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Computer-assisted discovery of novel amino acid derived sulfides for enantioselective epoxidation of aldehydes

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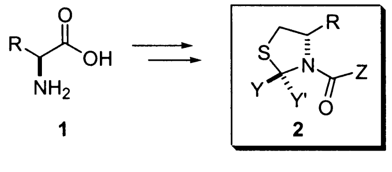
Abstract—With the aid of molecular modeling, thiazolidine derivatives have been designed as catalysts for epoxidation of aldehydes. Accessible from amino acids, the thiazolidine derivatives can be synthesized in both enantiomeric forms and with a diverse array of substituents. A representative member, (*S*)-*N*-*tert*-butoxycarbonyl-2,2-dimethyl-4-isopropyl thiazolidine, of the thiazolidine family has been prepared, and it has been shown to catalyze the formation of *trans*-stilbene oxide with high enantioselectivity. Experimental and theoretical characterization has allowed the evaluation of the factors affecting enantioselectivity, facilitating the design of second-generation thiazolidines and other chiral sulfides as epoxidation catalysts. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

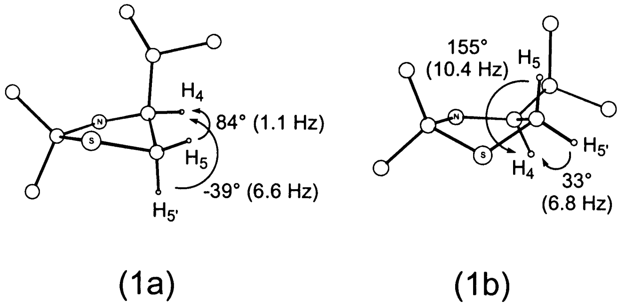
Chiral sulfides, via the corresponding sulfonium ylides, are becoming increasingly important sources of chirality in asymmetric transformations, finding applications in enantioselective epoxidation,[1,2a–d] cyclopropanation[2a,e,f] and aziridination[2a,g,h] reactions. Furthermore, the recently introduced carbene-based conditions allow the use of catalytic amounts of sulfides and have expanded the scope of the reactions to base-sensitive substrates, such as enolizable aldehydes.[3] As different applications are likely to have different optimal chiral sulfides, easy fine tuning is a highly desirable property. Here, we describe the computer-assisted design of *a novel family of chiral sulfides* **2** that (1) offers a high degree of variability, (2) can be synthesized using a general route from common starting materials **1** and (3) is accessible in both enantiomeric forms (Scheme 1).[4] We demonstrate the potential of **2** in providing high enantioselectivities by synthesizing a representative member of **2** and using it in catalytic epoxidation of aldehydes, coupled with experimental and theoretical evaluation of the factors contributing to enantioselectivity. Our molecular design effort reported here, building on our previous theoretical studies,[5] serves as an example in designing other types of chiral sulfides and other chiral catalysts.

As a large and diverse group of compounds often available in both enantiomeric forms, amino acids appeared attractive starting materials for new chiral sulfides. Considerations of minimal synthetic sequence, sulfur electron pair selectivity,[2b] a related crystal structure[6] and the ability to better accommodate the advantageous gem-dimethyl (see below) and related moieties led to a five-membered cyclic scaffold. Computational[7] and conceptual exploration of several substituted alternatives pointed to the thiazolidine family **2**, due to its modularity and sufficiently rigid ring system. Thus,



R = *i*-Pr, *t*-Bu; Z = O-t-Bu, O-Bz, Ph; Y/Y' = H/H, H/Me, Me/H, Me/Me, H/i-Pr...

Scheme 1.



(1a) (1b)

Figure 1. Pseudoaxial (1a) and pseudoequatorial (1b) conformations of **11** with the calculated coupling constants. The BOC group has been omitted for clarity.

Keywords: catalysis; epoxidation; thiazolidines; molecular modeling; enantioselectivity.

