Synthesis of an Enantiomerically Pure 1,3-Thiazole-5(4*H*)-thione and Its Stereoselective 1,3-Dipolar Cycloaddition with an Azomethine Ylide

by **Andreas Gebert**[1]) and **Heinz Heimgartner***

Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich

Starting from the enantiomerically pure 2*H*-azirin-3-amines (*R*,*S*)-**4** and (*S*,*S*)-**4**, the enantiomeric, optically active 4-benzyl-4-methyl-2-phenyl-1,3-thiazole-5(4*H*)-thiones (*R*)-**1** and (*S*)-**1**, respectively, have been prepared (*Schemes 2* and *3*). In each case, the reaction of **1** with *N*-(benzylidene)[(trimethylsilyl)methyl]amine (**2**) in HMPA in the presence of CsF and trimethylsilyl triflate gave a mixture of four optically active spirocyclic cycloadducts (*Scheme 4*). Separation by preparative HPLC yielded two pure diastereoisomers, *e.g.*, (4*R*,5*R*,9*S*)-**10** and (4*R*,5*R*,9*R*)-**10**. The regioisomeric compounds **11** were obtained as a mixture of diastereoisomers. The products were formed by a 1,3-dipolar cycloaddition of **1** with *in situ* generated azomethine ylide **3**, which attacks **1** stereoselectively from the sterically less-hindered side, *i.e.*, with (*R*)-**1** the attack occurs from the *re*-side and in the case of (*S*)-**1** from the *si*-side.

1. Introduction. – Since the first [2 + 3] cycloadditions, described by *Huisgen* and co-workers [1–5], azomethine ylides became a well-known class of 1,3-dipoles, and they found many applications in the synthesis of five-membered heterocycles [6–17]. The 1,3-cycloaddition with olefins and acetylenes has frequently been used for the preparation of pyrrolidines and pyrroles with a large range of substitution [3][7][18–24], and *DeShong et al.* described an intramolecular variation for the synthesis of bicyclic pyrrolidines and pyrroles [25]. Azomethine ylides were also used in the synthesis of indolizines [26] and other natural products [12][27–29], recent examples being those of *epibatidine* and *epiboxidine*, which were found to have potential analgesic activity [30][31]. On the other hand, analogous reactions with thiocarbonyl compounds leading to 1,3-thiazolidines are rarely described [32–37], but recently, *Gallagher* and co-workers published an elegant synthesis of penam and penem skeletons by 1,3-dipolar cycloadditions of azomethine ylides with thioketones [38].

Convenient methods to generate nonstabilized azomethine ylides are the desilylation of α-silyliminium salts [11][12][39][40] and α-cyano-α'-silylamines, [32] or the treatment of α-silylated imines with trimethylsilyl triflate [41] (for other methods see [42–50]).

For many years, our research interest has been focused on the reactivity of the thiocarbonyl group in 1,3-dipolar cycloaddition reactions [51–56]. In the last few years, we reported on the cycloadditions of azomethine ylides with aromatic thioketones [57][58] and 1,3-thiazole-5(4*H*)-thiones [59][60]. Recently, we reported on a stereoselective cycloaddition of an azomethine ylide, generated *via* thermal ring opening of *cis*-1-methyl-2,3-diphenylaziridine, with a chiral 1,3-thiazole-5(4*H*)-thione [61].

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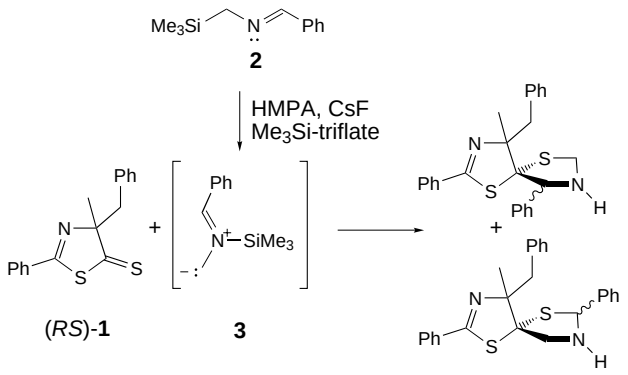
[1]) Part of the Ph.D. thesis of *A. G.*, Universität Zürich, 2001; present address: *F. Hoffmann-La Roche AG*, Basel.

