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REACTIVITY OF (*R*)-4-PHENYLOXAZOLIDINE-2-THIONE CHIRAL AUXILIARY: FROM DEPROTECTION TO HETEROCYCLIC INTERCONVERSION

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Abstract - Using (*R*)-3-benzyl-4-phenyloxazolidin-2-thione (**2**) as model compound, a sequence of reactions has been established that allows the chiral auxiliary deprotection to furnish a primary amine. Treatment of **2** with ethyl triflate (**3b**) followed by ring opening with RbI (**4b**) and HI elimination with DBU, in a one pot process, gave *S*-ethyl-*N*-benzyl-*N*-1-phenylvinylcarbamothioate (**5**, 95% yield) which acid hydrolysis (**9**) and saponification liberated benzylamine. Through a mechanistic study, we showed that the activated chiral oxazolidin-2-thione **3b** is a tunable intermediate towards the corresponding oxazolidin-2-one **7**, thiazolidin-2-one **8** and thiazolidin-2-thione **10**. All those reactions were chemoselective and preserved the chiral center. A structural analysis of this series of heterocycles, by NMR and X-ray diffraction, has been performed.

INTRODUCTION

Homochiral oxazolidin-2-(thi)ones and thiazolidin-2-(thi)ones[1,2] have found synthetic applications mainly as vehicle to transfer chirality, with predictable stereochemistry of the newly formed stereocenters.[3] Contrary to chiral catalysts, chiral auxiliaries are used in stoichiometric amounts and their involvement in organic chemistry is based on the “protecting group” concept: their attachment to the substrate has to be

stable under the reaction conditions but their deprotection at the end of the synthesis has to be easy, complete and smooth, to avoid degradation, isomerisation, … of the target-molecule. Ideal situation is reached when the recycling of the chiral source is possible; this is the case when the Evan's type chiral auxiliaries are anchored on the substrate via an acyl function as illustrated in **Figure 1** (exocyclic hydrolysis).[4-6] But occasionally, the heterocyclic nitrogen atom is designed to make part of the final target-molecule and hence, the chiral auxiliaries have to be sacrified by a ring opening reaction (**Figure 1**, endocyclic hydrolysis). This is also the situation if the nitrogen atom cannot be introduced via exocyclic aminolysis because of the absence of acyl-anchoring function.[3] Very few examples of endocyclic cleavage have been illustrated in the literature and moreover they have been specifically applied to oxazolidin-2-one (X = Y = O) chiral auxiliaries.[7-9]

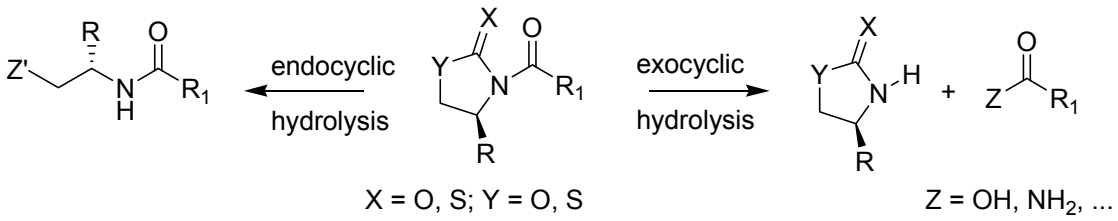


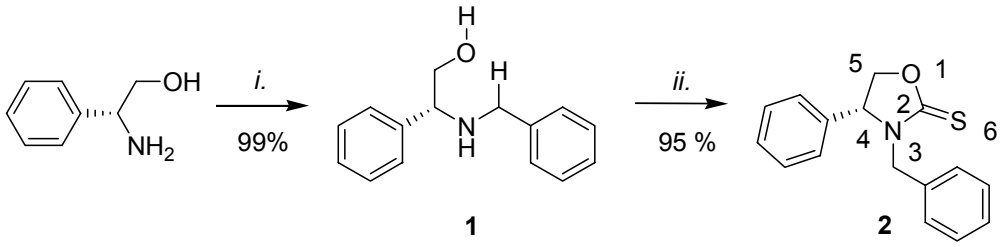
Figure 1. Cleavage modes of chiral auxiliaries from the literature

We have previously developed a novel 1-amino-diene, *N*-protected with a chiral oxazolidin-2-thione moiety.[10] This reagent revealed very useful in [4+2] Diels-Alder reactions, giving cycloadducts with very high diastereoselectivities, particularly in the case of phosphonodienophiles.[3] This stimulates our interest in the selective ″deprotection″ of oxazolidin-2-thione chiral auxiliaries. Our objective was to replace the heterocycle with a free primary amine function, which nitrogen atom comes from the heterocycle.

In this paper, we illustrate an original deprotection method validated on the model compound **2** featuring a masked benzylamine. A one-pot protocol involving four steps leads efficiently to the free amine. On the way, novel chemo- and stereoselective heterocyclic rearrangements have been discovered. The structural analysis of all heterocycles based on NMR and crystallographic data, is fully described.

RESULTS AND DISCUSSION

1. GENERAL STRATEGY. While oxazolidin-2-thione derivatives are commonly prepared by condensation of carbon disulfide with *β*-aminoalcohols, we successfully made use of a less toxic reagent, *i.e.* 1,1'-thiocarbonyldiimidazole for the condensation with **1** furnishing nearly quantitatively the model compound **2**.[11]



Reagents and conditions: *i.* Benzaldehyde (1 eq.), $MgSO_4$, MeOH, rt, 5 h; then $NaBH_4$, rt, 30 min.; *ii.*Thiocarbonyldiimidazole (1.5 eq.), DCM, rt, 5 h.

Scheme 1. Synthesis of model compound **2**

The precursor **1** was obtained by reductive amination[12] of (*R*)-phenylglycinol (**Scheme 1**). It is well known that this kind of heterocycle **2** is resistant to the cleavage by hydrogenolysis and the most popular method for achieving ″deprotection″ employs sodium or lithium in liquid ammonia,[13] experimental conditions incompatible with a wide range of chemical functions. Accordingly, we decided to exploit the thiocarbonyl reactivity in a first activation step (via a *S*-alkylation reaction), followed by an endocyclic S_N2-like opening step (chemoselective nucleophilic attack on C5); elimination providing an enamine-type intermediate and hydrolysis were planned to achieve the release of the free amine (**Figure 2**).