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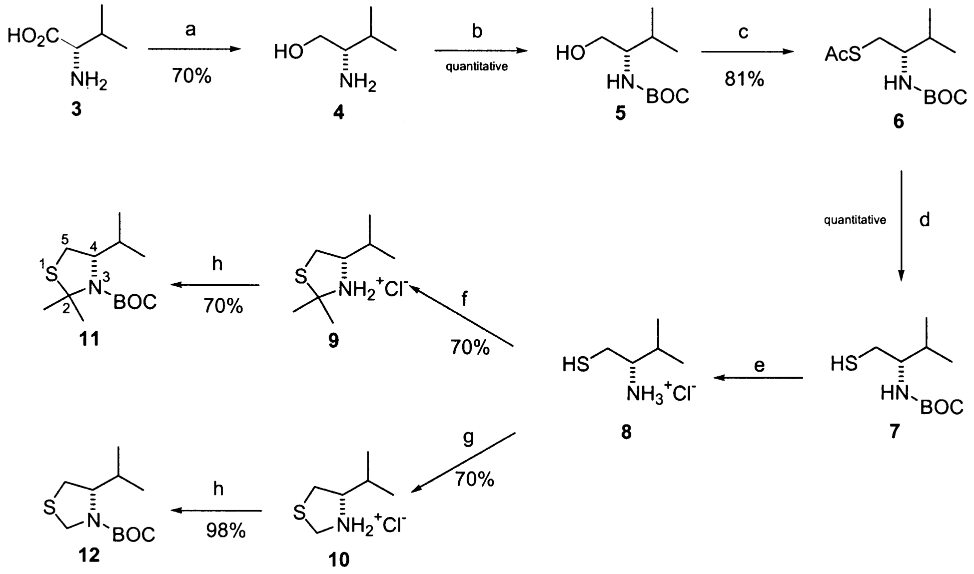


Scheme 2. Synthesis of **11** and **12**. *Reagents and conditions*: (a) $LiAlH_4$, THF; (b) $(BOC)_2O$, CH_2Cl_2; (c) DIAD, Ph_3P, AcSH, THF; (d) KOH, MeOH; (e) 1:1 MeOH:HCl (conc.), rfx; (f) 5:2 acetone:2,2-DMP; (g) HCHO (aq.), EtOH; (h) $(BOC)_2O$, MeCN, 50°C.

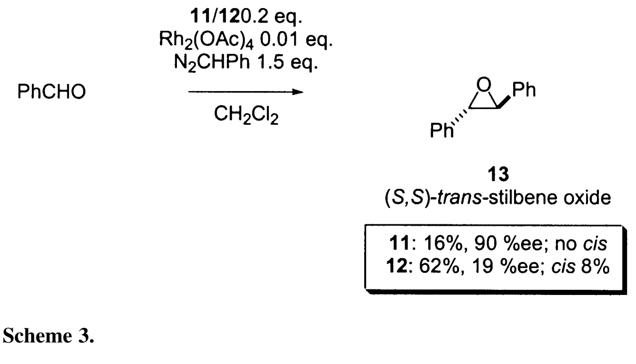
substituent R α to an sp^2 like nitrogen carrying an exocyclic acyl substituent was required to freeze pseudorotation of the ring. In the global energy minimum of **2**, R prefers the pseudoaxial orientation (Fig. 1, 1a, R=*i*-Pr and Z=O-*t*-Bu), and modeling suggested that suitable R groups can extend over the pseudoaxial electron pair of sulfur, if necessary, to prevent its reaction with electrophiles. In **2**, Y/Y′ control ylide facial selectivity while Z, pointing away from the reactive center, can contain auxiliary functions, such as a chromophore or an attachment point to resin. Since R, Y/ Y′ and Z can all be easily varied in **2**, a highly tunable system was designed.

2. Results and discussion

Thiazolidines **2** can be synthesized from cysteine (R=CO_2R' or nucleophilic addition products of it) or from other amino acids via reduction and O to S exchange (Scheme 1, R=amino acid side chain). We chose the latter route, using valine with its bulky, hydrophobic side chain as our starting material (Scheme 2). We prepared (*S*)-*N*-*tert*-butoxycarbonyl-2,2-dimethyl-4-isopropyl thiazolidine **11** (Y=Y′=Me) for proposed high enantioselectivity and (*S*)-*N*-*tert*-butoxycarbonyl-4-isopropyl thiazolidine **12** (Y=Y′=H) as our control compound to study the 'background' enantioselectivity of **11**.

