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Synthesis of Isothiocineole and Application in Multigram-Scale Sulfur Ylide Mediated Asymmetric Epoxidation and Aziridination

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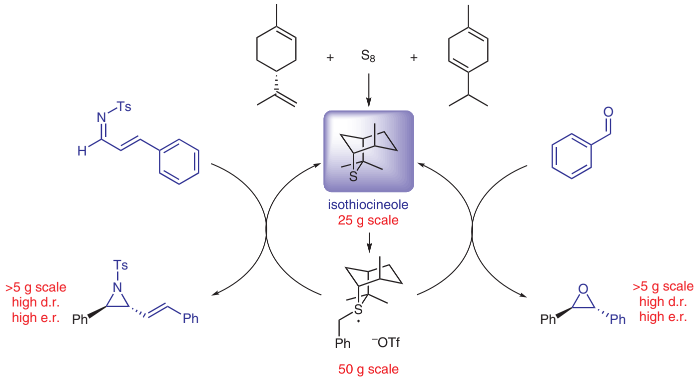

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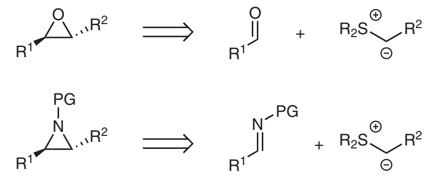
Abstract The synthesis of the chiral sulfide isothiocineole from limonene and elemental sulfur on multi-gram scale and its alkylation to make >50 g of the corresponding benzylsulfonium salt are described. The application of this salt to the sulfur ylide-mediated asymmetric epoxidation of aldehydes and 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 isothiocineole (**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 isothiocineole (**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

Isothiocineole (**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 isothiocineole (**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]

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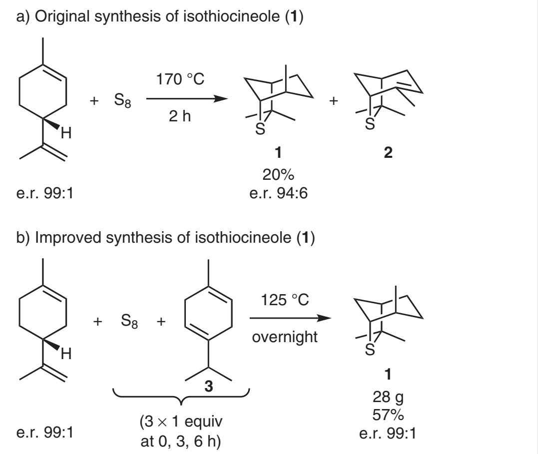
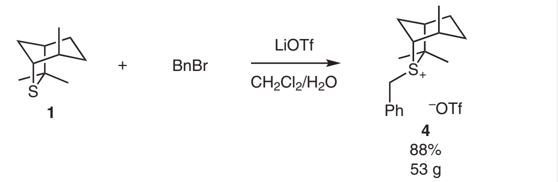

a) Original synthesis of isothiocineole (**1**)

b) Improved synthesis of isothiocineole (**1**)

Scheme 2 Syntheses of isothiocineole (**1**)

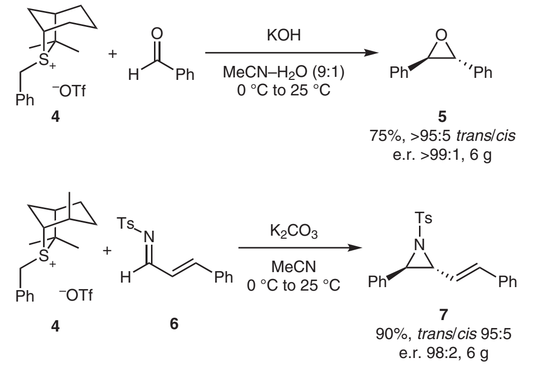
The procedure we describe allows the sulfide to be isolated in pure form by vigreux distillation. The complete separation from *p*-cymene can be difficult, however, in most instances the presence of small amounts of *p*-cymene does not interfere with subsequent reactions. If the sulfide is to be converted into 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 HBF_4 in Et_2O 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, $P(O)Ph_2$, 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 scaleable synthesis of isothiocineole (**1**), and its application to the asymmetric epoxidation aldehydes and aziridination of imines using simple procedures. We have previously provided a clear rationale of 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 TLC, carried out using aluminum-backed silica plates (60 F_{254}) and the eluents stated; visualization was accomplished using UV light (254 nm) and a stain of $KMnO_4$ (3 g) in aq 1% NaOH (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 r.t. 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 and ^{13}C NMR spectra were recorded in $CDCl_3$ in 300 MHz or 400 MHz spectrometer. For quantitative NMR spectroscopy, the ^1H NMR sample was made up in $CDCl_3$ and submitted with a 25 s delay at pulse angle of 45°.