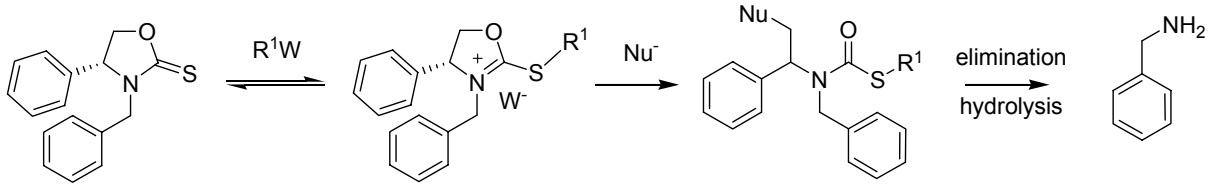


Figure 2. Strategy to cleave the chiral oxazolidin-2-thione moiety

Alkylation of thioamide-containing heterocycles is generally accomplished by using alkyl halides (R^1W; W = Cl, Br, I), while a lot of other alkylating reagents such as propiolactone, diazomethane, α-chloroacetates, isonitriles and *N*-acetyl-chloroacetaldimine[14-19] are able to react on the sulphur atom of C=S bonds with enhanced nucleophilicity due to the presence of two vicinal heteroatoms. The resulting alkyl thionium species generally undergo rapid dealkylation (W = halogen)[19] or evolve towards rearrangement products (W ≠ halogen; see **Figure 2**).[14-19] Alkyl triflates are well known as efficient alkylating agents[20,21] they generate a non-nucleophilic counter-anion $CF_3SO_3^-$, thus avoiding dealkylation. Accordingly, we used methyl, ethyl and isopropyl triflates for the oxazolidin-2-thione activation step. Reaction with **2** in anhydrous acetonitrile at room temperature furnished quantitatively the corresponding alkylated heterocycles **3a**, **3b** and **3c**, after 15 min, 30 min and 15 h respectively (**Figure 3**). We never observed polymerization reactions under those conditions.[22] Intermediates **3** could not be purified, but the crude products were properly characterized by the usual spectroscopies (see Experimental Section). According to the literature, this kind of activated heterocycles offers three sites for further reactions, with

different hardness/softness properties, named **A**, **B** and **C** as shown in **Figure 3**. The **A** and **B** sp^3 soft sites have been respectively involved in polymerization reactions towards optically active polyurethanes[22] and in the above mentioned dealkylation[19] reactions. The **C** sp^2 hard reactive center has been exploited in a novel methodology for opening reactions of thiolactams.[23] In agreement with the strategy outlined in **Figure 2**, we decided to exploit the reactivity of the soft methylene center **A** by opposing metal iodides as soft nucleophiles. In order to possibly control the competition with the reactive site **B** (dealkylation), we considered substrates **3** with various steric hindrance of the SR^1 substituent.

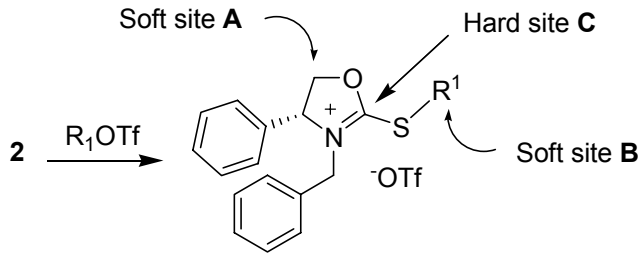


Figure 3. Possible reactions of intermediate **3**

2. MECHANISTIC STUDY. The ring opening of **3** has been investigated through reactions with a stoichiometric amount of alkaline earth metal iodides (MI; M = Rb, K and Li) in view of producing the alkyl iodide derivative **4**, precursor of the enamine compound **5** (**Scheme 2**). Surprisingly, after 15 h of treatment with potassium iodide (KI), in acetonitrile at 0 °C or 20 °C, the starting material **3** was recovered unchanged, independently of the nature of R^1 (**a**, Me; **b**, Et; **c**, *i*Pr). However, in refluxing acetonitrile (MeCN), with a small excess of lithium iodide (LiI), (*R*)-3-benzyl-4-phenylthiazolidin-2-thione (**8**) was quantitatively generated (**Table 1**, entries 1 and 2). Using a more polar solvent, dimethylformamide (DMF), we recovered in all cases (**3a-c** with KI or LiI) a mixture of three products: the desired iodide **4**, the previously obtained heterocycle **8** and (*R*)-3-benzyl-4-phenyloxazolidin-2-one (**7**).[11] Their relative amounts were variable, depending on the nature of R^1 and M. Interestingly, the dealkylation product **2** was never observed. Therefore, we continued our mechanistic study with **3a** and **3b**, more easily accessible than **3c** because the corresponding triflate reagents are commercially available. The behaviour of **3a-b** versus MI, in solution, appeared tunable and the relevant parameters were the following, by order of importance: (a) M softness/hardness; (b) relative concentration [**3**]/[I^-], dilution and rate of addition; (e) solvent nature and dryness (**7** results from hydrolysis of **3**); (d) temperature; (e) R^1 steric hindrance. As shown in **Table 1**, optimal formation of the target compound **4** was reached by slow addition of rubidium iodide (RbI) in 0.19 M DMF solution to a 0.38 M solution of **3** at 0 °C, with R^1 = Et (**4b**, entry 8).

