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Synthesis of Isothiocineole and Application in Multi-gram Scale Sulfur Ylide-mediated Asymmetric Epoxidation and Aziridination.

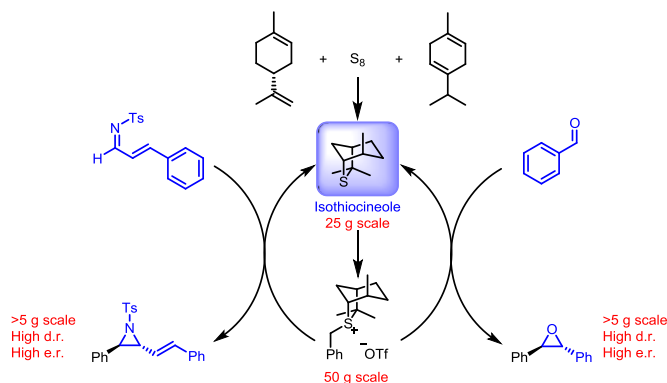
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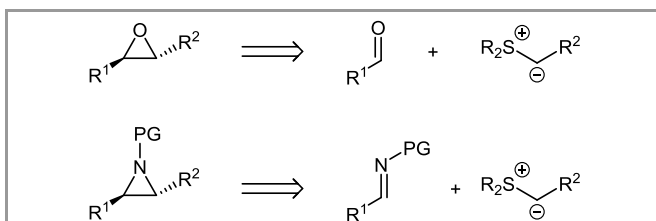
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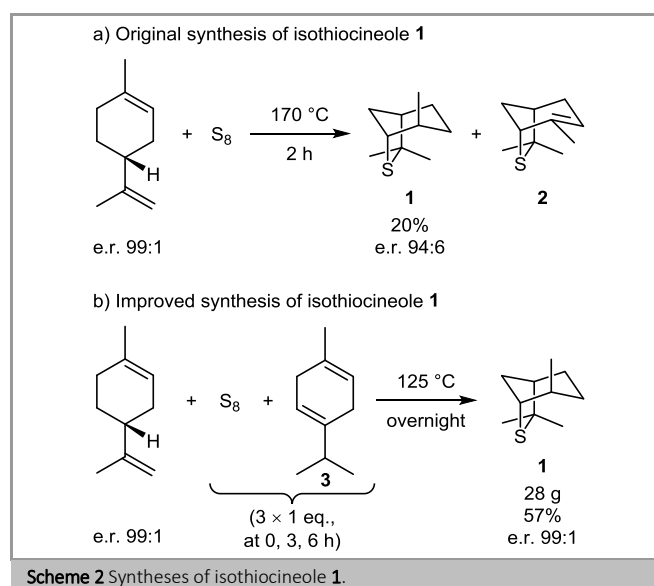
Abstract The synthesis of the chiral sulfide isothiocieneole from limonene and elemental sulfur on multi-gram scale and its alkylation to make >50 g of the corresponding benzylium salt are described. The application of this salt to the sulfur ylide-mediated asymmetric epoxidation of aldehydes and the asymmetric aziridination of imines on a >5 g scale is demonstrated.

Key words Sulfur Ylide, Asymmetric Epoxidation, Asymmetric Aziridination, Chiral Sulfide

The use of sulfur ylides to synthesize epoxides and aziridines represents a valuable strategic disconnection wherein both a C-C bond and a C-Heteroatom bond are made in a single step (Scheme 1).¹ It provides an alternative route to these valuable synthetic intermediates which is complementary to alkene oxidation processes.² We have shown that isothiocieneole **1** is an effective chiral sulfide for use in asymmetric epoxidations and aziridinations.^{2,3} We have demonstrated a wide reaction scope, and delineated the factors that affect enantioselectivity and diastereoselectivity. This enables isothiocieneole **1** to be employed with confidence in a synthetic plan. Furthermore it can be made in one step from sulfur and limonene, and is now commercially available. Indeed since our first publication, several other groups have made use of this sulfide in epoxidations, aziridinations, and other reactions that required a chiral sulfide.⁴



Scheme 1 The sulfur ylide disconnection for epoxides and aziridines.



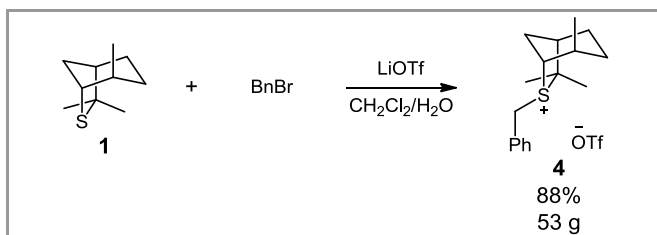
Scheme 2 Syntheses of isothiocieneole **1**.

Isothiocieneole **1** had previously been made in the 1930s and 1950s using simply limonene and sulfur (Scheme 2).^{5,6} However, under the reported conditions a degree of racemization occurred leading to sulfide that was less enantiopure than the limonene precursor. Under these original conditions the limonene acts as a source of hydrogen as well as a source of the carbon skeleton of **1**. Sulfide **2** was also formed as an undesired by-product and was quite difficult to separate from **1**. We found that readily available γ -terpinene **3** acts as a source of hydrogen atoms enabling milder conditions to be used which gave no loss in enantiospecificity, and no sulfide **2** was generated. However the γ -terpinene is also consumed by side-reactions and thus several equivalents are required. Reaction monitoring led us to discover that adding aliquots of γ -terpinene and sulfur during the reaction led to higher yields of isothiocieneole **1**. The γ -

terpinene is converted into *p*-cymene by the reaction and can be separated from the product by distillation. We had found that 1,4-cyclohexadiene also can fulfil this role but it is more expensive and we wanted to avoid the production of stoichiometric quantities of benzene. Limonene is readily available in both enantiomeric forms at low cost. The *S*-enantiomer is normally available as a 90:10 mixture of enantiomers. (+)-isothiocineole with e.r. 99:1 can be obtained through low temperature recrystallization of 90:10 mixtures from pentane.³