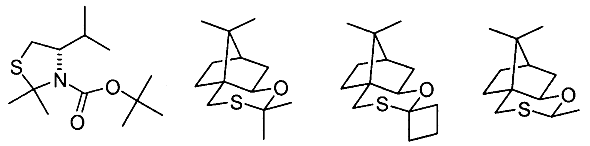
Standard reduction[8] and protection of L-valine yielded N-BOC-valinol **5**. The corresponding amino thiol **7** was synthesized via a thioacetate obtained by a modified Mitsunobu reaction,[9] followed by clean saponification with no disulfide formation.[10] We first attempted a direct ring closure to afford **11**, as such ring closure has been reported in the synthesis of oxazolidines.[11,12] Unfortunately, we were unsuccessful,[13] and we developed an alternative approach, employing the known formation of thiazolidines from unprotected amino thiols.[14–16] Consequently, a sequence of deprotection, ring closure and reprotection was carried out for **7**. While the deprotection required harsh conditions, the ring closure proceeded smoothly, with the product precipitating from the reaction medium. Finally, the BOC group was reintroduced using a slow but clean procedure (14d, 50°C, MeCN), avoiding the intractable mixtures obtained in the presence of DMAP or excess of base.[17] Acetylation and benzoylation were also tested in the final protection step, but were found unsatisfactory due to their preferential reactivity towards sulfur.[18–20]

We examined **11** in the previously reported conditions for catalytic epoxidation of aldehydes.[3] As the primary focus of our molecular design efforts is stereoselectivity, the literature conditions[3] were mimicked as closely as possible so that the stereoselectivity of **11** could be directly compared to those of reported catalysts.[2b] With **11**, (*S*,*S*)-*trans*-stilbene oxide **13** was obtained in 90 %ee (Scheme 3),[21] demonstrating that high enantioselectivities can be obtained with thiazolidines **2**. As expected, the control compound **12** yielded the product with the same absolute configuration but with low enantioselectivity, underlining the crucial role of the gem-dimethyl function. The absolute stereochemistry of the product is consistent with the previously proposed reaction mechanism[3,5] and the stereochemistry of **11**. The yield observed in the epoxidation with **11** as a catalyst was low (16%) but is well in line with the structurally corresponding catalyst **14** (11%)[2b], (Table 1). Sterically less hindered catalyst **12** gave *trans*-epoxide **13**



Scheme 3.

Table 1. Correlation between ring pseudorotation and enantioselectivity.



11 **14** **15** **16**

Compound	Ring conformers (low E–high E)	ΔE / kcal/mol[a]	Limiting %ee[b]	Observed %ee[c]
11	*i*-Pr pseudo-ax.–pseudo-eq.	1.9	92	90
14	oxathiane ring chair – twist	0.7	53	70[d]
15	oxathiane ring chair – twist	1.1	73	89[d]
16	oxathiane ring chair – twist	3.1	98.9	93[d,e]

[a] The relative energy of the ring conformers calculated at the B3LYP/6-31G*//HF/3-21G* level.

[b] Calculated from ΔG=−RTlnK at 25°C, assuming ΔG=ΔE.

[c] In the formation of *trans*-stilbene oxide in the catalytic conditions.[3]

[d] From literature.[2b]

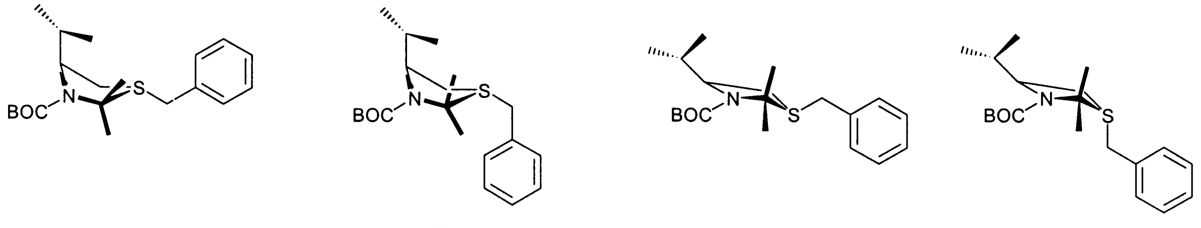
[e] *trans*-Mesitylenyl phenyl oxirane was obtained with 98 %ee.[2b]

with 62% yield. The choice of the transition metal catalyst affects yields.[2b] In order to avoid decomposition of sulfide catalysts we were forced to replace $Cu(acac)_2$ by $Rh_2(OAc)_4$, thought.