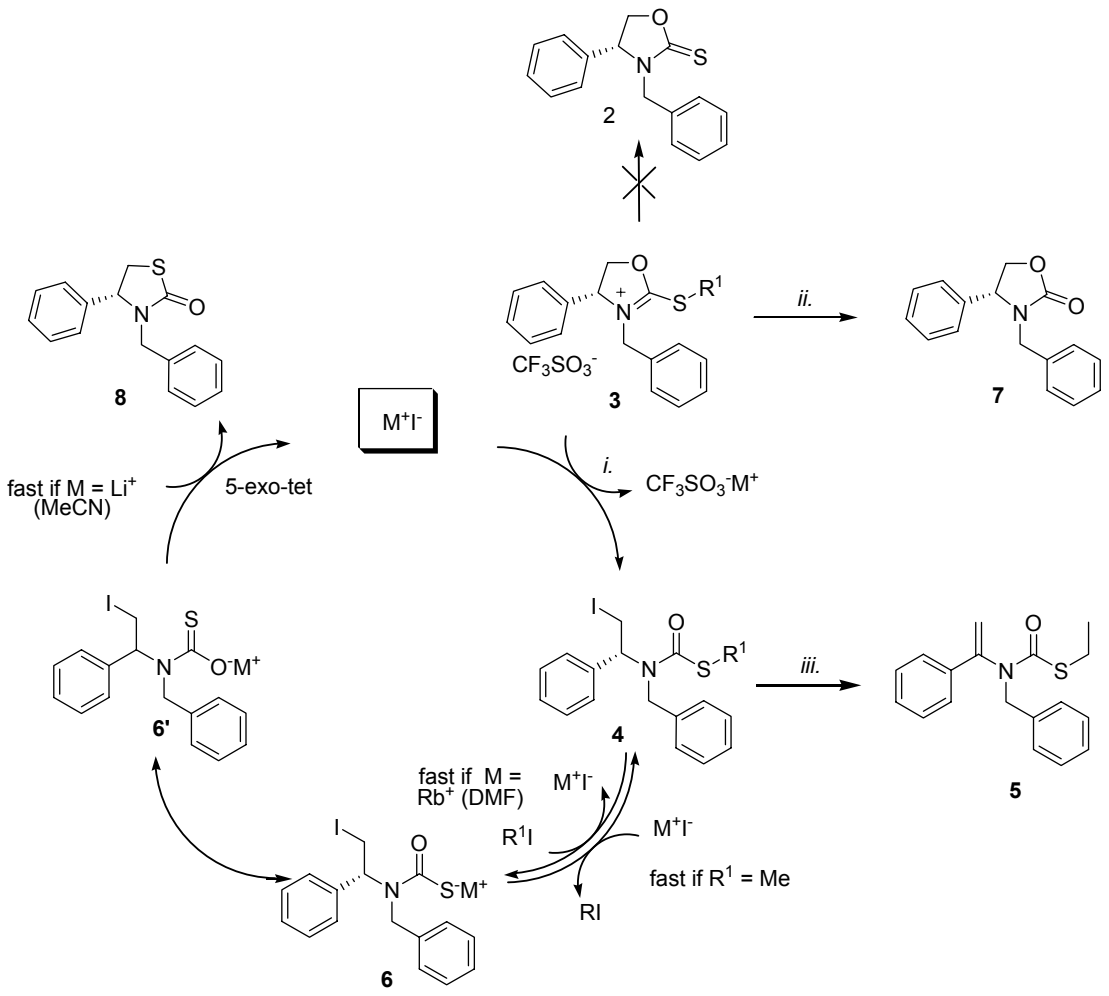
Table 1. Reactions of **3** with MI

Entry	Solvent	T (°C)	Reagent	MI (eq.)	[I] (M)	4 (%) [a]	7 (%) [a]	8 (%) [a]
1	MeCN	0-20	**3a-c**	KI (1)	/ [b]	0	0	0
2	MeCN	reflux	**3a-c**	LiI (1,5)	/ [b]	0	0	> 99
3	DMF	0	**3a**	LiI (1)	0.19 [c]	24	14	53
4	DMF	0	**3a**	KI (1)	0.19 [c]	36	18	45
5	DMF	0	**3a**	RbI (1)	0.19 [c]	58	20	22
6	DMF	0	**3b**	LiI (1)	0.19 [c]	29	6	65
7	DMF	0	**3b**	KI (1)	0.19 [c]	36	15	49
8	DMF	0	**3b**	RbI (1)	0.19 [c]	62	31	6

[a] Determined from ^{1}H NMR (500 MHz) analysis of the crude mixtures; [b] Addition of neat MI in one portion; [c] Slow addition (5 mL/h) of freshly prepared DMF solution (0.19 M) to a 0.38 M solution of **3**.

Formation of **8** remains intriguing under those mild reaction conditions, although isomerization of *O*-alkyl thiocarbamates into *S*-alkylthiolcarbamates in acyclic series[24] and in cyclic series, under Lewis acid activation of the thiocarbonyl moiety, has been previously reported.[25] Formation of **7** implies the reaction of the hard site **C** with residual water (addition-elimination process). This side reaction could be prevented by working with drastically dried solvents and reagents and in the presence of molecular sieve (see Experimental Section).

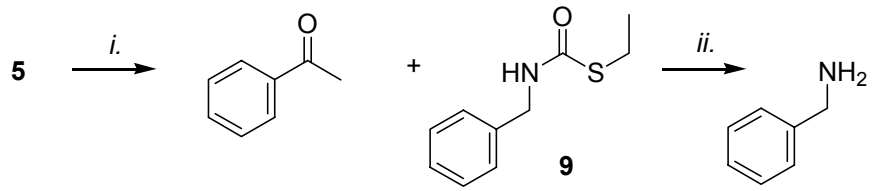
The behavior of *S*-alkyl-3-benzyl-4-phenyloxazolidin-2-thionium triflates (**3**) towards MI implies most probably the soft heterocyclic methylene site **A**. The first supposed step is the desired ring opening leading to **4** which existence could be transitory in the presence of MI. Iodide-dependent dealkylation of **4** led to the transient species **6** (resonance form **6'**) susceptible to undergo (a) the *5-exo-tet* ring closure into **8** in the presence of hard counter-cation and less polar solvent or (b) the realkylation into **4** in the presence of stabilizating factors, namely soft counter-cation and highly polar solvent.[26] As a matter of fact, treatment of **3b** with 1.5 equivalents of LiI in refluxing MeCN furnished **8** in quantitative yield, while the slow addition of 1 equivalent of RbI to **3b** in diluted DMF solution, produced mainly **4b**. Moreover, treatment of **4b** with LiI in MeCN at room temperature led to **8** after a few days, consistently to the proposed mechanism of **Scheme 2**.



Reagents and conditions: *i.* MI (1 eq.), DMF, 0°C, 2.5 h; *ii.* residual water; *iii.* DBU (1.5 eq.), 0°C to rt, overnight.