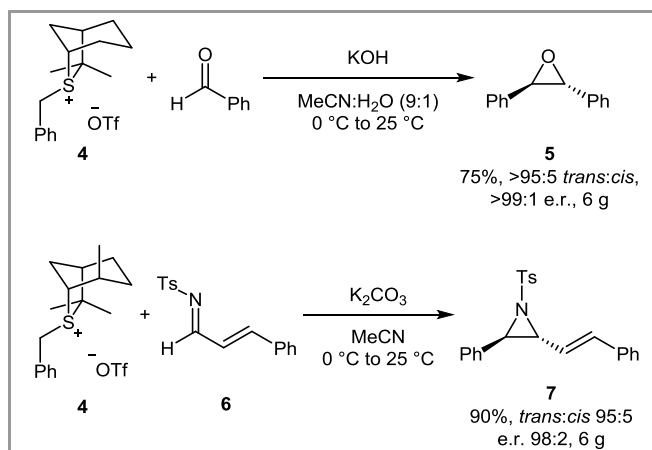
The procedure we describe allows the sulfide to be isolated in pure form by vigreux distillation. The complete separation from *p*-cymene can be difficult, however in most instances the presence of small amounts of *p*-cymene doesn't interfere with subsequent reactions. If the sulfide is to be converted to a sulfonium salt as is described here then it is easier to separate the *p*-cymene after salt formation.

The subsequent salt formation reaction is quite robust and high yielding (Scheme 3). We noted that the tetrafluoroborate analogue of **4** showed poor solubility and hence the triflate was favored. However, for other salts the tetrafluoroborate analogue can be made directly from the corresponding alcohol using HBF₄ in Et₂O and those salts work well in the epoxidation and aziridination reactions – this can be more cost effective in some cases. A non-nucleophilic counterion is favored to improve the stability of the salt.



Scheme 3 Alkylation of sulfide **1** to form sulfonium salt **4**.

We describe our standard procedures for the synthesis of epoxides from aryl aldehydes, and for the synthesis of tosyl aziridines (Scheme 4). In all cases excellent enantioselectivity is achieved. Although we have found that the sulfide is not suitable for use under catalytic conditions, we note that the sulfide is inexpensive, and can be recovered in moderate-to-good yields in most cases so there is less impetus to develop a catalytic method. Finally, we note that the diastereoselectivity obtained in the aziridination shown in Scheme 4 (95:5) is our best example, but diastereomeric ratios generally ranged from 3:1 to 9:1 in aziridinations. We have shown that tosyl, P(O)Ph₂ and BOC-protected imines are suitable substrates.^{2,3,7} We note that chromatography on large scale reactions with the sulfide can prove troublesome (solvent mixtures which seemed appropriate by TLC did not lead to good separation on flash columns in some cases), so it is generally more convenient to remove remaining aldehyde or sulfide by Kugelrohr distillation where possible prior to column chromatography.



Scheme 4 Asymmetric epoxidation of aldehydes and asymmetric aziridination of imines using sulfonium salt **4**.

In summary, herein we have described the scalable synthesis of isothiocineole **1**, and its application to the asymmetric epoxidation of aldehydes and aziridination of imines using simple procedures. We have previously provided a clear rationale for why the sulfide succeeds in providing high enantioselectivity and diastereoselectivity, and described the wide scope for these reactions.^{2,3} We hope the availability of this information will increase the use of the sulfur ylide disconnection in asymmetric synthesis.

Reactions were monitored using analytical thin layer chromatography, carried out using aluminum-backed silica plates (60 F₂₅₄) and the eluents stated; visualization was accomplished using UV light (254 nm) and a stain of KMnO₄ (3 g) in 1% NaOH solution (300 mL). Flash column chromatography was performed using silica gel [Davisil, 230–400 mesh (40–63 μm)]. Products were concentrated *in vacuo* using both a Büchi rotary evaporator (bath temperatures up to 50 °C) and a high vacuum line at room temperature. Mass spectra were recorded by the University College Dublin, School of Chemistry mass spectrometry service. High-performance liquid chromatography was performed on an Agilent Technologies 1260 series instrument equipped with a 6 column-switching device, auto sampler and multiple wavelength detector. ¹H NMR, ¹³C NMR spectra were recorded in CDCl₃ in 300 MHz or 400 MHz spectrometers. For quantitative NMR spectroscopy, the ¹H-NMR sample was made up in CDCl₃ and submitted with a 25 s delay at pulse angle of 45°.