Benzaldehyde (≥99%, 25 mL) obtained from Sigma-Aldrich was washed with aq 10% Na_2CO_3 (2 × 25 mL) until no more evolution of CO_2 was observed. It was then washed with sat. aq Na_2SO_3 followed by H_2O (25 mL), then dried ($MgSO_4$) for 15 min before distilling under N_2 atmosphere at reduced pressure.[8] KOH (>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 reac-

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tion flask. If left for too long in atmospheric conditions, the ground KOH absorbs H_2O. Imine **6** was synthesized from benzaldehyde and tosylamide by the method of Senanayake[9] using $B(OCH_2CF_3)_3$ as catalyst (which is commercially available) made by the method of Sheppard.[10]

(*R*)-Isothiocineole has a pungent odor. 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 the 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[11] (H_2O 29% w/w, *c*-hexane 11.9% w/w and *i*-PrOH 58.5% w/w) in a slight modification to the method of Menger and Elrington[11] to which bleach was added and all glassware submerged in this cleaning system for 12 h.

(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-bottomed flask equipped with a magnetic stirring bar (5 cm, oval), a reflux condenser in the right hand neck (16 cm) with a gas adapter at the top, a thermometer (± 2 °C), a 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 N_2 three times (turning to vacuum ~2 seconds then immediately back to N_2). The reaction vessel was placed in a pre-heated oil bath at 130 °C to achieve an internal temperature of 125 °C after 15 min under an atmosphere of N_2. 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 a syringe through the center neck of the flask with a slight positive flow of N_2. 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 a powder funnel followed by γ-terpinene (47 mL, 0.29 mol, 1.0 equiv) via a syringe through the center neck of the flask with a slight positive flow of N_2. The reaction was then left overnight at 125 °C under a N_2 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%.

The reaction was then cooled to r.t., disconnected from the N_2 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 N_2.

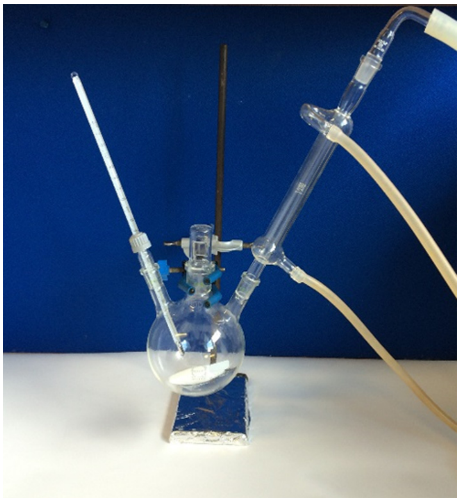

Figure 1 Reaction set-up for the synthesis of isothiocineole (**1**)

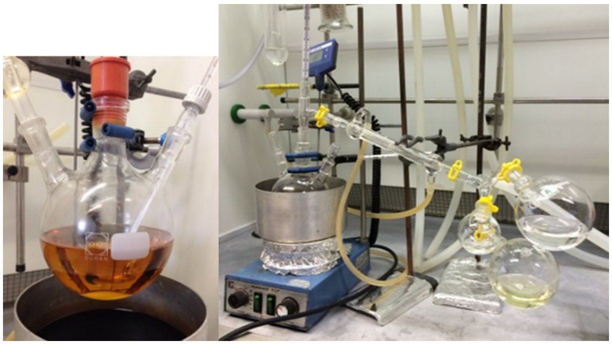

Figure 2 Crude reaction material and set-up for first distillation

At r.t. the volatile by-products were distilled into the first trap. Once the reaction mixture stopped bubbling and the vacuum had stabilized (0.70 mmHg manometer reading) the still pot was covered with aluminum 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 mmHg) 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 had 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 the receiving flask 3 (250 mL), which contained (*R*)-isothiocineole and *p*-cymene (44–46 °C/0.67 mmHg). The temperature of the oil bath was raised to 110 °C (at 0.60 mmHg) 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.