Scheme 2. Proposed mechanism leading to **4**, **5**, **7** and **8**

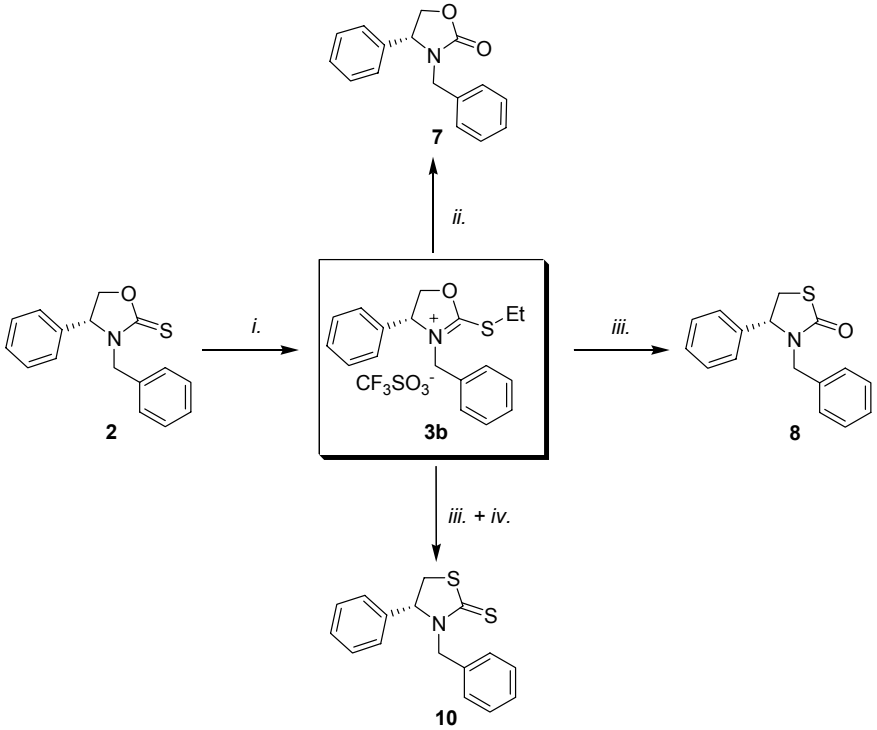
Practically, the optimal conditions for preparing **4b** required the slow addition of a diluted DMF solution of dried RbI to a cold solution of **3b**, in the presence of 4Å molecular sieve (MS) and 1 equivalent of $LiSO_3CF_3$, added to bring the reaction to completion within 1 hour. After column chromatography, pure **4b** could be isolated in 65% yield. However, this compound was poorly stable and the elimination reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) producing **5** (**Scheme 2**) had to be performed immediately. When the complete sequence was realized in a one-pot process, without intermediate purification of **4b**, *S*-ethyl-*N*-benzyl-*N*-1-phenylvinylcarbamothioate (**5**) was obtained in 95% yield. This enamine **5** was found to be quite reluctant to hydrolysis. The compound was stable in hot 6N HCl, but fortunately, could be hydrolyzed by treatment with a MeCN/AcOH/H_2O mixture at 80 °C: acetophenone and *S*-ethyl-*N*-benzylcarbamothioate (**9**)[27] were quantitatively formed (**Scheme 3**). In fact, isolation of **9** was not necessary; acid treatment of **5** as above followed by raising the pH with aqueous LiOH, directly produced benzylamine, thus achieving the complete deprotection of the oxazolidin-2-thione auxiliary.



Reagents and conditions: *i.* MeCN/AcOH/H_2O (2/2/1), 80 °C,17 h; *ii.* LiOH, H_2O, 70 °C, 17 h.

Scheme 3. Hydrolysis of **5**

In view to valorize the versatility of *S*-alkyl oxazolidin-2-thionium triflates (such as **3b**), each of the observed heterocyclic rearrangements was optimized for proposing efficient heterocyclic interconversion pathways. As depicted in **Scheme 4**, conversion of (*R*)-*S*-ethyl-3-benzyl-4-phenyloxazolidin-2-thionium triflate (**3b**) was chemo- and stereo-selective, and almost quantitative: treatment of **3b** with LiI in MeCN at 60 °C led to **8**; addition of LiOH monohydrate to a MeCN solution of **3b** at 60 °C led to **7**. This reaction provides an interesting ″formal oxidation″ process under mild conditions of oxazolidin-2-thiones to oxazolidin-2-ones.[24,28,29] Finally, thionation of **8** with Lawesson's reagent[30-33] in toluene at 85 °C furnished (*R*)-3-benzyl-4-phenylthiazolidin-2-thione (**10**) with 90 % yield.



Reagents and conditions: *i.* $EtSO_3CF_3$ (1.1 eq.), MeCN, rt, 30 min (quant.);
ii. LiOH.H_2O (1 eq.), MeCN, 60 °C, overnight (quant.);
iii. LiI (1.5 eq.), MeCN, 60 °C, overnight (quant.);
iv. Lawesson's reagent (1 eq.), toluene, 85 °C, overnight (90 %).

Scheme 4. Heterocyclic interconversion pathways

3. STRUCTURAL ANALYSIS. Our mechanistic proposal for the reaction of MI with oxazolidin-2-thione **2** relies upon the unambiguous identification of all the formed heterocycles. Compounds **2**, **7** and

8 (unfortunately not **10**) smoothly crystallized in hexane affording crystallographic structural data. The ORTEP[34] views of the crystal structures for heterocycles **2**, **7** and **8** are pictured in **Figures 4**, **5** and **6** respectively. Absolute configuration at C4 was unambiguously determined by X-ray diffraction for compounds **2** and **8**. The antipodal compound (*S*)-**2** has been synthesized from (*S*)-phenylglycinol by using the same protocol as described above, and further engaged in all the described reactions. $[\alpha]_D$ measurements were consistent with stereoselective transformations in both *R* and *S* series (see Experimental Section).

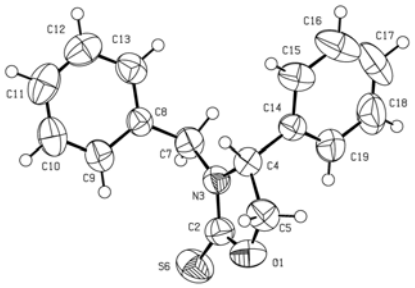


Figure 4. View and atom labelling of (*R*)-3-benzyl-4-phenyloxazolidine-2-thione (**2**)

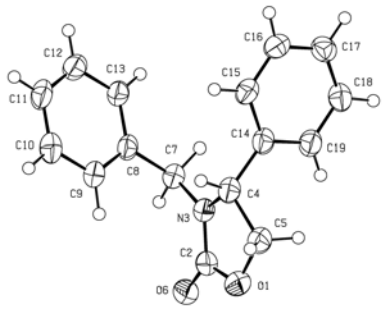


Figure 5. View and atom labelling of (*R*)-3-benzyl-4-phenyloxazolidin-2-one (**7**)

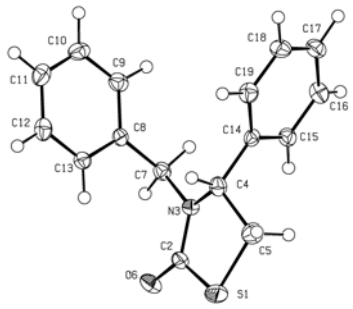


Figure 6. View and atom labelling of (*R*)-3-benzyl-4-phenylthiazolidin-2-one (**8**)

For the three structures, the conformation of the 5-membered heterocycle showed slight modifications: the observed conformation of **2** is half-chair, with two-fold axis passing through the thiocarbonyl function; compound **7** shows a heterocycle conformation as an envelope with the mirror plane passing through the C4 chiral atom, whereas **8** features an intermediate conformation between those two limits.

