene was carefully removed under reduced pressure to afford the crude material, which was carefully purified via flash chromatography (silica gel; CH_2Cl_2:MeOH 9:1) to afford **2a:2b** as a brown oil (0.65 g, 70%) in a 51:49 diastereomeric ratio, contaminated with a trace of starting material. R_f 0.45 (CH_2Cl_2:MeOH, 9:1); υ_{max} (neat)/cm^{-1} 2890 (C—H), 2850 (C—H), 1645 (C=N), 1055 (C—N); δ_H (400 MHz; $CDCl_3$); 2.88 (2H, d, *J* 15.1, 2 × SC*H*H), 2.85–2.81 (1H, m, SCH), 2.78 (2H, dt, *J* 10.4, 8.2, 2 × NCH), 2.69–2.64 (0.5H, m, SCH), 2.62–2.60 (0.5H, m, SCH), 2.44 (2H, d, *J* 15.1, 2 × SCH*H*), 2.35–2.21 (4H, m, 4 × C*H*H), 2.19–1.98 (6H, m, 6 × CH*H*,), 1.95 (2H, m, 2 × C*H*H), 1.91–1.83 (2H, m, 2 × C*H*H), 1.81–1.68 (4H, m, 4 × CH*H*), 1.67–1.46 (2H, m, 2 × C*H*H), 1.40–1.25 (6H, m, 4 × C*H*H, 2 × CH), 1.09 (3H, s, CH_3), 0.91 (3H, s, CH_3), 0.84 (6H, s, 2 × CH_3); δ_C (101 MHz, $CDCl_3$) 179.0 (C=N), 179.1 (C=N), 68.5 (C1), 68.4 (C1), 62.9 (C15), 62.8 (C15), 51.8 (SCH), 50.0 (SCH), 49.0 (NCH), 44.8 (NCH), 44.5 (C12), 43.3 (C12), 34.3 (SCH_2), 34.2 (SCH_2), 33.0 (CH_2), 31.5 (CH_2), 31.4 (CH_2), 30.4 (CH_2), 30.3 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 27.1 (CH_2), 27.0 (CH_2), 26.8 (CH_2), 22.0 (CH_2), 21.9 (CH_2), 21.1 (CH_3), 21.0 (CH_3), 19.2, (CH_3), 19.1 (CH_3); *m/z* (%) (EI^+) 249.2 (57, M^+), 141.1 (68), 100.0 (61), 67.0 (100); HRMS (EI) $C_{15}H_{23}NS$ requires 249.1551; found 249.1539.

Reduction of Imines 2a:2b to Amino Sulfides 1a:1b:1c:1d Using $NaBH_4$

$NaBH_4$ (0.83 g, 22 mmol) was added carefully in small proportions to a solution of imine **2a**:**2b** (51:49) (1.09 g, 4.37 mmol) in dry MeOH (15 mL), while stirring the reaction mixture, over a period of 30 minutes. The reaction was further stirred for 30 minutes at rt, and then water (20 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3 × 15 mL), and the combined organic layers were the extracted with 1N HCl (20 mL); the resulting aqueous layer was treated with sat. $NaHCO_3$ until basic (pH 8), then extracted with CH_2Cl_2 (3 × 15 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield **1a:1b:1c:1d** as mixture of four diastereoisomers. We were unable to determine the ratio of diastereoisomers from the crude NMR, as the spectrum was difficult and complex. The crude material was however purified via flash chromatography (silica gel; petrol:EtOAc, 99:1, 1% $NH_{3(aq)}$) to afford **1a** (0.06 g, 6%), **1b** (0.20 g, 18%), **1c** (0.19 g, 17%), and **1d** (0.04 g, 4%). The assigned stereochemistries of the diastereoisomers are based on COSY, HMQC, HMBC, NOE spectra and X-ray structures of derivatives of **1a** and **1b** (see below).