Scheme 1



In the present paper, we present our results on the stereoselectivity of the cycloaddition of azomethine ylide **3**, generated *via* α-desilylation of *N*-(benzylidene)[(trimethylsilyl)methyl]amine (**2**) with CsF as desilylation reagent in the presence of trimethylsilyl triflate [41][43], with enantiomerically pure 4-benzyl-4-methyl-2-phenyl-1,3-thiazole-5(4*H*)-thiones **1** (*Scheme 1*).

2. Results and Discussion. – A few years ago, *Bucher et al.* developed a synthesis and a preparative method for the chromatographic separation of the diastereoisomeric 2-benzyl-2-methyl-3-amino-2*H*-azirines (*R*,*S*)-**4** and (*S*,*S*)-**4** [62]. We synthesized the chiral amine **5** (*Scheme 2*) from (*S*)-proline in four steps according to the procedure of *Bucher et al.* While in [62] a malonic ester synthesis according to *Wipf* [63] was applied to prepare 2-methyl-3-phenylpropanoyl chloride, which was reacted with amine **5** to yield the amide **6**, we followed the procedure depicted in *Scheme 2*. Reaction of **5** with propanoyl chloride yielded amide **7** in accordance with the procedure described by *Brun et al.* [64]. Deprotonation with LDA followed by benzylation gave **6** in good yield as a mixture of two diastereoisomers (ratio *ca.* 0.6:1 (NMR)). Thionation with *Lawesson* reagent provided the thioamide **8** in 94% yield, which was converted to the 2-benzyl-2-methyl-2*H*-azirin-3-amine **4** as a mixture of two diastereoisomers[2]).

The diastereoisomers (*R*,*S*)-**4** and (*S*,*S*)-**4** were separated chromatographically according to [62], and the reaction with PhCOSH led to the monothioamides (*R*,*S*)-**9** and (*S*,*S*)-**9**, respectively (*Scheme 3*). The enantiomerically pure 4-benzyl-4-methyl-2-phenyl-1,3-thiazole-5(4*H*)-thiones (*R*)-**1** and (*S*)-**1** were obtained in 69 and 65% yield, respectively, *via* thionation and cyclization of (*R*,*S*)-**9** and (*S*,*S*)-**9** with *Lawesson* reagent in toluene at 80–90°[3]). In both cases, the IR, NMR, and MS data were identical with those of *rac*-**1** [65]. The optical rotation in $CHCl_3$ was $[\alpha]_D^{22} = +106.4$ for (*R*)-**1** and −120.6 for the (*S*)-**1** isomer.

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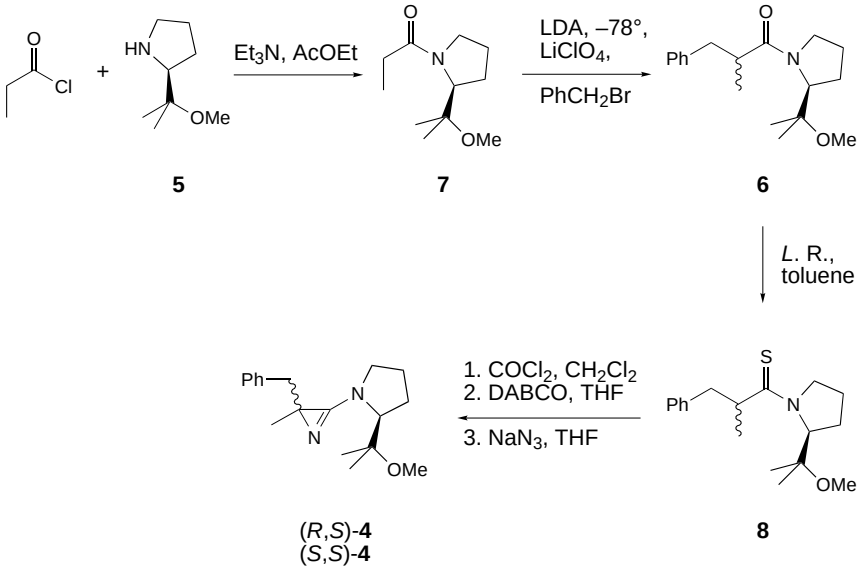
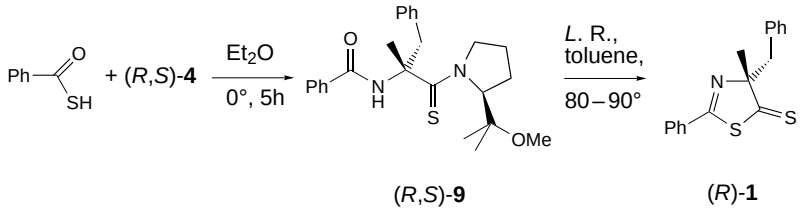
[2]) The detour *via* **8** gave a better yield (57%) of the azirine **4** compared with the direct treatment of **6** with $COCl_2$. One reason is that the reaction *via* thioamide **8** is much faster, thereby suppressing the formation of side products. Another advantage is that one can use commercially available 2M $COCl_2$ solution in toluene instead of condensing $COCl_2$ into the reaction vessel.