We have calculated the asymmetry parameter from a perfect half-chair conformation using the procedure of Duax *et al.*[35]; it was in the range 0.7-7 ° indicating only small deformations from the perfect conformation (**Table 2**).

Table 2. Comparison of the torsion angles (degrees; $\sigma = 1°$).

Torsion angle	**2**	**7**	**8**
N3-C2-O1-C5	3	-3	-6
C2-O1-C5-C4	-9	11	22
O1-C5-C4-N3	10	14	-31
C5-C4-N3-C2	-9	13	29
C4-N3-C2-O1	4	-7	-13
ΔC_s(C4)		**2.9**	**6.5**
ΔC_2(C2)	**0.7**		**7**

^{1}H NMR analysis of compounds **2**, **7**, **8** and **10** showed typical features for 5-membered heterocycles. Generally in such heterocycles, *cis* coupling constants (^3J_H) are higher than the corresponding *trans*. For compounds **2**, **7**, **8** and **10**, the *cis* ^3J_H values are indeed higher than the corresponding *trans*, by a range of 1.7 to 3.6 Hz.[36] Representative chemical shifts are collected in **Table 3**. Protons *cis* to the phenyl group showed signals at δ 3.13-4.63, whereas protons *trans* to the phenyl group showed signals at δ 3.54-4.75. An additional observation was that the proton on C4 appears systematicaly at lower field when Y = S than for Y = O.

Table 3. Typical 500 MHz ^{1}H NMR features for compounds **2**, **7**, **8** and **10**.

	δ				**J**			
	H-C_4	H-C_5 *trans*	H-C_5 *cis*	H-C_7	^3J *trans*	^3J *cis*	$^2J_{H\text{-}H(C5)}$ *gem*	$^2J_{H\text{-}H(C7)}$ *gem*
2	4.7	4.4	4.7	3.8-5.5	5.8	9.4	8.2	14.7
7	4.5	4.1	4.6	3.6-4.9	5.8	9.2	7.5	14.7
8	4.6	3.1	3.5	3.5-5.1	6.5	8.2	11.3	14.7
10	5.0	3.1	3.6	3.8-5.9	5.3	8.9	11.2	14.7

CONCLUSION

Through this work, we have emphasized the importance of *S*-alkyl oxazolidin-2-thionium triflate (**3**), obtained quantitatively by alkylation of an oxazolidin-2-thione precursor **2** with alkyl

trifluoromethanesulfonate, as key intermediate both for *N*-deprotection purpose and controlled heteroatom permutations in heterocyclic chemistry. Compound **3** is an activated oxazolidine-2-thione **2** in which the C5 methylene electrophilicity has been greatly enhanced (125 MHz ^{13}C: δ 80.38 (**3b**) versus 73.6 (**2**)) and behaves as a tunable intermediate, contrary to the **2**:LA (Lewis Acid) complex previously described.[25] Exploitation of the reactivity of **3b** towards iodide associated with a stabilizating soft counter-cation led us to disclose the first example of oxazolidin-2-thione moiety deprotection into free amine. During our study of deprotection optimization, we highlighted a useful rearrangement. Treatment of **3b** with iodide associated with a hard counter-cation supplied (*R*)-phenylthiazolidin-2-one **8** through *5-exo-tet* recyclisation. This protocol allows a clean preparation of thiazolidin-2-ones working without aminothiols intermediates.[24] Although thiazolidin-2-ones are not usually exploited as chiral auxiliaries, they are precursors for the preparation of chiral thiazolidin-2-thiones (**10**) by efficient thionation using Lawesson's reagent. Those heterocycles are useful compounds as chiral auxiliaries, as well as bactericides, fungicides and catalysts for photopolymerisation.[37] Finally, simple hydrolysis of **3b** offers under mild conditions a formal oxidation process of **2**, leading to oxazolidin-2-one **7**, for which several validated endocyclic deprotection techniques are described.[7-9]

Beyond the chemistry of chiral auxiliary deprotection, our work has demonstrated interesting heterocyclic conversion pathways linking the four members of the (thia)oxazolidin-2-(thi)one family. Since such motifs are present on several biologically active molecules,[37-40] our research provides a chemo- and stereoselective methodology for bioisosteric modifications.

EXPERIMENTAL

1. Methods. X-Ray intensity data were collected at low temperature for **7** and **8** (120K) and at room temperature for **2** with a MAR345 image plate detector using MoKα (λ= 0.71069Å) monochromatized radiation. The crystal data and the data collection parameters are summarized in the synthesis section. The unit cell parameters were refined using all the collected spots after the integration process. **Figures 4-6** are drawn in the ORTEP style.[34] All the structures were solved by direct methods with SHELXS97 and refined by full-matrix least-squares on F^2 using SHELXL97.[41] All the non hydrogen atoms were refined with anisotropic temperature factors. The hydrogen atoms were located from Fourier difference or calculated with AFIX and included in the refinement with a common isotropic temperature factor. The structures **2**, **7** and **8** have been deposited within the Cambridge Crystallographic data Centre, n° CCDC 661559, 661560 and 661561, respectively. NMR spectra were measured at room temperature on a Bruker Avance 500 or on a Bruker Avance II 300 spectrometer; *J* values are given in Hz. IR spectra were recorded on Shimadzu FTIR-8400S spectrometer; values are reported in cm^{-1}. Mass spectra were performed on a LCQ Finnigan MAT spectrometer at the UCL mass spectrometry service, in APCI mode

(Atmospheric Pressure Chemical Ionosation) or ESI mode (Electron Spray Ionization). HRMS were measured at the University of Mons-Hainaut (Belgium) in the service of Prof. R. Flammang. Elemental analyses were measured at the analytical service of Imperial College of London, UK. $[\alpha]_D$ values are given in deg.cm³.dm^{-1}.g^{-1} and concentrations are given in g/100 cm³. Mps are uncorrected.