Benzaldehyde (≥99%, 25 mL) obtained from Sigma-Aldrich was washed with 10% Na₂CO₃ solution (2 × 25 mL) until no more evolution of CO₂ was observed. It was then washed with saturated Na₂SO₃ solution followed by H₂O (25 mL) then dried with MgSO₄ for 15 minutes before distilling under nitrogen atmosphere at reduced pressure.⁸ Potassium hydroxide (>85%) was obtained from Fischer Scientific. The KOH was first weighed as pellets then ground using a pestle and mortar before immediately weighing the required amount using weighing paper and then transferring this to the reaction flask. If left for too long in atmospheric conditions the ground KOH absorbs water. Imine **6** was synthesized from benzaldehyde and tosylamide by the method of Senanayake⁹ using B(OCH₂CF₃)₃ as catalyst (which is commercially available) made by the method of Sheppard.¹⁰

(*R*)-Isothiocineole has a pungent odour. Containment is necessary. In addition to working in a well ventilated fumehood, we recommend wearing gloves and transferring these to a bleach bath (see below) in the fumehood before taking hands out of the fumehood. Cleaning glassware and avoiding stench: All glassware which has been in contact with isothiocineole will have a pungent odor and must be treated in the following way. Preparation of microemulsion **6** (water 29% w/w, *c*-hexane 11.9% w/w and *iso*-propanol 58.5% w/w) in a slight

modification to the method of Menger and Elrington¹¹ to which bleach was added and all glassware submerged in this cleaning system for 12 h.

Synthesis of (1*R*,4*R*,5*R*)-Isothiocineole (1).

[CAS Reg. No. 5718-75-2:]

Elemental sulfur (9.3 g, 0.29 mol, 1 equiv.) was placed in a 500 mL three-necked round bottom flask equipped with a magnetic stirring bar [5 cm, oval], a reflux condenser in the right hand neck (16 cm) with a gas adapter in the top, a thermometer (± 2 °C) and thermometer adaptor in the left neck (to note the internal temperature) and a glass stopper in the center neck (Figure 1). All joints were lightly greased with silicone grease. (*R*)-(+)-Limonene **1** (47 mL, 0.29 mol, 1 equiv., 99:1 e.r.) and γ -terpinene (47 mL, 0.29 mol, 1 equiv.) were added under an atmosphere of air. After the addition of all the reagents the vessel was quickly evacuated and backfilled with nitrogen three times (turning to vacuum ~ 2 seconds then immediately back to nitrogen). The reaction vessel was placed in a pre-heated oil bath at 130 °C to achieve an internal temperature of 125 °C after 15 minutes under an atmosphere of nitrogen. After 3 h at 125 °C, elemental sulfur (9.3 g, 0.29 mol, 1.0 equiv.) was added to the reaction mixture *via* powder funnel followed by γ -terpinene (47 mL, 0.29 mol, 1.0 equiv.) *via* syringe through the center neck of the flask with a slight positive flow of nitrogen. The mixture was then allowed to stir at 125 °C for another 3 h (total time 6 h) before adding more elemental sulfur (9.3 g, 0.29 mol, 1.0 equiv.) to the reaction mixture *via* powder funnel followed by γ -terpinene (47 mL, 0.29 mol, 1.0 equiv.) *via* syringe through the center neck of the flask with a slight positive flow of nitrogen. The reaction was then left overnight at 125 °C under a nitrogen atmosphere (total time 24 h). The yield of isothiocineole present in the crude reaction mixture was determined by comparison to an internal standard to be 81%.

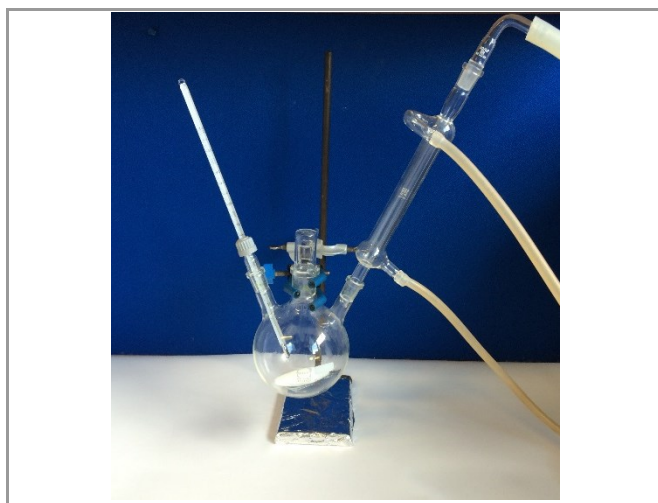


Figure 1 Reaction set-up for the synthesis of isothiocineole 1.

The reaction was then cooled to room temperature, disconnected from the nitrogen atmosphere and the flask was fitted for a vacuum distillation (Figure 2). The condenser in the right-hand neck was replaced with a glass stopper and the center neck was fitted with a still-head connected to a quick-fit thermometer (± 2 °C) and a condenser (16 cm). The condenser was fitted with a three-neck pig-type receiver with 3 receiver flasks (250 mL, 50 mL, 250 mL). The pig-type receiver was connected to an in-line manometer using a three-way tap which was then connected to a vacuum cold trap. This cold trap was then connected to a Schlenk line which contained another vacuum cold trap before connecting to a vacuum pump. All joints were lightly greased with silicone grease and the distillation apparatus was gradually placed under vacuum using the three-way tap to avoid bumping and the traps were immediately cooled with liquid nitrogen.



Figure 2 Crude reaction material and set-up for first distillation.

At room temperature the volatile by-products were distilled into the first trap. Once the reaction mixture stopped bubbling and the vacuum had stabilized (0.70 mm Hg manometer reading) the still pot was covered with aluminium foil. The oil bath was then heated to 40 °C (approximately 5 °C per 5 min) and a fraction was collected (24–26 °C/0.70 mm Hg) in receiving flask 1 (250 mL). The vacuum tended to slowly deteriorate due to *p*-cymene collecting in the first trap. The distillation can be stopped to empty the trap and then resumed, allowing time for the vacuum to stabilize. Once *p*-cymene has been collected and the rate of *p*-cymene distillation slowed, the oil bath was heated to 80 °C and a second fraction was collected in receiving flask 3 (250 mL) which contains (*R*)-isothiocineole and *p*-cymene (44–46 °C/0.67 mm Hg). The temperature of the oil bath was raised to 110 °C (at 0.60 mm Hg) in order to remove the remaining isothiocineole from the undistilled crude material. Attempts to distil *p*-cymene from (*R*)-isothiocineole in the first distillation using fractionating columns were unsuccessful. Performing a simple distillation to separate the majority of the *p*-cymene from (*R*)-isothiocineole followed by a Vigreux distillation was the most efficient method to purify (*R*)-isothiocineole in our hands.