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

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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 aluminum 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 mmHg). As the rate of *p*-cymene distillation slowed the vacuum improved causing a mixture to slowly distil (34 °C/0.48 mmHg). 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 mmHg, approximately 2 mL). After 15 min 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 mmHg, approximately 25 mL).[5] This fraction containing (*R*)-isothiocineole (**1**) (Figure 4) was obtained as a clear colorless oil 57% (28.2 g); 99:1 e.r.; $[\alpha]_D^{25}$ –69.5 (*c* 1.00, $CHCl_3$) {Lit.[2] $[\alpha]_D^{25}$ –69.1 (neat)}.

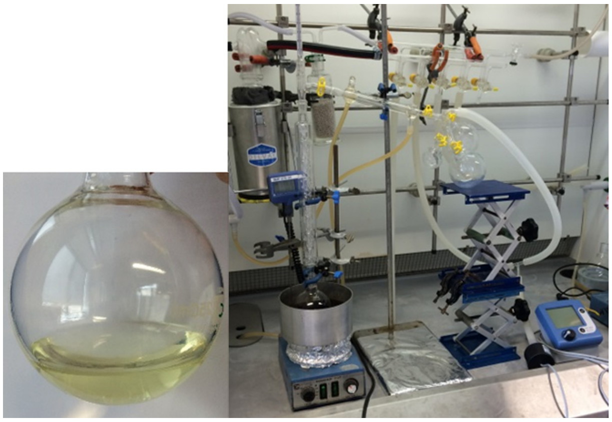

Figure 3 Distillate from first distillation and set-up for second distillation of isothiocineole (**1**)

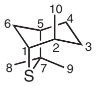

Figure 4 Structure of (*R*)-isothiocineole (**1**) with numbering for NMR assignments

Chiral Phase GC: Supelco AlphaDex 120 column (30 m length × 0.25 mm diameter × 25 μm 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) t_R = 48.7 min and *S*-enantiomer (minor) t_R = 49.6 min.

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

^1H NMR (400 MHz, $CDCl_3$): δ = 3.32–3.30 (1 H, m, C^1H), 2.38–2.26 (1 H, m, C^3*H*H), 2.13–2.00 (2 H, m, C^6H_2), 1.94–1.85 (1 H, m, C^2H), 1.85–1.80 (1 H, m, C^5H), 1.68–1.43 (2 H, m, C^4H_2), 1.51 (3 H , s, CH_3), 1.39 (3 H, s, CH_3), 1.19–1.12 (1 H, m, C^3H*H*), 1.07 (3 H, d, *J* = 7.4 Hz, $C^{10}H_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 53.0 (C1), 52.6 (C7), 47.4 (C5), 35.5 (C2), 35.0 (CH_3), 34.5 (C6), 25.5 (CH_3), 24.4 (C3), 23.9 (C4), 18.8 (C10).

Anal. Calcd for $C_{10}H_{18}S$: C, 70.52; H, 10.65; S, 18.82. Found: C, 70.42; H, 10.42; S, 19.2.[6]