2. Synthesis. The reagents were purchased from commercial sources (Aldrich and Fluka) and used without further purification. LiI, RbI and $LiSO_3CF_3$ were washed with THF and dried under high vacuum. The solvents (anhydrous grade; H_2O < 0.001 %) were purchased from Fluka and stored under argon atmosphere over molecular sieve. The vessel was flamed and dried under high vacuum, and then cooled under argon atmosphere. TLC analyses were performed on aluminium plates coated with silica gel 60 F_{254} from Merck and visualized with UV (254 nm) or $KMnO_4$ solution (3 g $KMnO_4$, 20 g K_2CO_3, 5 cm³ AcOH 5% and 300 cm³ water). Column chromatographies were performed on silica gel Merck 60 (40-63 μm). *i*-Propyl trifluoromethanesulfonate was synthesized as described in the literature.[20]

Preparation of (*R*)-2-(benzylamino)-2-phenylethanol (1):[11] A solution of (*R*)-phenylglycinol (5 g, 36.5 mmol) in dry MeOH (150 cm³) was treated under magnetic stirring by freshly distilled benzaldehyde (3.37 cm³, 33.18 mmol) at rt. The reaction was monitored by TLC. Upon complete addition, the mixture was then carefully treated with sodium borohydride (1.38 g, 36.5 mmol) over 10 min. After complete addition, the mixture was left under stirring over 30 min, before dilution by 1N NaOH and Et_2O extraction (3x). Combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to dryness. The crude product was purified by crystallization in hexane with 10 % EtOAc to give **1** as white crystals (99 %): mp 91-92 °C; $[\alpha]_D^{20}$ -65.4 (c 1.07 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.23 to 7.37 (m, 10 H), 3.82 (dd, *J*=4.8 Hz and *J*=4.8 Hz, 1H), 3.75 (d, *J*=10.6 Hz, 1H), 3.7 (dd, *J*=10.6 Hz and *J*=4.8 Hz, 1H), 3.59 (dd, *J*=8.5 Hz and *J*=1.9 Hz, 1H), 3.55 (d, 1H), 2.88 (broad s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.47, 140.04, 128.87, 128.59, 128.39, 127.87, 127.44, 127.27, 66.95, 63.97, 51.38; IR (NaCl, ν, cm^{-1}) 3330, 3060, 3027, 2926, 2837, 1602, 1494, 1454, 1201, 1116, 1049, 1027; ESI MS *m/z* for $C_{15}H_{18}NO$ [M+H$^+$]: 228.1.

(*S*)-1: same procedure and structural assignment: $[\alpha]_D^{20}$ +65.2 (c 1.23 in $CHCl_3$).

Preparation of (*R*)-3-benzyl-4-phenyloxazolidine-2-thione (2):[11] To a stirred solution of **1** (6.79 g, 29.86 mmol) in dry CH_2Cl_2 (150 cm³) was added 1,1′-thiocarbonyldiimidazole (8.4 g, 44.79 mmol) in one portion. The reaction mixture was stirred for 5 h at rt. The organic layer was washed with water, dried over $MgSO_4$ and finally concentrated under vacuum. The resulting crude material was purified by column chromatography [silica gel: hexane/Et_2O (1/1)] to give **2** as a white solid (95 %): R_f [hexane/ Et_2O (1/1)] = 0.35; mp 114-115 °C; $[\alpha]_D^{20}$ +12.0 (c 1.59 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.19 to 7.42 (m, 10H), 5.51 (d, *J*=14.7 Hz, 1H), 4.75 (dd, *J*=8.2 Hz and *J*=9.4 Hz, 1H), 4.70 (dd, *J*=5.8 Hz and *J*=9.4 Hz, 1H), 4.36 (dd, *J*=8.2 Hz and *J*=5.8 Hz, 1H), 3.81 (d, *J*=14.7 Hz, 1H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ: 187.97, 136.28, 134.32, 129.39, 128.67, 128.46, 128.16, 127.14, 73.62, 62.15, 49.27; IR (NaCl, ν, cm^{-1}) 3029, 2915, 1494, 1479, 1453, 1295, 1237; APCI MS *m/z* for $C_{16}H_{16}NOS$ [M+H^+]: 270.1; Anal. Calcd for $C_{16}H_{15}NOS$: C, 71.34; H, 5.61; N, 5.20. Found: C, 71.34; H, 5.75; N, 5.19; XR: $C_{16}H_{15}NOS$, Mr = 269.35, orthorhombic, $P2_12_12_1$ (Nr 19) a = 7.119(3), b = 12.207(5), c = 16.274(6) Å, V = 1414(1) $Å^3$, Z = 4, Dx = 1.26 $g.cm^{-3}$, T= 293K. A total of 8650 reflections were collected; 1470 independent reflections (Rint = 0.084), 2Θmax = 41.6°. R = 0.037 for 1366 observed reflections and WR2 = 0.092 all data. Flack absolute structure parameter 0.14 (14). Selected bond lengths (Å): O(1)-C(2) = 1.348(4), C(2)-S(6) = 1.649(4), C(2)-N(3) = 1.329(4), N(3)-C(4) = 1.472(4), C(4)-C(5) = 1.531(5), O(1)-C(5) = 1.445(4), N(3)-C(7) = 1.448(4), C(4)-C(14) = 1.497(4).

(*S*)-2: same procedure and structural assignment: $[\alpha]_D^{20}$ -12.2 (c 2.1 in $CHCl_3$).

General procedure for alkylation of (*R*)-3-benzyl-4-phenyloxazolidin-2-thione (2) by alkyl triflates: A stirred solution of **2** (5 g, 18.56 mmol) in anhydrous MeCN (100 cm^3) was treated dropwise by alkyl triflate (20.42 mmol) at rt. The reaction was monitored by TLC. After completion, the residue was concentrated under vacuum to dryness. The crude material was used further without any purification.

(*R*)-*S*-methyl-3-benzyl-4-phenyloxazolidin-2-thionium triflate (3a): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.12 to 7.45 (m, 10H), 5.68 (dd, *J*=10.4 Hz and *J*=9.3 Hz, 1H), 5.55 (dd, *J*=8.4 Hz and *J*=10.4 Hz, 1H), 4.95 (dd, *J*=9.3 Hz and *J*=8.4 Hz, 1H), 4.78 (d, *J*=15.2 Hz, 1H), 4.44 (d, *J*=15.2 Hz, 1H), 2.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 180, 132.21, 130.71, 129.84, 129.49, 129.16, 129.07, 128.28, 126.85, 80.4, 67.15, 50.71, 15.25; ESI(+) MS *m/z* for $C_{17}H_{18}NOS$ [M^+]: 284.01; ESI(-) MS *m/z* for CF_3SO_3 [M^-]: 149; IR (NaCl, ν, cm^{-1}) 1550, 1240, 705.