In an effort to evaluate the relative energies of the ring conformers (Fig. 1), 1D ^1H NMR spectra of **11** were recorded at −50–+100°C. Unfortunately, separate sets of signals could not be detected for the two ring conformers, an observation in line with the very low interconversion barrier subsequently calculated by quantum chemical methods.[22] However, the preferred ring conformation could be identified by comparison of calculated [23,24] (Fig. 1) and experimental (1.1 and 6.0 Hz at rt in $(CDCl_2)_2$) vicinal coupling constants between H_4 and $H_5/H_{5'}$. Consequently, the pseudoaxial ring conformation used in the design was also implicated by experiment.

In the absence of experimental value, quantum chemical methods were used to estimate the relative energy of the ring conformers in **11**, and, for reference purposes, in the published sulfides **14–16** (Table 1). The two ring conformers of **11** are expected to lead to enantiomeric products. In pseudoaxial conformation of **11** (Fig. 1, 1a) the *iso*-propyl group extends over the pseudoaxial electron pair of sulfur preventing its reaction with electrophiles. The ylide derived from the remaining reactive sulfur lone pair can adopt two conformations (Fig. 2, 2a and 2b). Because the *anti* ylide **2b** suffers from 1,3 interactions between the phenyl and methyl groups and even between the phenyl and pseudoaxial $H_{5'}$, the only possible ylide conformation resulting from pseudoaxial conformation of **11** is **2a** (*syn*). In corresponding pseudoequatorial conformation of **11** the *iso*-propyl moiety is pseudoequatorial leaving both sulfur electron pairs reactive. The resulting two different ylide conformations **2c** and **2d** (Fig. 2) lead to opposite enantiomeric products. Assuming that the kinetic properties of the reaction pathways involving the two ring conformers are equivalent, %ee values were calculated from the relative energies of the ring conformers. Given the simplicity of the assumptions and the possible errors[25] in the calculated energy values, surprisingly good correlation with the experimental %ee values is observed. Apparently, the rigidity of the ring may place an upper limit to the enantioselectivity that can be achieved with a particular system. Thus, even if facial selectivity caused by the gem-dimethyl group in **11** warranted 99+ %ee, ring pseudorotation in **11** seems to limit enantioselectivity to 92 %ee. On the other hand, with **16** the limiting 98.9 %ee is not reached in stilbene oxide formation due to insufficient facial selectivity. However, it is realized when the phenyl group is exhanged to the more sterically demanding mesityl group.[2b]

In an attempt to evaluate the contributions from enantiofacial selectivity and ring pseudorotation separately, the transition states (TS) derived from the low energy ring conformers of **11** and **16** and leading to *trans*-stilbene oxide formation were calculated using a quantum chemical approach and simplified model molecules (Fig. 3). Additionally, the TS calculations allowed separate estimation of the directional and facial contributions to ylide facial selectivity. Although the energy values appear



(2a) (2b) (2c) (3d)

Figure 2.

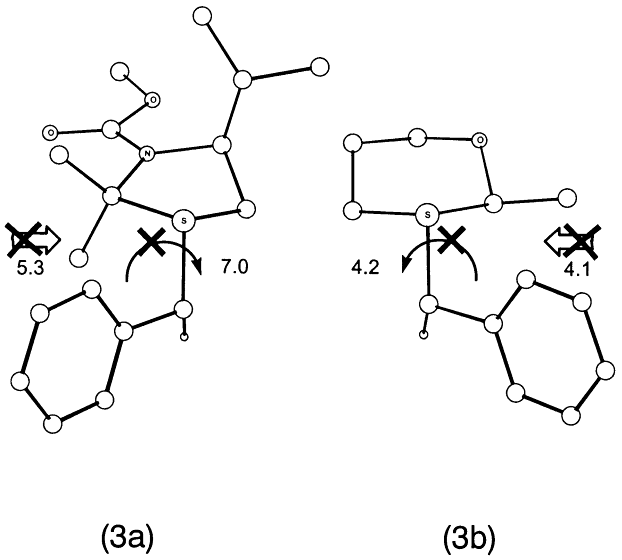


Figure 3. Model transition states (TS) of *trans*-stilbene oxide formation corresponding to **11** (3a) and **16**[5] (3b). Large arrows represent the approach of PhCHO from the more hindered side, and curved arrows represent the TSs with the *anti* ylide conformation.[5] Energies (in kcal/mol, B3LYP/6-31+G*//HF/3-21G* level) of the TSs leading to minor enantiomers are shown. In each case, the energies are relative to the TSs leading to the major enantiomers, illustrated above without the PhCHO component.