[3]) Only the reaction sequence leading to (*R*)-**1** is shown.

Scheme 2



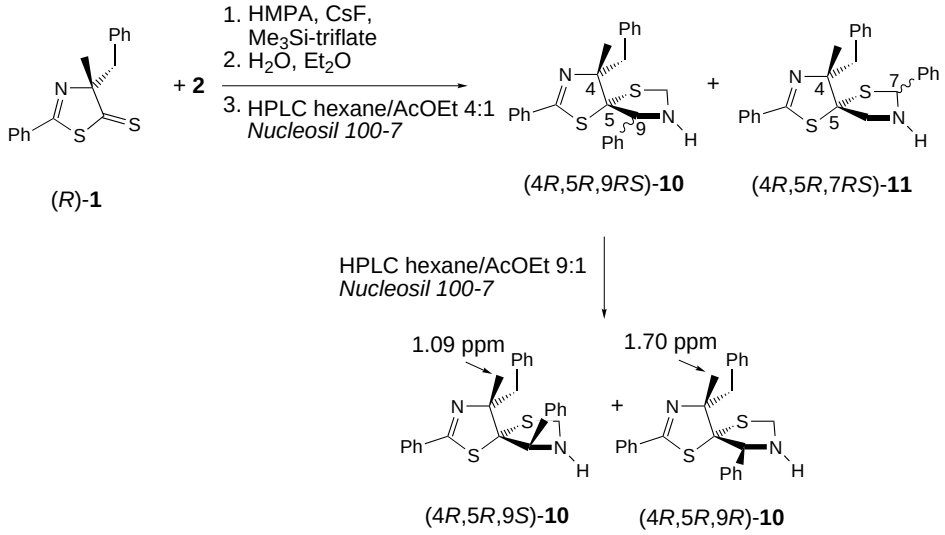
Scheme 3



A solution of equimolar amounts (0.8 mmol) of (*R*)-**1** and (*S*)-**1**, respectively, and imine **2** in HMPA was slowly dropped into a solution of 0.2 mmol trimethylsilyl triflate and 0.2 mmol of CsF in HMPA. The mixture was stirred at room temperature for 3 d. After that time, **1** was completely consumed, and after the usual workup, the mixture of four isomers was separated by preparative HPLC (SiO_2). The first separation with hexane/AcOEt 4 : 1 gave two fractions with **10** and **11**, respectively, both as mixtures of diastereoisomers (*Scheme 4*). The more-polar fraction was separated in a second run with hexane/AcOEt 9 : 1 to yield pure diastereoisomers of **10**. The diastereoisomers of **11** (less-polar fraction) could not be separated by preparative HPLC.