(*R*)-*S*-ethyl-3-benzyl-4-phenyloxazolidin-2-thionium triflate (3b): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.12 to 7.45 (m, 10H), 5.7 (dd, *J*=10.4 Hz and *J*=9.3 Hz, 1H), 5.55 (dd, *J*=8.4 Hz and *J*=10.4 Hz, 1H), 4.95 (dd, *J*=9.3 Hz and *J*=8.4 Hz, 1H), 4.75 (d, *J*=15.2 Hz, 1H), 4.46 (d, *J*=15.2 Hz, 1H), 3.53 (m, 2H), 1.55 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 179.87, 133.81, 131.65, 130.56, 129.9, 129.76, 129.5, 129.32, 129.04, 128.16, 126.85, 80.38, 66.94, 50.83, 28.42, 14.08; ESI (+) MS *m/z* for $C_{18}H_{20}NOS$ [M^+]: 298.13; ESI(-) MS *m/z* for CF_3SO_3 [M^-]: 149; IR (NaCl, ν, cm^{-1}) 1558, 1259, 702; ESI HRMS *m/z* for $C_{18}H_{20}NOS$ [M^+]: calcd 298.1266. Found 298.1259.

(*R*)-*S*-isopropyl-3-benzyl-4-phenyloxazolidin-2-thionium triflate (3c): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.03 to 7.42 (m, 10H), 5.57 (dd, *J*=10.5 Hz and *J*=9.6 Hz, 1H), 5.42 (dd, *J*=8.6 Hz and *J*=10.5 Hz, 1H), 4.95 (dd, *J*=9.6 Hz and *J*=8.6 Hz, 1H), 4.68 (d, *J*=15.3 Hz, 1H), 4.31 (d, *J*=15.3 Hz, 1H), 4.23 (m, 1H), 1.59 (d, 3H), 1.57 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 179.53, 130.78 to 128.37, 128.85, 80.67, 66.71, 50.67, 42.63, 23.72; ESI(+) MS *m/z* for $C_{19}H_{22}NOS$ [M^+]: 312.09; ESI(-) MS *m/z* for CF_3SO_3 [M^-]: 149; IR (NaCl, ν, cm^{-1}) 1550, 1262, 704.

Preparation of *S*-ethyl-*N*-benzyl-*N*-(*R*)-2-iodo-1-phenylethylcarbamathioate (4b): To a stirred solution of **3b** (0.83 g, 1.86 mmol) in anhydrous DMF (10 cm³) at 0 °C containing MS 4Å was added anhydrous lithium triflate (0.23 g, 1.86 mmol) under argon flux in one portion, and the reaction mixture was stirred for 30 min. Afterwards, the reaction mixture was treated dropwise for 1 h with a freshly prepared 0.19 M DMF solution of anhydrous rubidium iodide (1.86 mmol). After completion, the organic layer was diluted with Et_2O, washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The resulting dark, highly moisture sensitive, residue was purified by column chromatography [silica gel: cyclohexane/EtOAc (5/1)] to give **4b** as a yellow oil (65 %): R_f [cyclohexane/EtOAc (5/1)] = 0.79; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.27 (m, 10H), 5.59 (broad t, 1H), 4.59 (broad s, 1H), 4.18 (broad s, 1H), 3.67 (broad s, 1H), 3.4 (t, 1H), 3.03 (q, 2H), 1.37 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.34, 136.88, 136.28, 128.46, 128.29, 127.39, 62.38, 49.43, 25.22, 15.07, 4.19; APCI MS *m/z* for $C_{18}H_{21}INOS$ [M+H$^+$]: 425.78.

Preparation of *S*-ethyl-*N*-benzyl-*N*-1-phenylvinylcarbamothioate (5): To a stirred solution of **3b** (0.83 g, 1.86 mmol) in anhydrous DMF (5 cm³) at 0 °C containing MS 4Å was added anhydrous lithium triflate (0.23 g, 1.86 mmol) under argon flux in one portion. After 30 min, the reaction mixture was treated dropwise for 1 h with a freshly prepared 0.19 M DMF solution of anhydrous RbI (1.86 mmol) at 0 °C. The solution was stirred for additional 30 min and then treated with a freshly prepared DMF solution (2.5 cm³) of DBU (0.42 cm³, 2.79 mmol) at 0 °C. The mixture was allowed to slowly warm up to rt and was then stirred overnight. The organic layer was diluted with ethyl acetate, washed with water and then brine, dried over $MgSO_4$, filtered and finally concentrated under vacuum. The oily residue was purified by column chromatography [silica gel: hexane/Et_2O (2/1)] to give **5** as a pale yellow oil (95 %): R_f [hexane/Et_2O (2/1)] = 0.81; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.22 to 7.39 (m, 10H), 5.68 (s, 1H), 5.1 (s, 1H), 4.64 (broad s, 2H), 2.89 (q, 2H), 1.27 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.78, 144.91, 137.55, 135.46, 129.48, 129.24, 128.82, 127.91, 126.74, 118.09, 51.54, 25.59, 15.54; APCI MS *m/z* for $C_{18}H_{20}NOS$ [M+H$^+$]: 297.92; IR (NaCl, ν, cm^{-1}) 1645, 1625, 1265, 968; ESI HRMS *m/z* $C_{18}H_{20}NOS$ [M+H]: calcd 298.1266. Found 298.1265.

Preparation of *S*-ethyl-*N*-benzylcarbamothioate (9):[27] *S*-ethyl-*N*-benzyl-*N*-1-phenylvinyl-carbamothioate (**5**) (0.18 g, 0.6 mmol) was diluted in a mixture MeCN/AcOH/H_2O (2/2/1, 5 cm³) and vigorously stirred at 80 °C overnight. To the reaction mixture was then carefully added K_2CO_3 portion-wise to neutral pH and then 3N KOH to pH = 9. The mixture was extracted several times with CH_2Cl_2. Organic layers were washed with water, dried over $MgSO_4$, filtered and concentrated under high vacuum in order to evaporate acetophenone. This left **9** as yellow needles (99%): R_f [hexane/Et_2O (2/1)] = 0.4; mp 62-63 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.24 to 7.31 (m, 5H), 5.55 (broad s, 1H), 4.46 (br d, *J*=5.7 Hz, 2H), 2.94 (q, 2H), 1.3 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.5, 137.52, 133.53, 128.80, 128.04,

45.61, 24.82, 16.13; APCI MS *m/z* for $C_{10}H_{14}NOS$ [M+H$^+$]: 196; IR (NaCl, ν, cm^{-1}) 3309, 1645, 698; ESI HRMS *m/z* $C_{10}H_{13}NONaS$ [M+Na$^+$]: calcd 218.0616. Found 218.0616.