to be overestimates,[5] comparison of corresponding energies between **11** and **16** suggests that the gem-dimethyl group in **11** significantly improves ylide conformational selectivity while providing at least the same level of directional selectivity as the single methyl group in **16**. Even though the TS data suggests **11** should yield higher enantioselectivity than **16** in stilbene oxide formation, the data should be considered in conjunction with the limiting 92 %ee of **11** (Table 1) caused by ring pseudorotation. However, according to the TS data, thiazolidines **2** could perhaps offer even higher enantioselectivities if their rings could be made more rigid. To this end, we are currently synthesizing additional examples of **2** with R=*t*-Bu and/or Y=Me, Y′=H. Initial molecular modeling suggests that the latter type of modification introducing a (pseudo)axial methyl group, while unfavorable in the case of **14**, both rigidifies the thiazolidine ring and selectively destabilizes the *anti* sulfonium benzylide conformation. Decreasing the sterical bulkiness adjacent to sulfur should even result in enhanced yields of epoxide.[2b]

3. Conclusion

In conclusion, intimate coupling of theory and experiment has facilitated the design of a family of chiral sulfides **2** demonstrating high enantioselectivity. Furthermore, careful consideration of the factors contributing to enantioselectivity has provided a consistent hypothesis suggesting why **2** work and how they can be further improved. In addition to the new members of **2** discussed above, we are investigating other related sulfides using our computer-assisted approach. Results from these studies will be reported in due course.

4. Experimental

4.1. General methods

THF was distilled prior to use from sodium/benzophenone, CH_3CN from phosphorus pentoxide, methanol from magnesium methoxide and CH_2Cl_2 from CaH_2. All other solvents and reagents, unless otherwise noted, were used as obtained from the supplier without further purification. Melting points were measured with Gallenkamp melting point apparatus MFB-595 and are uncorrected. NMR spectra were determined on Bruker AM200 (^{1}H 200.13 MHz, ^{13}C 50.32 MHz). Chemical shifts are reported in ppm (δ) with respect to scale calibrated to solvent's residual signal. Unless aqueous, all reactions were carried out under protective atmosphere (Ar). Temperatures refer to bath temperatures unless otherwise noted. Organic extracts were first treated with brine, dried over Na_2SO_4, filtered and evaporated with a Büchi rotary evaporator (water aspirator) followed by static evaporation with an oil pump The Kieselgel 60 F_{254} impregnated aluminum plates were used for analytical TLC. The TLC plates were visualized with UV (λ=254) and either phosphomolybdic acid in 90% EtOH (10 mg/100 ml), ninhydrin/glacial acetic acid/EtOH (1 g/0.1 ml/100 ml) or with vanillin/H_2SO_4/EtOH (12 g/5 ml/100 ml). The chromatographic separations were done with MPLC using Silica gel 60 (E. Merck) as the stationary phase. Chiral HPLC chromatograms were measured using the following columns: Daicel chiralcel OD 25 cm×0.46 cm with Daicel chiralcel OD 5 cm×0.46 cm precolumn. In all cases a racemic sample was run to check the retention times of the enantiomers. The mass spectra were measured by the University of Oulu mass spectrometry laboratory on a Kratos 80 mass instrument. Elemental analyses were performed by the University of Oulu Trace Element Laboratory. Optical rotations were determined with Perkin–Elmer 243 B polarimeter (c=g/100 mL).

4.2. L-Valinol (1-Butanol, 2-amino-3-methyl-, (*S*)-) (4)

L-valine **3** (9.92 g, 84.5 mmol, 100 mol %) was carefully added to a stirred suspension of lithium aluminium hydride (4.81 g, 126.8 mmol, 150 mol %) in THF (110 mL) at 0°C. The reaction mixture was allowed to warm up to room temperature. After the most vigorous reaction had settled the reaction mixture was refluxed for 16 hours. After cooling to ambient temperature Et_2O (80 mL) was added, the reaction was very cautiously quenched with water (2.0 ml, 110 mmol, 130 mol %) and the resulting mixture was stirred for 2 hours. Slightly greyish alumina was removed by filtration and washed with Et_2O. The filtrate was evaporated to dryness and the yellowish crude product was purified by Kugelrohr distillation (58°C, 0.11 torr) to yield **4** (6.10 g, 59.2 mmol, 70%) as a white solid. mp 29–31°C, literature[26] mp 29–31°C. $[\alpha]_D^{20}$=+12.4 (c=0.93, MeOH). The ^{1}H NMR spectrum was identical to literature data.[8]