Diastereoisomer 1a (0.06 g, 6%); R_f 0.58 (petrol:EtOAc, 9:1, 2.5% NEt_3); υ_{max} (neat)/cm^{-1} 3340 (N−H), 2890 (C−H), 2850 (C−H), 1053 (C−N); δ_H (400 MHz; $CDCl_3$); 3.02 (1H, dd, *J* 9.0, 6.1, $C^{10}H$), 2.87 (1H, d, *J* 14.4, SC*H*H), 2.67 (1H, ddd, *J* 11.8, 9.6, 7.1, C^8H), 2.51 (1H, d, *J* 14.4, SCH*H*), 2.47 (1H, ddd, *J* 11.8, 9.5, 7.1, C^4H), 1.96–1.65 (7H, m, C^5HH, C^6HH, C^7HH, C^6HH, $C^{12}H$, $C^{11}HH$, $C^{13}HH$), 1.60–1.53 (1H, m, $C^{14}HH$), 1.47–1.32 (4H, m, C^5HH, C^7HH, $C^{11}HH$, $C^{14}HH$), 1.18–1.07 (2H, m, $C^{13}HH$, NH), 1.06 (3H, s, CH_3), 0.81 (3H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 74.3 (C8), 68.5 (C10), 57.5 (C4), 55.8 (C15), 47.4 (C1), 45.7 (C12), 39.5 (C11), 34.7 (C2), 34.4 (C14), 31.0 (C7), 29.0 (C5), 26.8 (C13), 20.8 (CH_3), 20.7 (C6), 19.8 (CH_3); *m/z* (%) (EI^+) 251.2 (32, M^+), 141.1 (18), 128.1 (100), 100.1 (17), 67.1 (26); HRMS (EI^+) $C_{15}H_{25}NS$ requires: 251.1708; found 251.1707; $[\alpha]_D^{20}$ +16.0 (*c* 1.00, $CHCl_3$); Anal. Calc'd for $C_{15}H_{25}NS$: C, 71.7; H, 10.0; N, 5.6; found: C, 71.9; H, 10.1; N, 5.4.

Diastereoisomer 1b (0.20 g, 18%); R_f 0.21 (petrol:EtOAc, 9:1, 2.5% NEt_3); υ_{max} (neat)/cm^{-1} 3340 (N−H), 2890 (C−H), 2850 (C−H), 1055 (C−N); δ_H (400 MHz; $CDCl_3$); 3.39 (1H, ddd, *J* 10.6, 4.0, 2.2, $C^{10}H$), 3.21 (1H, dt, *J* 10.4, 7.3, C^8H), 2.76 (1H, dt, *J* 10.4, 8.6, C^4H), 2.60 (1H, d, *J* 13.9, SC^2HH), 2.33 (1H, d, *J* 13.9, SC^2HH), 2.35–2.26 (1H, m, $C^{11}HH$), 2.20–1.86 (4H, m, C^5HH, C^7HH, $C^{14}HH$, NH), 1.78–1.59 (3H, m, C^6HH, $C^{13}HH$, C^6HH), 1.56 (1H, t, *J* 4.6, $C^{12}H$), 1.49–1.27 (3H, m, C^5HH, C^7HH, $C^{14}HH$), 1.18 (1H, ddd, *J* 12.9, 8.6, 4.6, $C^{13}HH$), 0.87 (3H, s, CH_3), 0.85 (3H, s, CH_3), 0.72 (1H, 13.2, 4.0, $C^{11}HH$); δ_C (101 MHz, $CDCl_3$) 68.1 (C8) 57.9 (C10), 55.8 (C15 or C1), 50.7 (C1 or C15), 48.2 (C4), 44.6 (C12), 39.7 (C11), 34.8 (C2), 34.7 (C14), 30.7 (C7), 27.9 (C13), 25.7 (C5), 21.3 (C6), 20.6 (CH_3), 18.6 (CH_3); *m/z* (%) (EI^+) 251.2 (50, M^+), 141.1 (33), 128.1 (100), 100.1 (25), 67.1 (37); HRMS (EI^+) $C_{15}H_{25}NS$ requires: 251.1708; found: 251.1706; $[\alpha]_D^{24}$ +39.3 (*c* 0.53, $CHCl_3$); Anal. Calc'd for $C_{15}H_{25}NS$: C, 71.7; H, 10.0; N, 5.6; found: C, 71.6; H, 9.9; N, 5.4.