For example, from the reaction of (*R*)-**1** with **2** (*Scheme 4*), a mixture of products was isolated in 59% yield. After HPLC, the regioisomer **11** was obtained as a *ca.* 1 : 1 mixture of diastereoisomers ((4*R*,5*R*,7*RS*)-**11**) in 23% yield, whereas (4*R*,5*R*,9*S*)-**10** (19%) and (4*R*,5*R*,9*R*)-**10** (17%) were obtained as pure diastereoisomers. The ratio of the isolated regioisomers **10** and **11** was, therefore, 1.6 : 1.

Scheme 4



The two stereoisomers of type **10** differ in the orientation of the Ph group at C(9). In the case of (4*R*,5*R*,9*S*)-**10**, the Ph group is *cis*-oriented to the Me group located at C(4), whereas the relation is *trans* in (4*R*,5*R*,9*R*)-**10**. Therefore, the Me signal in the ^{1}H-NMR spectrum is shifted to higher field (1.09 ppm) in the case of (4*R*,5*R*,9*S*)-**10** as a consequence of the anisotropic effect of Ph, while it appears in the expected range at 1.70 ppm in (4*R*,5*R*,9*R*)-**10**.

Analogous reactions were carried out with the enantiomeric 1,3-thiazole-5(4*H*)-thione (*S*)-**1**. The cycloadducts were isolated in a total yield of 48% after workup and preparative HPLC. Under the same HPLC conditions as in the case of (*R*)-**1**, the diastereoisomers (4*S*,5*S*,9*R*)-**10** and (4*S*,5*S*,9*S*)-**10** were obtained in 11 and 15% yield, respectively. The second regioisomer **11** was obtained in 22% yield as a mixture of the diastereoisomers (4*S*,5*S*,7*RS*)-**11**. The regioisomers **10** and **11** were isolated in a ratio of 1.2 : 1.

The IR, NMR and MS data of compound (4*R*,5*R*,9*S*)-**10** were identical to those of (4*S*,5*S*,9*R*)-**10**, as well as the data for (4*R*,5*R*,9*R*)-**10** and (4*S*,5*S*,9*S*)-**10**, and for the two mixtures of diastereoisomers (4*R*,5*R*,7*RS*)-**11** and (4*S*,5*S*,9*RS*)-**11**, indicating enantiomeric structures in each case. On the other hand, $[\alpha]_D$ values were opposite, *e.g.*, $+52.3$ ($CHCl_3$) in the case of (4*R*,5*R*,9*R*)-**10** and -52.0 ($CHCl_3$) for (4*S*,5*S*,9*S*)-**10**. The presence of enantiomers is also shown by the CD spectra of (4*R*,5*R*,9*S*)-**10** and (4*S*,5*S*,9*R*)-**10**, measured in EtOH between 210 and 400 nm (*Fig.*).

The stereoselective formation of the [2 + 3] cycloadducts is the result of an addition of the azomethine ylide **3** from the sterically less-hindered side of the 1,3-thiazole-5(4*H*)-thione **1**, *i.e.*, *anti* to the $PhCH_2$ group at C(4). In the case of (*R*)-**1**, the attack occurs from the *Re* side, and from the *Si* side in (*S*)-**1**. Furthermore, for the formation of (4*R*,5*R*,9*S*)-**10** and its enantiomer, the Ph group in the azomethine ylide **3** has to be *cis*