Preparation of (*R*)-3-benzyl-4-phenyloxazolidin-2-one (7):[11] To a stirred solution of **3b** (8.3 g, 18.56 mmol) in MeCN (100 cm³) was added in one portion LiOH monohydrate (1.17 g, 27.84 mmol) at rt. After 15h, the reaction mixture was filtered through celite and concentrated under vacuum. The yellow oily residue was purified by column chromatography [silica gel: hexane/Et_2O (1/1)] and was then crystallized from hexane to give **7** as colourless crystals (95 %): R_f [hexane/Et_2O (1/1)] = 0.33; mp 72-73 °C; $[\alpha]_D^{20}$ -46.2 (c 2.2 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.13 to 7.41 (m, 10H), 4.86 (d, *J*=14.7 Hz, 1H), 4.55 (dd, *J*=7.5 Hz, and *J*=9.2 Hz, 1H), 4.52 (dd, *J*=9.2 Hz and *J*=5.8 Hz, 1H), 4.12 (dd, *J*=7.5 Hz and *J*=5.8 Hz, 1H), 3.64 (d, *J*=14.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 158.2, 137.29, 135.28, 129.2, 128.62, 128.60, 128.56, 127.84, 127.13, 69.78, 58.61, 45.7; APCI MS *m/z* for $C_{16}H_{16}NO_2$ [M+H$^+$]: 270; IR (NaCl, ν, cm^{-1}) 1751, 1458, 1413, 1259, 1172, 1035; Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.87; H, 6.02; N, 5.52; XR: $C_{16}H_{15}NO_2$, Mr = 253.29, orthorhombic, $P2_12_12_1$ (Nr 19) a = 9.011(3), b = 10.095(4), c = 14.298(5) Å, V = 1300.6(8) Å^3 , Z = 4, Dx = 1.29 gcm^{-3}, T= 120K. A total of 8796 reflections were collected using; 2105 independent reflections (Rint = 0.078), 2Θmax = 49°. R = 0.043 for 1935 observed reflections and WR2 = 0.113 all data. Selected bond lengths (Å): O(1)-C(2) = 1.362(3), C(2)-O(6) = 1.209(3), C(2)-N(3) = 1.340(3), N(3)-C(4) = 1.463(3), C(4)-C(5) = 1.536(4), O(1)-C(5) = 1.445(3), N(3)-C(7) = 1.452(3), C(4)-C(14) = 1.508(3).

(*S*)-7: same procedure and structural assignment: $[\alpha]_D^{20}$ +46.0 (c 1.7 in $CHCl_3$).

Preparation of (*R*)-3-benzyl-4-phenylthiazolidin-2-one (8): To a stirred solution of **3b** (0.83 g, 1.86 mmol) in MeCN (2 cm³) was added in one portion anhydrous LiI (0.37 g, 2.77 mmol). After 15h at 60 °C, the reaction mixture was filtered through celite and concentrated under vacuum. The dark oily residue was purified by column chromatography [silica gel: hexane/Et_2O (1/1)] and then crystallized from hexane to give **8** as colourless crystals (99 %): R_f [hexane/Et_2O (1/1)] = 0.56; mp 128-129 °C; $[\alpha]_D^{20}$ +93.2 (c 1.4 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7 to 7.5 (m, 10H), 5.08 (d, *J*=14.7 Hz, 1H), 4.58 (dd, *J*=6.5 Hz and *J*=8.2 Hz, 1H), 3.55 (dd, *J*=11.3 Hz and *J*=8.2 Hz, 1H), 3.54 (d, *J*=14.7 Hz, 1H), 3.14 (dd, *J*=6.5 Hz and *J*=11.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.28, 138.59, 135.57, 129.04, 128.75, 128.51, 128.34, 127.64, 126.8, 62.08, 46.62, 36.65; APCI MS *m/z* for $C_{16}H_{16}NOS$ [M+H$^+$]: 270.05; IR (NaCl, ν, cm^{-1}) 2387, 1670, 1492, 1396, 1195; Anal. Calcd for $C_{16}H_{15}NOS$: C, 71.34; H, 5.66; N, 5.20. Found: C, 71.05; H, 5.61; N, 5.12; XR: $C_{16}H_{15}NOS$, Mr = 269.35, orthorhombic, $P2_12_12_1$ (Nr 19) a = 10.071(4), b = 10.294(4), c = 13.296(5) Å, V = 1378.4(9) Å^3 , Z = 4, Dx = 1.30 gcm^{-3}, T= 120K. A total of 12086 reflections were collected; 2520 independent reflections (Rint = 0.060), 2Θmax = 50.7°. R = 0.032 for 2421 observed reflections and WR2 = 0.083 all data. Flack absolute structure parameter 0.04 (8).

Selected bond lengths (Å): S(1)-C(2) = 1.777(2), C(2)-O(6) = 1.217(3), C(2)-N(3) = 1.358(3), N(3)-C(4) = 1.463(3), C(4)-C(5) = 1.542(3), S(1)-C(5) = 1.813(2), N(3)-C(7) = 1.464(2), C(4)-C(14) = 1.509(3).

(*S*)-8: same procedure and structural assignment: $[\alpha]_D^{20}$ -93.0 (c 1.5 in $CHCl_3$).

Preparation of (*R*)-3-benzyl-4-phenylthiazolidin-2-thione (10): To a stirred solution of **8** (0.27 g, 1 mmol) in toluene (5 cm³) was added in one portion Lawesson's reagent (0.2 g, 0.5 mmol). The reaction mixture was stirred at 90 °C for 2 h, before a supplementary portion of Lawesson's reagent was added (0.2 g, 0.5 mmol). After 7 h at 90 °C, the reaction mixture was concentrated under vacuum and purified by column chromatography [silica gel: EtOAc/cyclohexane (7/3)] and then precipitated from hexane to give **9** as a colourless powder (90 %): R_f [EtOAc/cyclohexane (7/3)] = 0.81; ; mp 136-137 °C; $[\alpha]_D^{20}$ +57.8 (c 1.9 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.17 to 7.42 (m, 10H), 5.93 (d, *J*=14.7 Hz, 1H), 5.04 (dd, *J*=5.3 Hz and *J*=8.9 Hz, 1H), 3.75 (d, *J*=14.7 Hz, 1H), 3.65 (dd, *J*=8.9 Hz and *J*=11.2 Hz, 1H), 3.13 (dd, *J*=5.3 Hz and *J*=11.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.93, 137.99, 135.21, 129.59, 129.42, 129.00, 128.56, 128.31, 127.41, 70.23, 50.52, 35.46; ESI MS *m/z* for $C_{16}H_{16}NS_2$ [$M+H^+$]: 286.26; IR (NaCl, ν, cm^{-1}) 1495, 1446, 1419, 1224, 1171, 1080, 1031, 906; Anal. Calcd for $C_{16}H_{15}NS_2$: C, 67.33; H, 5.30; N, 4.91. Found: C, 67.33; H, 5.29; N, 4.87.

(*S*)-10: same procedure and structural assignment: $[\alpha]_D^{20}$ -57.5 (c 1.1 in $CHCl_3$).

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