Diastereoisomer 1c (0.19 g, 17%); R_f 0.47 (petrol: EtOAc, 9:1, 2.5% NEt_3); υ_{max} (neat)/cm^{-1} 3341 (N−H), 2889 (C−H), 2853 (C−H), 1055 (C−N); δ_H (400 MHz; $CDCl_3$); 3.54 (1H, dt, *J* 9.7, 7.3, C^8H), 3.33 (1H, dt, *J* 9.7, 7.8, C^4H), 3.31 (1H, d, *J* 13.9, SC*H*H), 3.21 (1H, dd, *J* 8.6, 5.4, $C^{10}H$), 2.18 (1H, d, *J* 13.9, SCH*H*), 2.11–1.99 (2H, m, C^5HH, C^7HH), 1.77–1.64 (5H, m, C^6HH, C^6HH, $C^{12}H$, $C^{11}HH$, $C^{13}HH$), 1.58–1.17 (6H, m, $C^{11}HH$, C^5HH, C^7HH, $C^{14}HH$, $C^{14}HH$, NH), 1.14–1.02 (1H, m, $C^{13}HH$), 1.04 (3H, s, CH_3), 0.81 (3H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 62.2 (C8), 61.9 (C10), 55.1 (C15), 47.4 (C1), 45.4 (C12),

42.8 (C4), 38.8 (C11), 35.5 (C5), 33.9 (C7), 33.8 (C14), 29.9 (SCHH), 26.5 (C13), 22.3 (C6), 21.1 (CH_3), 19.9 (CH_3); *m/z* (%) (EI^+) 251.2 (31, M^+), 141.1 (19), 128.1 (100), 100.0 (21), 67.1 (33); HRMS (EI^+) $C_{15}H_{25}NS$ requires: 251.1708; found 251.1706; $[\alpha]_D^{24}$ +43.0 (*c* 1.00, $CHCl_3$); Anal. Calc'd for $C_{15}H_{25}NS$: C, 71.7; H, 10.0; N, 5.6; found: C, 71.6; H, 10.0; N, 5.4.

Diastereoisomer 1d (0.04 g, 4%); R_f 0.28 (petrol: EtOAc, 9:1, 2.5% NEt_3); υ_{max} (neat)/cm^{-1} 3340 (N—H), 2892 (C—H), 2852 (C—H), 1053 (C—N); δ_H (400 MHz; $CDCl_3$); 3.32 (1H, ddd, *J* 10.8, 4.9, 2.2, $C^{10}H$), 2.97–2.87 (2H, m, C^8H, C^4H), 2.92 (1H, d, *J* 13.4, SC*H*H), 2.48 (1H, d, *J* 13.4, SC*H*H), 2.29 (1H, dddd, *J* 12.9, 10.8, 4.6, 3.2, $C^{11}HH$), 2.10–1.94 (3H, m, C^5HH, C^7HH, $C^{14}HH$,), 1.79–1.38 (7H, m, C^6HH, C^6HH, C^5HH, C^7HH, $C^{14}HH$), 1.60 (1H, t, *J* $C^{12}H$), 1.21–1.14 (1H, m, $C^{13}HH$), 0.93 (3H, s, CH_3), 0.86 (3H, s, CH_3), 0.68 (1H, dd, *J* 12.9, 4.9, $C^{11}HH$); δ_C (101 MHz, $CDCl_3$) 68.7 (C8), 64.4 (C10), 55.1 (C15), 52.7 (C4), 50.7 (C1), 45.3 (C12), 38.1 (C11), 33.7 (C5), 33.4 (C7), 32.2 (C2), 28.5 (C13), 27.1 (C14), 22.1 (C6), 20.6 (CH_3), 18.7 (CH_3); *m/z* (%) (EI^+) 251.2 (24, M^+), 141.1 (13), 128.1 (100), 100.0 (13), 67.1 (23); HRMS (EI^+) $C_{15}H_{25}NS$ requires 251.1708; found: 251.1706; $[\alpha]_D^{24}$ +87.0 (*c* 1.00, $CHCl_3$);