(1*R*,4*R*,5*R*,6*R*)-6-Benzyl-4,7,7-trimethyl-6-thiabicyclo[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 CH_2Cl_2 (60 mL) in a one-necked 500 mL round-bottomed 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 LiOTf (68 g, 0.44 mol, 3 equiv) in deionized H_2O (50 mL) via a funnel followed by washings of deionized H_2O (2 × 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/EtOAc 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 $KMnO_4$/NaOH. The mixture was transferred to a 1 L separatory funnel. Washings of H_2O (90 mL) and CH_2Cl_2 (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 CH_2Cl_2 (3 × 60 mL). The combined organic layers were dried ($MgSO_4$) for 15 min, filtered using a sintered funnel (porosity 2) and a 500 mL Büchner flask with washings of CH_2Cl_2 (2 × 20 mL). The solvent was removed by rotary evaporation (40 °C/262.5 mmHg) and the sample was subsequently dried under high vacuum (0.5 mmHg) at r.t. to give an off-white solid (52.79 g). The crude product was dissolved in CH_2Cl_2 (200 mL) and poured into rapidly stirring Et_2O (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 × 5 cm height) and Büchner flask (2 L), and was washed with Et_2O (3 × 200 mL). Et_2O (200 mL) was used to wash out the conical flask. The white solid was ground using a pestle and mortar, then dried under high vacuum (0.4 mmHg) for 1 h at r.t. Sulfonium salt **4** (Figure 5) was obtained as a colorless amorphous solid (52.8 g, 88%) with d.r. >95:5; mp 138–139 °C (Et_2O/CH_2Cl_2) [Lit.[3] mp 142–145 °C (Et_2O/CH_2Cl_2)]; $[\alpha]_D^{25}$ –142 (*c* 1.00, $CHCl_3$) {Lit.[3] $[\alpha]_D$ –142 (*c* 1.01, $CHCl_3$)}.

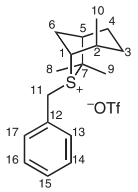

Figure 5 Structure of the sulfonium salt **4** with numbering of C-atoms

IR (neat): 2945, 1458, 1258, 1223, 1149, 1028, 774 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.56 (2 H, m, 2 × ArH), 7.40–7.30 (3 H, m, 3 × ArH), 4.91 (1 H, d, *J* = 12.5 Hz, $C^{11}H$*H*), 4.52 (1 H, d, *J* = 12.7 Hz, C^{11}*H*H), 3.84–3.79 (1 H, m, C^1H), 2.79–2.68 (1 H, m, C^6*H*H), 2.40–

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2.30 (2 H, m, C^5H and C^6H*H*), 2.10–1.98 (1 H, m, C^2H), 1.79 (3 H, s, CH_3), 1.75 (3 H, s, CH_3), 1.85–1.40 (4 H, m, C^3H_2, C^4H_2), 1.07 (3 H, d, J = 7.1 Hz, axial $C^{10}H_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 130.6 (ArCH), 129.7 (ArCH), 129.7 (ArCH), 129.2 (C12), 120.9 (q, J = 320 Hz, CF_3), 72.5 (C7), 63.9 (C1), 50.5 (C5), 42.1 (C11), 32.1 (C2), 31.7 (C6), 25.5 (CH_3), 25.2 (C3), 23.2 (CH_3), 22.2 (C4), 17.8 (C10).

HRMS (ESI$^+$): m/z calcd for $C_{17}H_{25}S^+$ (M – $CF_3SO_3^-$): 261.1671; found: 261.1674.

Anal. Calcd for $C_{18}H_{25}F_3O_3S_2$: C, 52.66; H, 6.14. Found; C, 52.64; H, 5.94.[2]

An X-ray crystal 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 MeCN and deionized H_2O (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 benzaldehyde[8] (6.5 g, 61 mmol, 1.5 equiv) was added via a syringe. The flask was then placed in a 0 °C ice/water mixture in a Dewar flask for 20 min and then freshly ground KOH (3.4 g, 60 mmol, 1.5 equiv) was added via a 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/EtOAc 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 $KMnO_4$/NaOH (Figure 6). An aliquot from the reaction mixture at 23 h showed no sulfonium salt to be present by ^1H NMR spectroscopy.