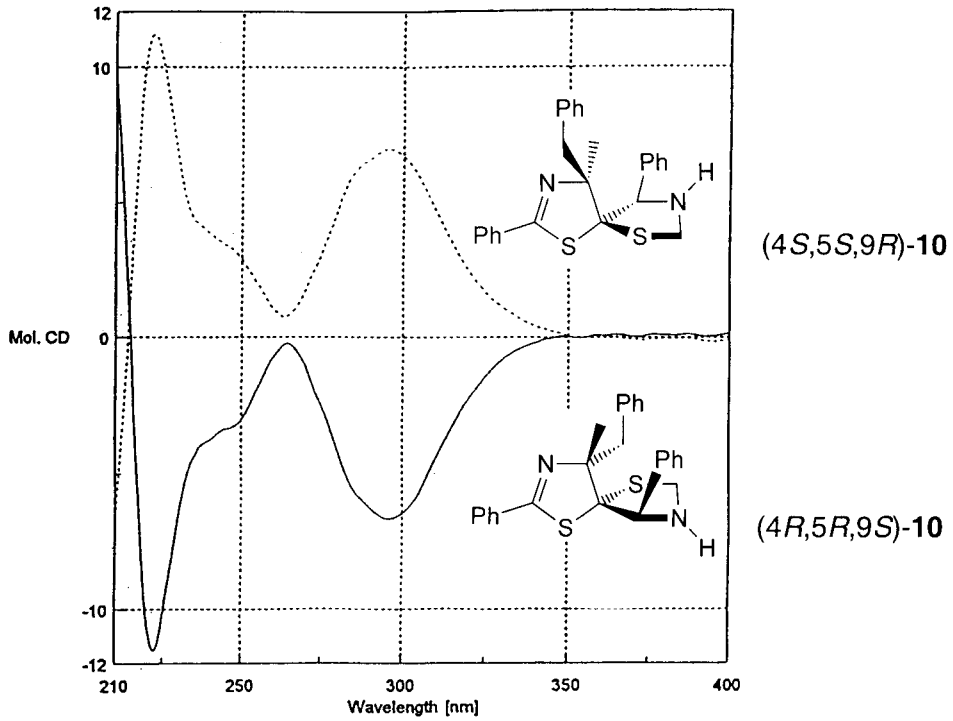


Figure. *CD Spectra of the enantiomers (4*R,5R,9S*)*-**10** *and* (4*S*,5*S*,9*R*)-**10**

in relation, whereas the reaction with the *trans*-configured azomethine ylide leads to (4*R*,5*R*,9*R*)-**10** and (4*S*,5*S*,9*S*)-**10** (*Scheme 5*)[4]).

The formation of the 7-Ph derivatives occurs also stereoselectively by addition of *cis*- and *trans*-azomethine ylide from the less-hindered side of **1**, but with the other regioselectivity.

3. Conclusions. – In conclusion, we have shown that the *in situ* generated azomethine ylide **3** can be trapped by the unsymmetrically substituted 1,3-thiazole-5(4*H*)-thione **1** in a stereoselective [2 + 3] cycloaddition reaction. The attack of the ylide occurs stereoselectively from the *Re* side with (*R*)-**1** and from the *Si* side with (*S*)-**1**. The regioselectivity of the reaction is low.

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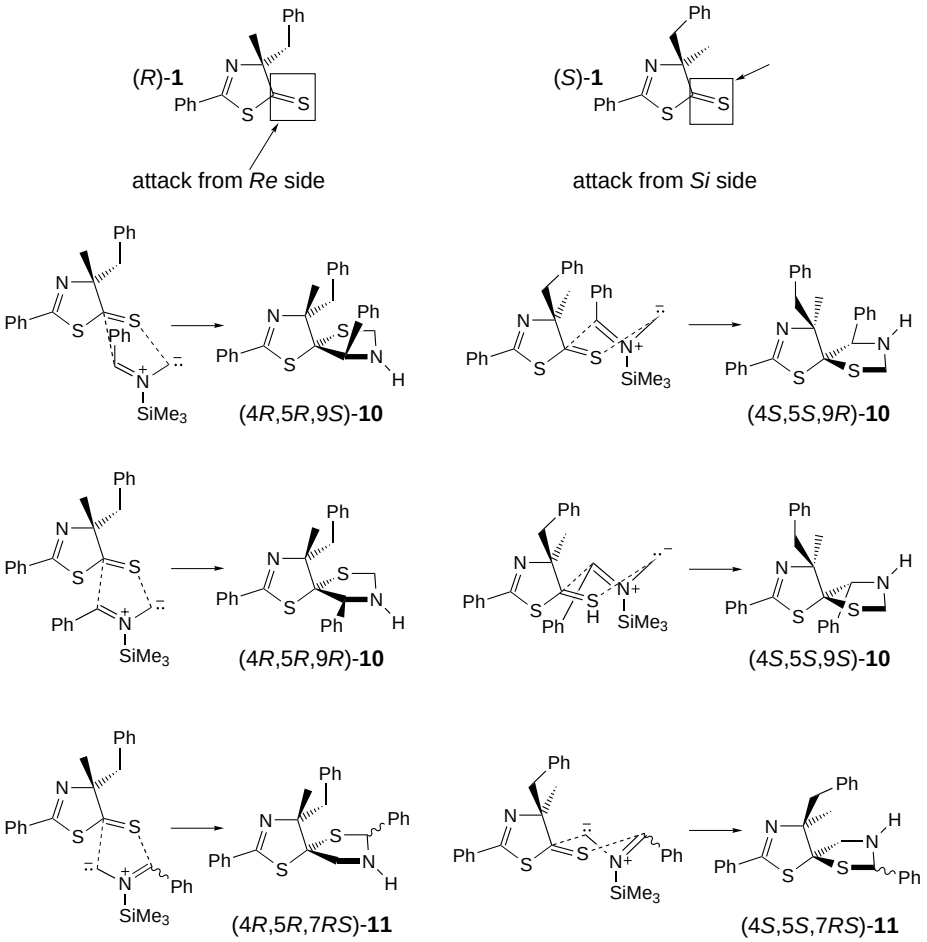
Experimental Part