Preparation of Sulfonium Salt 11

A solution of sodium tetrafluoroborate (0.220 g, 1.99 mmol) in water (2.5 mL) was added to a solution of amino sulfide **1b** (100 mg, 0.39 mmol) and benzyl bromide (0.24 mL, 1.99 mmol) in CH_2Cl_2 (2.5 mL). The biphasic mixture was stirred vigorously at rt overnight. Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL); the combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the crude sulfonium salt **11** as a white solid. The crude product was dissolved in the minimum amount of CH_2Cl_2 (~2 mL), then ether (~3–4 mL) was added until the solution started to become cloudy. After standing for ~30 min, the solution was filtered to give sulfonium salt **11** as colorless crystals (171 mg, 83%) and as a single diastereoisomer; mp 189–190°C (CH_2Cl_2/Et_2O); R_f 0.33 (CH_2Cl_2:MeOH, 9:1); υ_{max} (neat)/cm^{-1} 2890 (C—H), 2850 (C—H), 1053 (C—N), 1630 (C=C), 1625 (C=C); δ_H (400 MHz; $CDCl_3$); 7.49–7.40 (2H, m, 2 × ArCH), 7.35–7.25 (3H, m, 3 × ArCH), 7.25–7.10 (5H, m, 5 × ArCH), 4.72 (1H, d, *J* 13.0, SC*H*HPh), 4.64 (1H, d, *J* 13.0, SCH*H*Ph), 4.04 (1H, d, *J* 16.1, NC*H*HPh), 4.01 (1H, dt, *J* 10.0, 7.7, C^8H), 3.84 (1H, d, *J* 16.1, NCH*H*Ph), 3.70–3.61 (1H, m, $C^{10}H$), 3.48 (1H, dt, *J* 10.0, 8.2, C^4H), 3.44 (1H, d, *J* 12.4, SC^2HH), 2.86 (1H, d, *J* 12.4, SC^2HH), 2.16–2.03 (3H, m, $C^{11}HH$, $C^{13}HH$, C^7HH), 1.79–1.66 (3H, m, C^5HH, C^6HH, $C^{14}HH$), 1.63 (1H, t, *J* 4.6, $C^{12}H$), 1.63–1.46 (2H, m, $C^{13}HH$, C^6HH) 1.44–1.17 (4H, m, C^5HH, C^7HH, $C^{11}HH$, $C^{14}HH$), 1.01 (3H, s, CH_3), 0.78 (3H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 141 (2 × ArC), 130.5 (ArCH), 129.8 (ArCH), 129.5 (2 × ArCH), 128.3 (ArCH), 128.0 (2 × ArCH), 127.1 (ArCH), 126.8 (2 × ArCH), 68.6 (C8), 60.1 (C10), 57.2 (C4), 55.2 (NCH_2), 53.1 (C15), 52.4 (C1), 45.1 (C2), 44.8 (SCH_2Ph), 44.7 (C12), 34.1 (C11), 28.2 (C14), 27.9 (C7), 26.9 (C13), 25.6 (C5), 21.7 (C6), 19.8 (CH_3), 18.6 (CH_3); HRMS (ESI^+) [$C_{29}H_{38}NS^+$] ([M–BF_4^-]$^+$) requires: 432.2719; found: 432.2721; $[\alpha]_D^{24}$ +107 (*c* 0.23, $CHCl_3$).