4.3. *N*-(*tert*-Butoxycarbonyl)-L-valinol (5)

L-valinol **4** (5.00 g, 48.5 mmol, 100 mol %) was dissolved in CH_2Cl_2 (18 mL) and the mixture was cooled to 0°C. To this solution was carefully added di-*tert*-butyldicarbonate (10.07 g, 46.2 mmol, 95 mol %) in CH_2Cl_2 (7 mL). The reaction mixture was allowed to warm up to room temperature and stirred for 45 minutes. The reaction mixture was washed with 3×30 ml of 20% citric acid and once with brine (40mL). The organic layer was evaporated to dryness to yield pure **5** (9.85 g, 48.5 mmol, quant.) as a yellow, viscous oil. R_f (1:1 MeOH:EtOAc)=0.40. $[\alpha]_D^{20}=-15.2$ (c=1.0, MeOH). The ^1H NMR spectrum was identical to literature data.[27]

4.4. (*S*)-1-Thio-acetyl-2-amino-*N*-(*tert*-butoxycarbonyl)-3-methyl-butane (6)

Triphenylphosphine (17.69 g, 67.4 mmol, 200 mol %) was dissolved in THF (100 mL) and the solution was cooled to 0°C. Di-isopropyl azodicarboxylate (14.0 mL, 67.4 mmol, 200 mol %) was added and the reaction mixture was stirred for 30 minutes. A white precipitate formed. BOC-L-valinol **5** (6.85 g, 33.7 mmol, 100 mol %) and thiolacetic acid (5.0 mL, 67.4 mmol, 200 mol %) in THF (50 mL) was added dropwise over 15 minutes and the mixture was stirred for 1 hour at 0°C and 4 hours at ambient temperature. The resulting yellow solution was evaporated to dryness and dissolved in Et_2O. The precipitated triphenylphosphine oxide was filtered off, and the filtrate was evaporated to dryness. The precipitation procedure was repeated several times. The crude product was purified by MPLC (12.5% MTBE in hexanes) to yield **6** (7.13 g, 27.3 mmol, 81%) as a white solid. mp 59–60°C. R_f (1:1 MeOH:EtOAc)=0.40. $[\alpha]_D^{20}=+71.2$ (c=1.0, MeOH). The ^1H NMR spectrum was identical to literature data.[27]

4.5. (*S*)-1-Thio-2-amino-*N*-(*tert*-butoxycarbonyl)-3-methyl-butane (7)

Thiol acetate **6** (1.50 g, 5.74 mmol, 100 mol %) and KOH (644 mg, 11.5 mmol, 200 mol %) were dissolved in methanol (10 mL). The solution was stirred for 30 minutes at ambient temperature after which the reaction was quickly quenched with 50% citric acid (25 mL). CH_2Cl_2 (30mL) was added and the resulting organic layer was washed with 20% citric acid (2×20 mL) and once with brine (30 mL), dried and evaporated to dryness to yield **7** (1.26 g, 5.74 mmol, quant.) as a white solid. mp 48–49°C. R_f (33% MTBE in hexanes)=0.38. $[\alpha]_D^{20}=+2.2$ (c=1.0, MeOH). ^1H NMR ($CDCl_3$) δ 0.89 (d, 3H, J=6.8 Hz), 0.90 (d, 3H, J=6.8 Hz), 1.28 (t, 1H, J=8.3 Hz), 1.43 (s, 9H), 1.85 (app. septet, 1H, J=6.8 Hz), 2.66 (dd, 2H, J=8.3 Hz, 5.4 Hz), 3.49 (m, 1H), 4.61 (d, 1H, J=7.9 Hz). ^{13}C NMR ($CDCl_3$) δ 18.0, 19.4, 27.6, 28.3, 30.2, 57.1, 79.3, 155.7. HRMS *m/z* calcd. for $C_9H_{18}NO_2S$ $(M-CH_3)^+$ 204.1058, found 204.1091.