Figure 3 Distillate from 1st distillation and set-up for second distillation of isothiocineole 1.

The third receiving flask containing isothiocineole and *p*-cymene (35.5 g) which was a clear faint yellow liquid was set up for a similar styled distillation however with a Vigreux fractionating column (Figure 3). The flask was equipped with a stir bar [3 cm, oval] and a Vigreux column (30 cm) with a vacuum jacket. A still-head was used to connect the column, quick-fit thermometer (± 2 °C) and condenser (16 cm) together. The condenser was fitted with a three-neck pig-type receiver with 3 pre-weighed receiver flasks (250 mL, 50 mL, 250 mL). The pig-type receiver was connected to an in-line manometer using a three-way tap which was then connected to a vacuum cold trap. This cold trap was then connected to a Schlenk line which contained another vacuum cold trap which was then connected to a vacuum pump. All joints were lightly greased with silicone grease. The still pot and column were wrapped in aluminium foil for a more efficient distillation. The temperature of the oil bath was raised to 60 °C over 1 h and at 60 °C *p*-cymene was collected in the first

flask (250 mL) (24–30 °C/0.57 mm Hg). As the rate of *p*-cymene distillation slowed the vacuum improved causing a mixture to slowly distil (34 °C/0.48 mm Hg). The temperature was increased to 65 °C and a second fraction was collected in receiving flask 2 (50 mL) which contained a mixture of (*R*)-isothiocineole and *p*-cymene (36 °C/0.45 mm Hg, approximately 2 mL). After 15 minutes at this temperature the third fraction was collected, which contained (*R*)-isothiocineole. The temperature of the oil bath was raised to 85 °C in order to distill the remaining isothiocineole (35–38 °C/0.45 mm Hg, approximately 25 mL).⁵ This fraction containing (*R*)-isothiocineole was obtained as a clear colorless oil 57% (28.2 g) 99:1 e.r. $[\alpha]_D^{25} -69.5$ ($c = 1.00$, CHCl₃) [Lit.² $[\alpha]_D^{25} -69.1$ (neat)].

IR (cm⁻¹, neat): 2948, 2922, 1455, 1384, 1364, 1298, 1197, 1138, 1088, 1044, 980.

¹H NMR (400 MHz, CDCl₃) δ : 3.32–3.30 (1H, m, C¹H), 2.38–2.26 (1H, m, C³HH), 2.13–2.00 (2H, m, C⁶H₂), 1.94–1.85 (1H, m, C²H), 1.85–1.80 (1H, m, C⁵H), 1.68–1.43 (2H, m, C⁴H₂), 1.51 (3H, s, CH₃), 1.39 (3H, s, CH₃), 1.19–1.12 (1H, m, C³HH), 1.07 (3H, d, $J = 7.4$ Hz, C¹⁰H₃).

¹³C NMR (101 MHz, CDCl₃) δ : 53.0 (C1), 52.6 (C7), 47.4 (C5), 35.5 (C2), 35.0 (CH₃), 34.5 (C6), 25.5 (CH₃), 24.4 (C3), 23.9 (C4), 18.8 (C10).

Anal. calcd. for C₁₀H₁₈S: C, 70.52; H, 10.65; S, 18.82; found: C, 70.42; H, 10.42; S, 19.2.⁶

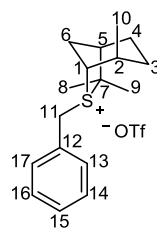
Chiral Phase GC: Supelco AlphaDex 120 column (30 m length \times 0.25 mm diameter \times 25 μ m film thickness). Inlet Temperature = 250 °C, Detector temperature = 250 °C. Oven conditions: T= 100 °C hold for 52 min then ramp (50 °C per min) until 150 °C hold for 3 min. Total runtime: 56 min. He carrier gas at 8.5 mL/min, 60 kPa pressure. Under these conditions, *R*-enantiomer (major) $R_t = 48.7$ and *S*-enantiomer (minor) $R_t = 49.6$.

(1*R*,4*R*,5*R*,6*R*)-6-Benzyl-4,7,7-trimethyl-6-thiabiocyclo[3.2.1]octan-6-ium trifluoromethanesulfonate (4).