Preparation of Sulfonium Salt 12

A solution of sodium tetrafluoroborate (106 mg, 0.97 mmol) in water (1 mL) was added to a solution of the amino sulfide **1a** (48.6 mg, 0.193 mmol) and benzyl bromide

(0.12 mL, 0.97 mmol) in CH_2Cl_2 (1 mL). The biphasic mixture was stirred vigorously at rt overnight. Water (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 5 mL); the combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the crude sulfonium salt **12** as a white solid. The crude material was dissolved in the minimum amount of CH_2Cl_2 (∼2 mL), and then ether (∼3–4 mL) was added until the solution started to become cloudy. After standing for ∼30 min, the solution was filtered to give sulfonium salt **12** as a colorless crystalline solid (66 mg, 80%) as a single diastereoisomer; mp 195–200°C (CH_2Cl_2/Et_2O); R_f 0.30 (CH_2Cl_2:MeOH, 9:1); υ_{max} (neat)/cm^{-1} 3324 (N−H), 2890 (C−H), 2850 (C−H), 1053 (C−N), 1630 (C=C), 1625 (C=C); δ_H (400 MHz; $CDCl_3$); 7.49–7.43 (2H, m, 2 × ArCH), 7.37–7.28 (3H, m, 3 × ArCH), 4.70 (1H, d, *J* 12.9, SC*H*HPh), 4.64 (1H, d, *J* 12.9, SCH*H*Ph), 3.76 (1H, d, *J* 13.2, C*H*HS), 3.48 (1H, dt, *J* 10.7, 7.1, C^8H), 2.99 (1H, dt, *J* 10.7, 7.1, C^4H), 2.93 (1H, d, *J* 13.2, CH*H*S), 2.72 (1H, dd, *J* 9.0, 5.6, C^{10}H), 2.19–2.13 (1H, m, C^7*H*H), 1.95–1.90 (1H, m, C^5*H*H), 1.83–1.74 (3H, m, C^5*H*H, C^6*H*H, C^{11}H*H*), 1.70–1.44 (5H, m, C^6H*H*, C^7H*H*, C^{11}H*H,* C^{12}H, C^{14}*H*H), 1.37–1.23 (2H, m, C^{13}*H*H, C^{14}H*H*), 1.18 (1H, br s, NH), 1.09–0.99 (1H, m, C^{13}H*H*), 1.01 (3H, s, CH_3), 0.71 (3H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 130.6 (2 × ArCH), 129.9 (ArCH), 129.5 (2 × ArCH), 127.6 (ArC), 69.8 (C8), 69.2 (C10), 64.2 (C4), 51.4 (C15 or C1), 49.6 (C1 or C15), 45.9 (SCH_2Ph), 45.1 (C12), 44.4 (C2), 39.5 (C11), 33.9 (C14), 29.9 (C7), 26.7 (C13), 26.6 (C5), 20.2 (C6), 20.1 (CH_3), 19.0 (CH_3); HRMS (ESI^+) [$C_{22}H_{32}NS^+$] ([M–BF_4^-) requires 342.2250; found 342.2249;