4.6. (*S*)-1-Thio-2-amino-3-methyl-butane hydrochloride salt (8)

Thiol **7** (1.32 g, 6.02 mmol, 100 mol %) was dissolved in methanol (10 mL) and concentrated HCl (10 mL, 37% aqueous solution) was added. The reaction mixture was refluxed for 8 hours. Evaporation to dryness followed by evaporation from a suspension with toluene yielded **8** (915 mg, 5.87 mmol, 98%) as a semi-solid mass. The substance was used for subsequent reactions without further purification.

4.7. (*S*)-2,2-Dimethyl-4-isopropyl-thiazolidine hydrochloride salt (9)

Thiol hydrochloride salt **8** (915 mg, 5.88 mmol, 100 mol %) was dissolved in acetone (25 mL) and 2,2-dimethoxypropane (10 mL) was added. The mixture was refluxed for 12 hours, with thiazolidine hydrochloride salt **9** gradually precipitating from the reaction medium. The crude product was filtered and washed several times with acetone to yield **9** (802 mg, 4.10 mmol, 70%) as a white solid. mp 220–223°C. R_f (25% MTBE in hexanes)=0.35. $[\alpha]_D^{20}=+30.8$ (c=1.0, MeOH). ^1H NMR (CD_3OD) δ 1.09 (d, 3H, J=6.6 Hz), 1.16 (d, 3H, J=6.6 Hz), 1.81 (s, 3H), 1.84 (s, 3H), 2.05 (m, 1H), 3.15 (dd, 1H, J=11.5 Hz, 9.2 Hz), 3.57 (dd, 1H, J=11.5 Hz, 7.3 Hz), 3.83 (m, 1H). ^{13}C NMR (CD_3OD) δ 20.0, 21.0, 27.6, 29.2, 32.6, 34.3, 69.4, 73.2. HRMS *m/z* calcd. for $C_8H_{17}NS$ $(M)^+$ 159.1082, found 159.1121. Anal. calcd. for $C_8H_{18}ClNS$ C 49.08, H 9.27, Cl 18.11, N 7.16, S 16.38; found C 49.16, H 9.26, N 7.34, S 16.68.

4.8. (*S*)-4-Isopropyl-thiazolidine hydrochloride salt (10)

Thiol hydrochloride salt **8** (258 mg, 1.66 mmol, 100 mol %) was dissolved in ethanol (2.5 mL) and 35% aqueous formaldehyde solution (131 μL,1.66 mmol, 100 mol %) was added. The mixture was stirred at ambient temperature for 30 minutes and then at 70°C for 30 minutes. The reaction mixture was cooled down and evaporated to dryness. The crude product was washed several times with acetone to yield **10** (194 mg, 1.16 mmol, 70%) as a white solid. mp 157–158°C. R_f (50% MTBE in hexanes)=0.38. $[\alpha]_D^{20}=+22.1$ (c=1.0, MeOH). ^1H NMR (CD_3OD) δ 1.09 (d, 3H, J=6.6 Hz), 1.15 (d, 3H, J=6.6 Hz), 2.07 (m, 1H), 2.99 (dd, 1H, J=11.5 Hz, 9.7 Hz), 3.47 (m, 2H), 4.35 (d, 1H, J=10.0 Hz), 4.42 (d, 1H, J=10.0 Hz). ^{13}C NMR (CD_3OD) δ 19.6, 20.3, 31.3, 33.3, 70.7. HRMS *m/z* calcd. for $C_6H_{13}NS$ $(M)^+$ 131.0769, found 131.0755.

4.9. (*S*)-2,2-Dimethyl-3-*tert*-butoxycarbonyl-4-isopropyl-thiazolidine (11)