[CAS Reg. No.: 1207974-86-4]

Sulfide **1** (25 g, 0.15 mol, 1 equiv.) was dissolved in dichloromethane (60 mL) in a 1-necked 500 mL round bottom flask equipped with a magnetic stirrer bar [5 cm, oval]. Benzyl bromide (35 mL, 0.29 mmol, 2 equiv.) was added using a syringe followed by a solution of lithium triflate (68 g, 0.44 mol, 3 equiv.) in deionized water (50 mL) *via* funnel followed by washings of deionized water (2 \times 20 mL). The resulting biphasic mixture was stirred at 25 °C in an oil bath for 29 h or until consumption of sulfide **1** was observed by TLC (cyclohexane: ethyl acetate, 99:1); isothiocineole $R_f = 0.85$, benzyl bromide $R_f = 0.69$ (0.18, benzyl bromide-decomposition product visible), sulfonium salt $R_f = 0.00$, visualized by UV light (254 nm) and KMnO₄/NaOH. The mixture was transferred to a 1 L separatory funnel. Washings of water (90 mL) and dichloromethane (60 mL) were added and the layers were separated. On separation an insoluble brown material was formed between the organic and the aqueous phases which was combined with the organic phase on the final extraction of the aqueous phase. The aqueous layer was extracted with dichloromethane (3 \times 60 mL). The combined organic layers were dried over MgSO₄ for 15 minutes, filtered using a sinter funnel [porosity 2] and a 500 mL Büchner flask with washings of dichloromethane (2 \times 20 mL). The solvent was removed by rotary evaporation (40 °C, 350 mbar) and the sample was subsequently dried under high vacuum (0.5 mm Hg) at room temperature to give an off-white solid (52.79 g). The crude product was dissolved in dichloromethane (200 mL) and poured into rapidly stirring diethyl ether (1.2 L) in a conical flask (2 L) with a [7 cm, oval] magnetic stir bar. The precipitate was collected by filtration using a Büchner funnel [10 cm diameter \times 5 cm height] and Büchner flask (2 L) and was washed with diethyl ether (3 \times 200 mL). Diethyl ether (200 mL) was used to wash the conical flask out. The white solid was ground using a pestle and mortar then dried under high vacuum (0.4 mm Hg) for 1 h at room temperature. Sulfonium salt **4** was obtained as a colorless amorphous solid (52.8 g, 88%) with d.r. >95:5. $[\alpha]_D^{25} -142$ ($c = 1.00$, CHCl₃) [Lit.³ -142 ($c = 1.01$, CHCl₃)].

IR (cm⁻¹, neat): 2945, 1458, 1258, 1223, 1149, 1028, 774.



¹H NMR (400 MHz, CDCl₃) δ : 7.64–7.56 (2H, m, 2 \times ArH), 7.40–7.30 (3H, m, 3 \times ArH), 4.91 (1H, d, $J = 12.5$, C¹¹HH), 4.52 (1H, d, $J = 12.7$, C¹¹HH), 3.84–3.79 (1H, m, C¹H), 2.79–2.68 (1H, m, C⁶HH), 2.40–2.30 (2H, m, C⁵H and C⁶HH), 2.10–1.98 (1H, m, C²H), 1.79 (3H, s, CH₃), 1.75 (3H, s, CH₃), 1.85–1.40 (4H, m, C³H₂, C⁴H₂), 1.07 (3H, d, $J = 7.1$, axial C¹⁰H₃).

¹³C NMR (101 MHz, CDCl₃) δ : 130.6 (ArCH), 129.7 (ArCH), 129.7 (ArCH), 129.2 (C12), 120.9 (q, $J = 320$, CF₃), 72.5 (C7), 63.9 (C1), 50.5 (C5), 42.1 (C11), 32.1 (C2), 31.7 (C6), 25.5 (CH₃), 25.2 (C3), 23.2 (CH₃), 22.2 (C4), 17.8 (C10).

mp 138–139 °C (Et₂O/CH₂Cl₂) [Lit.³ 142–145 °C (Et₂O/CH₂Cl₂)].

HRMS (ESI⁺) C₁₇H₂₅S⁺ (M–CF₃SO₃⁻) requires: 261.1671; found: 261.1674.

Anal. calcd. for C₁₈H₂₅F₃O₃S₂: C, 52.66; H, 6.14; found: C, 52.64; H, 5.94.²

An X-ray structure has previously been reported.²

trans-2,3-Diphenyloxirane (5).

[CAS Reg. No.: 25144-18-7]

Sulfonium salt **4** (16.4 g, 40 mmol, 1 equiv.) was dissolved in a 9:1 mixture of acetonitrile and deionized water (210 mL) in a 1 L round bottomed flask equipped with a magnetic stirrer [5 cm, oval] to form a clear colorless solution. Freshly purified benzaldehyde⁸ (6.5 g, 61 mmol, 1.5 equiv.) was added *via* syringe. The flask was then placed in a 0 °C ice/water mixture in a Dewar flask for 20 mins and then freshly ground KOH (3.4 g, 60 mmol, 1.5 equiv.) was added *via* powder funnel and the flask was stoppered. The solution was stirred in ice-water for 1 h before placing in an oil bath at 25 °C for a further 23 h. The reaction was monitored by TLC (pentane:ethyl acetate, 98:2); isothiocineole $R_f = 0.87$, epoxide $R_f = 0.50$, benzaldehyde $R_f = 0.32$, sulfonium salt $R_f = 0.00$, visualized by UV light (254 nm) and KMnO₄/NaOH (Figure 4). An aliquot from the reaction mixture at 23 h showed no sulfonium salt to be present by ¹H NMR spectroscopy.

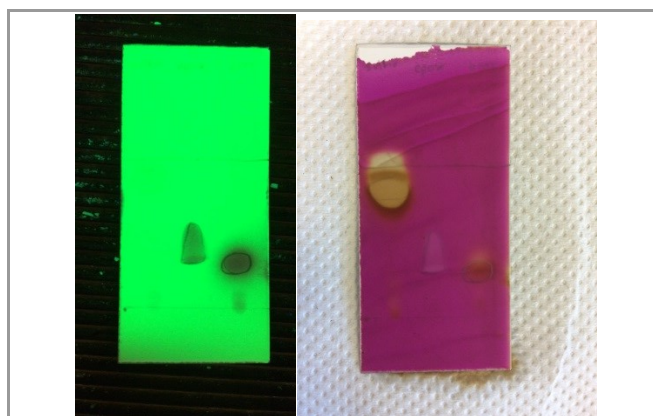


Figure 4 TLC monitoring of epoxidation reaction (pentane:ethyl acetate, 98:2); isothiocineole **1** $R_f = 0.87$ (left lane), epoxide **5** $R_f = 0.50$ (middle lane), benzaldehyde $R_f = 0.32$ (right lane), sulfonium salt **3** $R_f = 0.00$. Visualized by UV light (254 nm; left plate) and KMnO₄/NaOH (right plate).