1. *General.* See [64]. *N*-(Benzylidene)[(trimethylsilyl)methyl]amine (**2**) was prepared according to [66]. THF and toluene were dried over Na before distillation. TLC: *Merck 60 F_{254}* SiO_2-coated glass plates, 0.25 mm; detection of the substances on the TLC plates (*Merck*) under UV light of 254 nm wavelength. Column

[4]) A nonstereospecific two-step mechanism for the cycloaddition of **3** is another conceivable explanation.

Scheme 5



chromatography (CC): *Merck 60* 230–400 mesh SiO_2. Prep. HPLC: *Jasco PU-987*; UV detection (254 nm). $[\alpha]_D$ Values on a *Zeiss LEP-A2* instrument at 20–23°, in $CDCl_3$. CD Spectra in $CHCl_3$ on a *Jasco Spectropolarimeter J-715* with *Jasco Spectra-Manager*. If not otherwise stated, IR spectra in KBr, NMR spectra in $CDCl_3$ at 300 (^1H) and 50.4 (^{13}C) MHz, and CI-MS with NH_3.

2. *Synthesis of Chiral 1,3-Thiazole-5(4*H*)-thiones* **1**. *(*S*)-1-[2-(1-Methoxy-1-methylethyl)pyrrolidin-1-yl]propan-1-one* (**7**). A soln. of *2-(1-methoxy-1-methylethyl)pyrrolidine* (**5**; 16.67 g, 116 mmol) in AcOEt (800 ml) was cooled to −10° (acetone/ice), and Et_3N (16.2 ml, 11.74 g, 116 mmol) was added. Then, propanoyl chloride (10.14 ml, 10.73 g, 116 mmol) was slowly dropped into the cooled soln., keeping the temp. below +5°. After further stirring for 30 min and precipitation of $Et_3N \cdot HCl$, the mixture was washed with 2M HCl and sat. aq. NaCl soln. (400 ml each), dried ($MgSO_4$), and evaporated: 21.25 g (92%) of crude **7**, which was used directly for the next reaction. ^{1}H-NMR: 4.35 (*d*, *J* = 8.1, 1 H); 3.53–3.45 (*m*, 1 H); 3.43–3.40 (*m*, 1 H); 3.17 (*s*, MeO); 2.33 (*q*, *J* = 7.4, MeC*H*$_2$); 2.07–2.03, 1.81–1.73 (2*m*, 4 H); 1.14 (*t*, *J* = 7.45, Me); 1.13 (*s*, 2 Me). ^{13}C-NMR: 173.5 (*s*, CO); 78.3 (*s*, Me$_2$*C*); 62.9 (*d*, CHN); 49.1 (*q*, MeO); 47.5, 28.2, 25.1, 24.6 (4*t*, 4 CH_2); 22.7, 22.0 (2*q*, *Me*$_2$C); 9.25 (*q*, *Me*CH_2). CI-MS: 201 (23), 200 (100, $[M+1]^+$).