Thiazolidine hydrochloride salt **9** (673 mg, 3.44 mmol, 100 mol %) and di-*tert*-butyldicarbonate (998 mg, 4.57 mmol, 133 mol %) were dissolved in acetonitrile (10 mL). DIPEA (611 μl, 3.51 mmol, 102 mol %) was added dropwise to this solution at room temperature. The mixture was stirred at 50°C for 14 days. The reaction mixture was cooled down and evaporated to dryness. The crude product was purified by MPLC (14% MTBE in hexanes) to yield **11** (625 mg, 2.41 mmol, 70%) as a colorless liquid. R_f (25% MTBE in hexanes)=0.61. $[\alpha]_D^{20}=+43.7$ (c=0.38, MeOH). ^1H NMR ($(CDCl_2)_2$, 50°C) δ 0.96 (d, 1H, J=6.9 Hz), 0.97 (d, 1H, J=6.9 Hz), 1.48 (s, 9H), 1.77 (s, 3H), 1.80 (s, 3H), 2.20 (app. septet, 1H, J=6.9 Hz), 2.69 (dd, 1H, J=11.7 Hz, 1.5 Hz), 3.10 (dd, 1H, J=11.7 Hz, 6.4 Hz), 4.20 (app. td, 1H, J=6.4 Hz, 1.5 Hz). ^{13}C NMR ($CDCl_3$) δ 19.4, 19.9, 28.4, 29.4, 30.6, 31.6, 69.3, 70.0, 79.8, 153.3. HRMS *m/z* calcd. for $C_{13}H_{26}NO_2S$ $(M+H)^+$ 260.1684, found 260.1696.

4.10. (*S*)-3-*tert*-Butoxycarbonyl-4-isopropyl-thiazolidine (12)

Thiazolidine hydrochloride salt **10** (99 mg, 0.59 mmol, 100 mol %) and di-*tert*-butyldicarbonate (255 mg, 1.18 mmol, 200 mol %) were dissolved in acetonitrile (5 mL). DIPEA (105 μl, 0.60 mmol, 102 mol %) was added dropwise to this solution at room temperature. The mixture was stirred at 50°C for 24 hours. The reaction mixture was cooled down and evaporated to dryness. The crude product was purified by MPLC (14.29% MTBE in hexanes) to yield **12** (134 mg, 0.58 mmol, 98%) as a colorless liquid. R_f (25% MTBE in hexanes)=0.56. $[\alpha]_D^{20}=+102.5$ (c=3.46, MeOH). ^1H NMR ($CDCl_3$) δ 0.91 (d, 3H, J=6.8 Hz), 0.92 (d, 3H, J=6.7 Hz), 1.45 (s, 9H), 1.94 (app. septet, 1H, J=6.8 Hz), 2.86 (dd, 1H, J=11.0 Hz, 3.4 Hz), 2.99 (dd, 1H, J=11.0 Hz, 6.5 Hz), 4.06 (d, 1H, J=9.0 Hz), 4.13 (b s, 1H), 4.83 (b d, 1H, J=9.0 Hz). ^{13}C NMR ($CDCl_3$) δ 18.9, 19.1, 28.3, 30.3, 47.5, 65.0, 80.3, 153.9. HRMS *m/z* calcd. for $C_{11}H_{22}NO_2S$ $(M+H)^+$ 232.1371, found 232.1339.

4.11. Epoxidation with sulfide 11

Benzaldehyde (59 μl, 0.58 mmol) and phenyldiazomethane[28] (0.87 mmol in CH_2Cl_2 (1 mL)) in the presence of $Rh_2(OAc)_4$ (3 mg, 0.007 mmol) and sulfide **6** (30 mg, 0.12 mmol) in 0.3 ml of CH_2Cl_2 yielded *(S,S)-trans*-stilbene oxide **13** (18 mg, 0.092 mmol, 16%) with 90% enantiomeric excess. The retention times of enantiomers were 7.79 min *(S,S)* and 13.83 min *(R,R)*(5% isopropanol in hexanes, flow rate 1.0 ml/min). No *cis* epoxide was observed. The product was separated with MPLC (25% CH_2Cl_2 in hexanes) and the NMR spectrum compared favorably with literature data.[29]

4.12. Epoxidation with sulfide 12

Benzaldehyde (102 μl, 1.00 mmol) and phenyldiazomethane (1.50 mmol in CH_2Cl_2 (1 mL)) in the presence of $Rh_2(OAc)_4$ (4 mg, 0.01 mmol) and sulfide **7** (46 mg, 0.20 mmol) in 0.5 ml of CH_2Cl_2 yielded *(S,S)-trans*-stilbene oxide **8** (121 mg, 0.62mmol, 62%) and *cis*-stilbene oxide (17 mg, 0.08 mmol, 8%); (*cis:trans* 12:88). *(S,S)-trans*-stilbene oxide was formed with 19% enantiomeric excess. The retention times of enantiomers were 9.28 min *(S,S)* and 13.82 min *(R,R)*(5% isopropanol in hexanes, flow rate 1.0 ml/min).

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