Acetonitrile was then evaporated using rotary evaporation (45 °C, 150 mbar). Dichloromethane (150 mL) was added and the solution was transferred to a 1 L separatory funnel followed by water (2 \times 75 mL) washings. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 \times 100 mL). The organic phases were then combined, dried with MgSO₄ for 15 min, then filtered using a Büchner funnel [8 cm diameter \times 4 cm height] and a 1 L Büchner flask.

The filtrate was transferred with washings of dichloromethane (3 × 20 mL) to a 1 L round bottom flask and the solvent was removed using rotary evaporation (45 °C, 450 mbar) followed by high vacuum (0.3 mm Hg, 15 minutes) to give a white semi-crystalline solid suspended in isothiocieneole (18.1 g). Leaving mixtures containing sulfide **1** on high vacuum over prolonged periods can result in loss of the sulfide by evaporation. The *trans:cis* ratio was determined by ¹H-NMR from the crude reaction mixture to be >95:5 [the chemical shifts used to determine the *trans:cis* ratio were 3.87 ppm (s, 2H) and 4.36 ppm (s, 2H), respectively]. The crude material was transferred to a 100 mL flask suitable for a Kugelrohr distillation with washings of dichloromethane (3 × 10 mL) and the dichloromethane was removed by rotary evaporation (40 °C, 500 mbar) prior to the distillation. The flask was then fitted with two collection bulbs. Both collection bulbs were kept outside the oven during the Kugelrohr distillation (Figure 5). Isothiocieneole **1** and benzaldehyde were removed by Kugelrohr distillation (oven temperature 70 °C, 0.37 mm Hg) using cotton wool soaked in liquid N₂ for cooling the collection bulb nearest to the vacuum source. It is advised not to exceed 70 °C during the Kugelrohr distillation since higher temperatures were found to lead to decomposition of the epoxide.



Figure 5 Kugelrohr distillation.

The remaining material (9.6 g) containing epoxide **5** and traces of isothiocieneole and benzaldehyde was transferred to a 100 mL pear-shaped flask with dichloromethane (20 mL × 2). The dichloromethane was removed by rotary evaporation (45 °C, 750 mbar) before adding a stir-bar to the flask [3 cm, oval] and placing in an oil bath at 60 °C. A minimum amount of boiling *n*-hexane (~2.5 mL per 1 g)³ was used to dissolve the solid before allowing the material to cool (in the oil bath) to room temperature. The flask was then transferred to a fridge at 6 °C for 12 h before filtering the product with suction using a Büchner funnel [5 cm diameter × 3 cm height] and 250 mL Büchner flask and washing with ice-cold *n*-hexane (20 mL). The white crystalline product **5** was crushed using a pestle and mortar before drying under high-vacuum (0.3 mm Hg) for 2 h to achieve a yield of 69% (5.40 g). The yield was increased to 75% from the filtered mother liquor of the first crystallization to obtain a second crop of crystals (0.44 g) by following the same recrystallization procedure. Both crops were >95:5 *trans:cis* and >99:1 e.r. [α]_D²⁵ +261 (*c* = 1.00, CHCl₃) [Lit.¹² [α]_D²² +250.8 (*c* = 0.85, CHCl₃, >99:1 e.r.)].

IR (cm⁻¹, neat): 3035, 2989, 1492, 1453, 1281, 1102, 863, 845.

First crop: Anal. calcd. for C₁₄H₁₂O: C, 85.68; H, 6.16 found: C, 85.74; H, 6.16.

Second crop: Anal. Calcd. for C₁₄H₁₂O: C, 85.68; H, 6.16 found: C, 85.68; H, 6.14.

¹H NMR (300 MHz, CDCl₃) δ: 7.48-7.31 (m, 2 × 5H, ArH), 3.90 (s, 2H, 2 × CH).

¹³C NMR (101 MHz, CDCl₃) δ: 137.2, 128.7, 128.4, 125.6, 63.0.³

mp 69-70 °C (*n*-hexane) [lit.¹³ 65-67 °C (petrol)].

LRMS (ESI⁺) C₁₇H₂₅S⁺ (2M+H⁺) requires: 393.18; found: 393.25.

HPLC conditions: ChiralPak ASH column (length 25 cm, diameter 0.46 cm), 5% EtOH/heptane, 1 ml/min, 4.4 min ((*R,R*), major), 4.9 min ((*S,S*), minor).

Recovery of (1*R*,4*R*,5*R*)-Isothiocieneole **1** from Epoxidation.