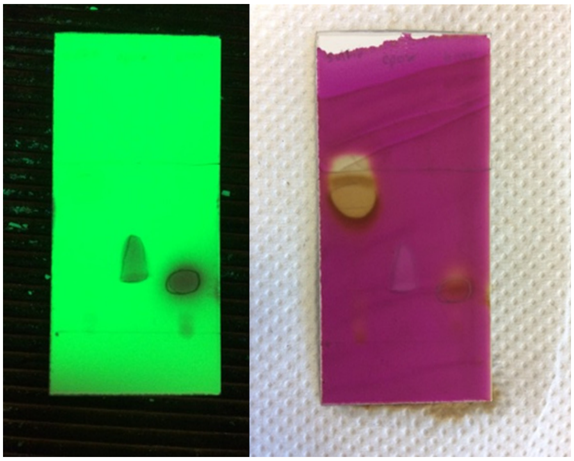

Figure 6 TLC monitoring of epoxidation reaction (pentane/EtOAc 98:2); isothiocineole **1** R_f = 0.87 (left lane), epoxide **5** R_f = 0.50 (middle lane), benzaldehyde R_f = 0.32 (right lane), sulfonium salt **4** R_f = 0.00. Visualized by UV light (254 nm; left plate) and $KMnO_4$/NaOH (right plate).

MeCN was then evaporated by rotary evaporation (45 °C/112.5 mmHg). CH_2Cl_2 (150 mL) was added and the solution was transferred to a 1 L separatory funnel followed by H_2O (2 × 75 mL) washings. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The organic phases were then combined, dried ($MgSO_4$) for 15 min, then filtered using a Büchner funnel (8 cm diameter × 4 cm height) and a 1 L Büchner flask. The filtrate was transferred with washings of CH_2Cl_2 (3 × 20 mL) to a 1 L round-bottomed flask and the solvent was removed using rotary evaporation (45 °C/337.5 mmHg) followed by high vacuum (0.3 mmHg/15 min) to give a white semi-crystalline solid suspended in isothiocineole (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, 2 H) and 4.36 ppm (s, 2 H), respectively]. The crude material was transferred to a 100 mL flask suitable for a Kugelrohr distillation with washings of CH_2Cl_2 (3 × 10 mL) and the CH_2Cl_2 was removed by rotatory evaporation (40 °C/375 mmHg) 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 7). Isothiocineole (**1**) and benzaldehyde were removed by Kugelrohr distillation (oven temperature 70 °C/0.37 mmHg) using cotton wool soaked in liquid N_2 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.

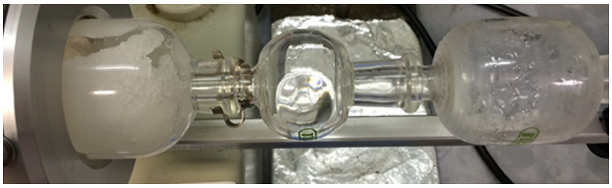

Figure 7 Kugelrohr distillation

The remaining material (9.6 g) containing epoxide **5** and traces of isothiocineole and benzaldehyde was transferred to a 100 mL pear-shaped flask with CH_2Cl_2 (2 × 20 mL). The CH_2Cl_2 was removed by rotatory evaporation (45 °C/562.5 mmHg) 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 r.t. 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 mmHg) 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.; mp 69–70 °C (*n*-hexane) [Lit.[12] mp 65–67 °C (PE)]; $[\alpha]_D^{25}$ +261 (*c* 1.00, $CHCl_3$) {Lit.[13] $[\alpha]_D^{25}$ +250.8 (*c* 0.85, $CHCl_3$, >99:1 e.r.)}.

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

IR (neat): 3035, 2989, 1492, 1453, 1281, 1102, 863, 845 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.31 (m, 2 × 5 H, ArH), 3.90 (s, 2 H, 2 × CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.2, 128.7, 128.4, 125.6, 63.0.[3]

LRMS (ESI$^+$): m/z calcd for $C_{17}H_{25}S^+$ (2 M + H$^+$): 393.18; found: 393.25.

First crop: Anal. Calcd for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.74; H, 6.16.

Second crop: Anal. Calcd for $C_{14}H_{12}O$: C, 85.68; H, 6.16: Found: C, 85.68; H, 6.14.