Asymmetric Epoxidation of Benzaldehyde with 11

Freshly distilled benzaldehyde (12 mg, 0.12 mmol) and powdered KOH (*care hygroscopic!)* (13 mg, 0.23 mmol) were added to a solution of sulfonium salt (60 mg, 0.12 mmol) in MeCN/H_2O (9:1; 5 mL) at 0°C. The reaction mixture (not homogeneous) was stirred at 0°C for 3 h. The solvent was removed under reduced pressure, and then the resultant residue was dissolved in Et_2O (12 mL), and the amino sulfide extracted with 1N HCl (3 × 3 mL). The organic layer was washed with brine (10 mL) and dried over $MgSO_4$ to give the crude epoxide, which was purified via flash chromatography (silica gel; petrol:EtOAc, 30:1) to afford the epoxide as a white solid (20 mg, 87%), mp 62–68°C (petrol) [lit., 65–66°C (petrol)]; *trans*:*cis* 90:10; er (*S,S*):(*R,R*) 15:85. The enantiomers were separated on a Chiralcel® OD (HPLC) column using hexane:i-PrOH as the eluent (98:2)[4j], 1 mL min^{-1}, retention times of *trans*-stilbene oxide; (*S,S*) major: 8.5 min, (*R,R*) minor: 16.0 min); R_f 0.40 (petrol:EtOAc, 30:1); υ_{max} (neat)/cm^{-1} 2970 (C−H), 2920 (C−H), 1606 (C=C), 892 (C−O), 791 (C−O); δ_H (400 MHz; $CDCl_3$); *trans*-isomer 7.35–7.22 (10H, m, ArH), 3.85 (2H, s, 2 × CHO); *cis*-isomer (not isolated) 7.10–7.07 (10H, m, ArH), 4.34 (2H, s, 2 × CHO). δ_C (101 MHz, $CDCl_3$); *trans*-isomer 137.2 (C), 128.6 (CH), 128.4 (ArCH), 125.6 (CH), 62.9 (OCH); *cis*-isomer (not isolated) 137.4 (C), 127.8 (CH), 127.5 (CH), 126.9 (CH), 59.8 (OCH). Spectra and HPLC data were consistent with the literature.[4j,23]

The aqueous layer was treated with 3N KOH until pH ∼ 7–8, then extracted with Et_2O (3 × 5 mL); the organic layers was washed with brine (10 mL) and dried over $MgSO_4$. After removal of solvent, the amino sulfide **13** was recovered as a colorless oil (38 mg, 98%). R_f 0.45 (petrol:EtOAc, 9:1); υ_{max} (neat)/cm^{-1} 2890 (C−H), 2850 (C−H), 1053 (C−N), 1630 (C=C), 1625 (C=C); δ_H (400 MHz; $CDCl_3$); 7.32–7.08 (5H, m, ArC-H), 3.96 (1H, d, *J* 16.7, NC*H*HPh), 3.79 (1H, ddd, *J* 10.7, 4.6, 2.0, C^{10}H), 3.68 (1H, d, *J* 16.7, NCH*H*Ph), 3.23 (1H, dt, *J* 10.2, 7.3, C^8H), 2.84 (1H, dt, *J* 10.2, 8.2, C^4H), 2.62 (1H, d, *J* 14.9, SC*H*H),

2.47 (1H, d, *J* 14.9, SCH*H*), 2.30–2.18 (1H, m, C^{11}*H*H), 2.08–1.88 (2H, m, C^{5}*H*H, C^{7}*H*H), 1.78–1.63 (1H, m, C^{14}*H*H), 1.57 (1H, t, *J* 4.6, C^{12}H), 1.50–1.11 (7H, m. C^{5}H*H*, C^{6}*H*H, C^{7}H*H*, C^{6}H*H*, C^{13}*H*H, C^{14}H*H*, C^{13}H*H*), 1.04 (1H, dd, *J* 12.5, 4.6, C^{11}H*H*), 0.92 (3H, s, CH_3), 0.81 (3H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 144.1 (ArC), 128.1 (2 ×ArCH), 127.0 (2 ×ArCH), 126.2 (ArCH), 69.6 (C8), 63.9 (C10), 54.3 (NCH_2Ph), 53.3 (C15 or C1), 50.1 (C1 or C15), 45.5 (C4), 42.2 (C12), 35.8 (C11), 32.7 (SCH_2), 31.4 (C14), 29.9 (C7), 29.8 (C5), 28.7 (C13), 21.7 (C6), 20.2 (CH_3), 19.0 (CH_3); *m/z* (%) (EI^+) 341.1 (12, M^+), 242.1 (54), 218.1 (78), 134.1 (27), 91.0 (100), 83.9 (27), 67.0 (29); HRMS (EI) $C_{22}H_{31}NS$ requires: 341.2177; found 341.2172; $[\alpha]_D^{24}$ +33.0 (*c* 1.0, $CHCl_3$).

CCDC 775878 (**11**) and 775879 (**12**) contain the supplementary crystallographic data for this article. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

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