Sulfide **1** can be recovered from the distillate by flash column chromatography: A fritted chromatography column (7 cm × 200 cm) was packed with silica (10 cm height, 300 mL) using petroleum ether (40-60

°C) as a slurry. The distillate was loaded directly onto the column. The tap was opened and the distillate was allowed to reach the level of the silica before adding a layer of sand (~5-10 mm) to prevent the surface of the silica from being disturbed. The material was eluted with petroleum ether (40-60 °C). 500 mL was eluted before fractions of 15 mL were collected. A further 3.5 L of petroleum ether (40-60 °C) was eluted before changing to petroleum ether: ethyl acetate (98:2, 150 mL) then (96:4, 400 mL) then (94:6, 550 mL). Sulfide **1** eluted in fractions 1-275. Fractions above this contained a mixture of sulfide **1** and benzaldehyde. The fractions were monitored by TLC (petroleum ether, isothiocieneole *R*_f = 0.27, benzaldehyde *R*_f = 0.05) visualized by UV light (254 nm) and KMnO₄/NaOH. The first fractions (1-275) were concentrated to give 4.24 g (64% recovery) of sulfide **1**, 99:1 e.r. Quantitative ¹H NMR using 1,3,5-trimethoxybenzene indicated >97% purity by mass.

(2*R*,3*R*)-2-Phenyl-3-[(*E*)-2-phenyl-1-ethenyl]-1-tosylaziridine (**7**)

[CAS Reg. No.: 911028-87-0]

Sulfonium salt **4** (7.5 g, 18 mmol, 1 equiv.) was dissolved in acetonitrile (200 mL) in a 500 mL one-necked round bottomed flask equipped with a magnetic stirrer [5 cm, oval]. Imine **6** (5.2 g, 18 mmol, 1 equiv.) was then added. The flask was then placed in a 0 °C ice/water bath and K₂CO₃ (5.1 g, 37 mmol, 2 equiv.) was added. The solution was stirred at 0 °C for 1 h before placing it in an oil bath at 25 °C for 23 h with stirring. The reaction was monitored by TLC (cyclohexane:ethyl acetate, 7:3); aziridine **7** *R*_f = 0.49, imine **6** *R*_f = 0.41, visualized under UV light (254 nm). Acetonitrile was then removed by rotary evaporator (45 °C, 200 mbar) to give a residue which was dissolved in dichloromethane (250 mL) and the solution was transferred to a 1 L separatory funnel followed by washings (2 × 25 mL). The organic layer was washed with a freshly made aq. saturated solution of NaHSO₃ (250 mL), aq. NaOH (250 mL, 1M) and brine (250 mL). The organic layer was dried over MgSO₄ for 20 min, filtered using a Büchner funnel [3 cm diameter × 8 cm height] and 500 mL Büchner flask and the filtrate was transferred to a 1 L round bottom flask with washings (2 × 25 mL). The solvent was removed by rotary evaporator (45 °C, 250 mbar) to give an off-white solid (11.4 g). The d.r. was determined to be 93:7 by ¹H NMR (the chemical shifts used to determine the *trans:cis* ratio were 7.84 (d, *J* = 8.2 Hz, 2H) and 7.89 (d, *J* = 8.3 Hz, 2H) in CDCl₃, respectively). The crude mixture was stirred rapidly in *n*-pentane (100 mL) for 30 min. The mixture was filtered using a Buchner funnel [8 cm diameter × 4 cm height] and 1 L Buchner flask and washed with *n*-pentane (3 × 50 mL). The filtered solid was air-dried by suction for 30 min before grinding with a mortar and pestle then subsequently drying on high vacuum (0.3 mm Hg) for 1 h. (2*R*,3*R*)-2-Phenyl-3-[(*E*)-2-phenyl-1-ethenyl]-1-tosylaziridine **7** was obtained as a white solid (6.1 g, 90%, *trans:cis* 95:5 e.r. 98:2). mp 142-143 °C (EtOAc/PE). [α]_D²⁵ +21.6 (*c* = 1.00, CHCl₃) [Lit.⁷ [α]_D²⁵ +8.9 (*c* = 0.90, CHCl₃)].

IR (cm⁻¹, neat): 1299, 1152, 1072, 968, 903.

¹H NMR (400 MHz, CDCl₃) δ: 7.84 (d, *J* = 8.2, 2H, ArH), 7.46-7.13 (m, 12H, ArH), 6.78 (d, *J* = 15.8, CH=CHPh), 6.66 (dd, *J* = 15.8, 9.5, CH=CHPh), 4.14 (d, *J* = 4.0, 1H, NCHPh), 3.44 (dd, *J* = 9.4, 4.2, 1H, NCHCH=), 2.37 (3H, s, CH₃).

¹³C NMR (101 MHz, CDCl₃) δ: 144.3, 137.5, 136.9, 136.0, 135.2, 129.3, 128.8, 128.7, 128.5, 128.4, 127.7, 126.8, 126.4, 122.2, 55.4, 48.8, 21.7.

HPLC conditions: ChiralPak IB column (length 25 cm, diameter 0.46 cm), 5% EtOH/heptane, 1.0 ml/min; *trans*-isomer: *R*_t: 9.94 min ((*S,S*), minor), 12.68 min ((*R,R*), major); *cis*-isomer; *R*_t: 8.05 (major), *R*_t: 8.81 (minor).

IR (cm⁻¹, neat): 1299, 1152, 1072, 968, 903.

Anal. calcd. for C₂₃H₂₁NO₂S: C, 73.57; H, 5.64; N, 3.73; found C, 73.47; H, 5.55; N, 3.59.

Recovery of Isothiocieneole **1** from Aziridination.