*(*R,S*)- and (*S,S*)-1-[2-(1-Methoxy-1-methylethyl)pyrrolidin-1-yl]-2-methyl-3-phenylpropan-1-one* (**6**). To a soln. of **7** (19.2 g, 96.5 mmol) in abs. THF (250 ml), $LiClO_4$ (10.2 g, 96.5 mmol) was added, the mixture was

cooled to −78° (acetone/dry ice), and LDA (58 ml, 116 mmol) was added. After stirring for 45 min, $PhCH_2Br$ (14 ml, 116 mmol) was added dropwise, and the mixture was stirred at r.t. overnight. Then, it was poured into 200 ml of ice/H_2O, acidified to pH 6 with 100 ml of 1N HCl, and extracted with EtO_2 (300 ml). The org. layer was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and the solvent was evaporated. The crude **6** was purified by distillation (150°/0.004 mbar) to yield 20.81 g (75%) **6** as a mixture of diastereoisomers (*ca.* 0.6:1). Colorless oil. IR (Film): 3055*w*, 3020*w*, 2970*s*, 2925*s*, 2820*m*, 1635*s*, 1450*m*, 1425*s*, 1380*m*, 1360*m*, 1320*w*, 1270*w*, 1175*m*, 1145*m*, 1085*s*, 1060*m*, 915*w*, 755*m*, 740*m*, 700*s*. ^{1}H-NMR: 7.25–7.12 (*m*, 5 arom. H); 4.32 (*d*, *J* = 6.7, 0.6 H); 3.81–3.74 (*m*, 0.4 H); 3.72–3.52 (*m*, 0.6 H); 3.36–3.25 (*m*, 1.4 H); 3.08, 3.04 (2*s*, MeO); 3.15–2.92 (*m*, 1.6 H); 2.90–2.75 (*m*, 0.4 H); 2.68–2.58 (*m*, 1 H); 2.02–1.91 (*m*, 1.4 H); 1.78–1.57 (*m*, 1.6 H); 1.50–1.26 (*m*, 1 H); 1.23, 1.10 (2*d*, 1.1:1.9, Me–C(2)); 1.04, 0.98, 0.93, 0.86 (4*s*, Me_2C). ^{13}C-NMR: 176.2, 175.1 (2*s*, CO); 140.1, 139.9 (2*s*, 1 arom. C); 128.9, 128.7, 128.0, 125.9 (4*d*, 5 arom. CH); 78.3, 78.0 (2*s*, Me_2C); 64.9, 62.6 (2*d*, CHN); 49.0, 48.8 (2*q*, MeO); 47.5, 45.8 (2*t*, $PhCH_2$); 42.1, 40.6 (2*t*, 1 CH_2); 40.0, 39.7 (2*d*, C(2)); 26.2, 24.9, 24.5, 22.2 (4*t*, 2 CH_2); 23.0, 21.7, 21.4, 19.1, 18.1, 16.8 (6*q*, *Me*–C(2), Me_2C). CI-MS: 291 (17), 290 (100, $[M+1]^+$), 200 (12).