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Recovery of (1*R*,4*R*,5*R*)-Isothiocineole (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 gel (10 cm height, 300 mL) using PE (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 gel before adding a layer of sand (~5–10 mm) to prevent the surface of the silica gel from being disturbed. The material was eluted with PE (40–60 °C). An amount of 500 mL was eluted before fractions of 15 mL were collected. A further 3.5 L of PE (40–60 °C) was eluted before changing to PE/EtOAc (98:2, 150 mL), then (96:4, 400 mL), and then (94:6, 550 mL). Sulfide **1** was eluted in fractions 1–275. Fractions above this contained a mixture of sulfide **1** and benzaldehyde. The fractions were monitored by TLC (PE, isothiocineole R_f = 0.27, benzaldehyde R_f = 0.05) visualized by UV light (254 nm) and $KMnO_4$/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 MeCN (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 K_2CO_3 (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/EtOAc, 7:3); aziridine **7** R_f = 0.49, imine **6** R_f = 0.41, visualized under UV light (254 nm). MeCN was then removed by rotary evaporator (45 °C/150 mmHg) 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 sat. aq $NaHSO_3$ (250 mL), aq NaOH (250 mL, 1 M), and brine (250 mL). The organic layer was dried over $MgSO_4$ 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-bottomed flask with washings (2 × 25 mL). The solvent was removed by rotary evaporator (45 °C/187.5 mmHg) to give an off-white solid (11.4 g). The d.r. was determined to be 93:7 by ^1H NMR analysis [the chemical shifts used to determine the *trans*:*cis* ratio were 7.84 (d, *J* = 8.2 Hz, 2 H) and 7.89 (d, *J* = 8.3 Hz, 2 H) in $CDCl_3$, respectively]. The crude mixture was stirred rapidly in *n*-pentane (100 mL) for 30 min. The mixture was filtered using a Büchner 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 mmHg) 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); $[\alpha]_D^{25}$ +21.6 (*c* = 1.00, $CHCl_3$) {Lit.[7] $[\alpha]_D^{25}$ +8.9 (*c* 0.90, $CHCl_3$)}.

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

IR (neat): 1299, 1152, 1072, 968, 903 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.2, 2 H, ArH), 7.46–7.13 (m, 12 H, ArH), 6.78 (d, *J* = 15.8, CH=C*H*Ph), 6.66 (dd, *J* = 15.8, 9.5, C*H*=CHPh), 4.14 (d, *J* = 4.0, 1 H, NC*H*Ph), 3.44 (dd, *J* = 9.4, 4.2, 1 H, NC*H*CH=), 2.37 (3 H, s, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): 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.

Anal. Calcd for $C_{23}H_{21}NO_2S$: C, 73.57; H, 5.64; N, 3.73. Found: C, 73.47; H, 5.55; N, 3.59.

Recovery of Isothiocineole (1) from Aziridination

Isothiocineole (**1**) can be isolated from the filtrate by a short-path distillation. The filtrate was concentrated in vacuo in a 50 mL round-bottomed flask using a rotatory evaporator (45 °C/375 mmHg), then high vacuum (0.5 mmHg) 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 (3 × 25 mL) was used. The still-pot was covered using aluminum foil and isothiocineole (**1**) was distilled under reduced pressure (32–35 °C/0.38 mmHg) into the first collecting flask with oil bath temperature 70–85 °C (2.5 g, 83% recovery); 99:1 e.r.

Anal. Calcd for $C_{10}H_{18}S$: C, 70.52; H, 10.65; S, 18.82. Found: C, 70.71; H, 10.69; S, 18.48.

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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: Stuttgart, **2011**, Chap. 2.6, 311. (c) Brière, J.-F.; Metzner, P. In *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T.; Bolm, C., Eds.; Wiley-VCH: Weinheim, **2009**, Chap. 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.

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(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. Patent 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) Nakatsuchi, A. *J. Soc. Chem. Ind. Japan (Suppl. Binding)* **1930**, *33*, 408. (b) Nakatsuchi, A. *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*, 6th 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) Berti, G.; Botari, F.; Ferrarini, P. L.; Macchia, B. J. *J. Org. Chem.* **1965**, *30*, 4091.

(13) Fox, D.; Pedersen, D.; Petersen, A.; Warren, S. *Org. Biomol. Chem.* **2006**, *4*, 3117.

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