Isothiocieneole **1** can be isolated from the filtrate by a short-path distillation. The filtrate was concentrated in vacuo in a 50 mL round bottom flask using a rotary evaporator (45 °C, 500 mbar) then high vacuum (0.5 mm Hg) for 10 min. The flask was equipped with a stir bar [2 cm, oval]. A short path distillation apparatus [16 cm] equipped with

vacuum connector, a thermometer (± 1 °C) and pig-type receiver with pre-weighed flasks (25 mL \times 3) was used. The still-pot was covered using aluminium foil and isothiocineole **1** was distilled under reduced pressure (32-35 °C, 0.38 mm Hg) into the first collecting flask with oil bath temperature 70-85 °C (2.5 g, 83% recovery), 99:1 e.r.

Anal. calcd. for C₁₀H₁₈S: C, 70.52; H, 10.65; S, 18.82; found: C, 70.71; H, 10.69; S, 18.48.

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Supporting Information

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Primary Data

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References

- (1) (a) McGarrigle, E. M.; Myers, E. L.; Illa, O.; Shaw, M. A.; Riches, S. L.; Aggarwal, V. K. *Chem. Rev.* **2007**, *107*, 5841. (b) Aggarwal, V. K.; McGarrigle, E. M.; Shaw, M. A. in *Science of Synthesis, Stereoselective Synthesis 2: Stereoselective Reactions of Carbonyl and Imino Groups*; Molander, G. A., Ed.; Georg-Thieme-Verlag KG: Stuttgart, **2011**. Chapter 2.6, 311. (c) Brière, J.-F.; Metzner, P. in *Organosulfur Chemistry in Asymmetric Synthesis*; Wiley-VCH: Weinheim, **2009**, Chapter 5.
- (2) Illa, O.; Namutebi, M.; Saha, C.; Ostovar M.; Chen C. C.; Haddow, M. F.; Nocquet-Thibault S.; Lusi, M.; McGarrigle, E. M.; Aggarwal V. K. *J. Am. Chem. Soc.*, **2013**, *135*, 11951.
- (3) Illa, O.; Arshad, M.; Ros, A.; McGarrigle, E. M.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 1828.
- (4) (a) Brichacek, M.; Villalobos, M. N.; Plichta, A.; Njardarson, J. T. *Org. Lett.* **2011**, *13*, 1110. (b) Brucks, A. P.; Treitler, D. S.; Liu, S.-A.; Snyder, S. A. *Synthesis* **2013**, *45*, 1886. (c) Midura, W. H.; Ścianowski, J.; Banach, A.; Zając, A. *Tetrahedron: Asymmetry* **2014**, *25*, 1488. (d) Luo, J.; Wu, B.; Chen, M. -W.; Jiang, G.-F.; Zhou, Y.-G. *Org. Lett.* **2014**, *16*, 2578. (e) Rousseau, O.; Delaunay, T.; Dequirez, G.; Trieu-Van, T.; Robeyns, K.; Robiette, R. *Chem. Eur. J.* **2015**, *21*, 12899. (f) Bigot, A.; Bouchard, H.; Brun, M. -P.; Clerc, F.; Zhang, J. PCT Int. Appl. WO 2017076998. **2017**. (g) Liu, L.; Yuan, Z.; Pan, R.; Zeng, Y.; Lin, A.; Yao, H.; Huang, Y. *Org. Chem. Front.* **2018**, *5*, 623. (h) Li, Q.-Z.; Zhang, X.; Zeng, R.; Dai, Q.-S.; Liu, Y.; Shen, X.-D.; Leng, H.-J.; Yang, K.-C.; Li, J.-L. *Org. Lett.* **2018**, *20*, 3700. (i) Cole, C. J. F.; Chi, H. M.; DeBacker, K. C.; Snyder, S. A. *Synthesis* **2018**, *50*, efirst, DOI: 10.1055/s-0037-1609754. (j) Luo, J.; Wu, B.; Chen, M.-W.; Jiang, G.-F.; Zhou, Y.-G. *Org. Lett.* **2014**, *16*, 2578. (k) Yuan, Z.; Fang, X.; Li, X.; Wu, J.; Yao, H.; Lin, A. *J. Org. Chem.* **2015**, *80*, 11123.
- (5) Weitkamp, A. W. *J. Am. Chem. Soc.* **1959**, *81*, 3430.
- (6) (a) A. Nakatsuchi. *J. Soc. Chem Ind. Japan (Suppl. Binding)*, **1930**, *33*, 408. (b) A. Nakatsuchi, *J. Soc. Chem Ind. Japan (Suppl. Binding)*, **1932**, *35*, 376.
- (7) Lowe, M. A.; Ostovar, M.; Ferrini, S.; Chen, C. C.; Lawrence, P. G.; Fontana, F.; Calabrese, A. A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.*, **2011**, *50*, 6370.
- (8) Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals* (Sixth Edition), Chai, W. L. F. A. L. L., Ed. Butterworth-Heinemann: Oxford, **2009**, 245.
- (9) Reeves, J. T.; Visco, M. D.; Marsini, M. A.; Grinberg, N.; Busacca, C. A.; Mattson, A. E.; Senanayake, C. H. *Org. Lett.* **2015**, *17*, 2442.
- (10) (a) Lanigan, R.; Starkov, P.; Sheppard, T., *J. Org. Chem.*, **2013**, *78*, 4515. (b) Starkov, P.; Sheppard, T., *Org. Biomol. Chem.*, **2010**, *5*, 1320.
- (11) Menger, F.; Elrington, A. R. *J. Am. Chem. Soc.* **1991**, *113*, 9621.
- (12) Fox, D.; Pedersen, D.; Petersen, A.; Warren, S. *Org. Biomol. Chem.* **2006**, *4*, 3117.
- (13) Berti, G.; Botari, F.; Ferrarini, P. L.; Macchia, B. J. *J. Org. Chem.* **1965**, *30*, 4091.