*(*R,S*)- and (*S,S*)-1-[2-(1-Methoxy-1-methylethyl)pyrrolidin-1-yl]-2-methyl-3-phenylpropan-1-thione* (**8**). A mixture of **6** (20.3 g, 70.24 mmol) and *Lawesson* reagent (17 g, 46.83 mmol) in abs. toluene (150 ml) was refluxed overnight. Then, the solvent was evaporated, and the crude product was purified by chromatography to yield 20.06 g (94%) of **8** as a mixture of diastereoisomers. Pale yellow solid. M.p. 91.5–92.3°. IR (Film): 2977*m*, 2828*w*, 1444*s*, 1381*m*, 1364*m*, 1224*m*, 1178*m*, 1086*m*, 1055*s*. ^{1}H-NMR: 7.26–7.13 (*m*, 5 arom. H); 4.26–4.15 (*m*, 1 H); 3.78 (*d*, *J* = 8.4, 0.8 H); 3.79–3.47 (*m*, 2.2 H); 3.20–2.73 (*m*, 2 H); 3.10, 3.02 (2*s*, MeO); 1.82–0.85 (*m*, 3.3 H); 1.41, 1.24 (2*d*, Me–C(2)); 1.10, 1.03, 0.97, 0.89 (4*s*, Me–C(2), Me_2C). ^{13}C-NMR: 208.6 (*s*, C=S); 139.9 (*s*, 1 arom. C); 129.3, 128.7, 128.1, 126.1 (4*d*, 5 arom. CH); 77.9, 77.3, 76.9, 76.5 (4*s*, Me_2C); 68.6, 68.3 (2*d*, CHN); 54.2, 50.8 (2*t*, $PhCH_2$); 48.9, 48.7, 46.7, 46.4 (4*q*, MeO); 45.2, 44.4 (2*t*, 1 CH_2); 45.2 (1*d*, C(2)); 26.0, 24.1, 21.4 (3*t*, 2 CH_2); 22.7, 22.5, 21.9, 19.9 (4*q*, *Me*–C(2), Me_2C). CI-MS: 308 (5), 307 (19), 306 (100, $[M+1]^+$), 217 (4), 216 (42).

*(*R,S*)- and (*S,S*)-1-[2-Benzyl-2-methyl-2*H*-azirin-3-yl]-2-(1-methoxy-1-methylethyl)pyrrolidine* ((*R,S*)-**4** and (*S,S*)-**4**). To a soln. of **8** (2.834 g, 9.29 mmol) and 3 drops of abs. DMF in abs. CH_2Cl_2 (9 ml) at 0°, a 2N $COCl_2$ soln. in toluene (6.5 ml, 9.29 mmol, 1.4 equiv.) was added, the mixture was stirred for 60 min at 0°, and then the solvent was evaporated. The pale yellow residue was dissolved in abs. THF (10 ml), 1,4-diazabicyclo[2.2.2]octane (DABCO; 1.04 g, 9.29 mmol, 1 equiv.) was added, and the mixture was stirred for another 20 min at 0°. After filtration, NaN_3 (1.208 g, 18.58 mmol, 2 equiv.) was added, the mixture was stirred at r.t. overnight, filtered over *Celite*, and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2, washed with sat. aq. $NaHCO_3$ soln. (2×), dried ($MgSO_4$), and evaporated. CC (SiO_2) yielded 530 mg (20%) of (*R,S*)-**4**, 611 mg of a mixture of diastereoisomers and 354 mg (13%) of (*S,S*)-**4** (total yield: 1.5 g (56%)). The mixture of diastereoisomers was separated by MPLC (hexane/AcOEt 1:1, flow: 46–47 ml/min, detect.: $\lambda = 254$ nm). TLC (hexane/AcOEt 1:1): R_f^1 0.53; R_f^2 0.43 (*cf.* [62]).

N-*((*R*)-1-Benzyl-1-methyl-2-{2-[(*S*)-1-methoxy-1-methylethyl]pyrrolidin-1-yl}-2-thioxoethyl)benzamide* ((*R,S*)-**9**). A soln. of (*R,S*)-**4** (2.18 g, 7.64 mmol) in dry Et_2O (40 ml) was cooled to 0°, and PhCOSH (1.05 g, 7.64 mmol) was slowly added. The mixture was stirred for 5 h, and the solvent was evaporated. CC (hexane/AcOEt 4:1) yielded 2.99 g (92%) of (*R,S*)-**9** as a white foam. IR: 3200*m* (br.), 2980*s*, 1670*s*, 1650*m*, 1580*w*, 1510*s*, 1485*s*, 1455*s*, 1430*s*, 1380*m*, 1140*w*, 1080*s*, 700*m*. ^{1}H-NMR: 8.30 (br. *s*, NH); 7.75–7.02 (4*m*, 10 arom. H); 5.74 (*d*, *J* = 6.6, CHN); 4.35–4.30 (*m*, 1 H); 4.12, 3.57 (*AB*, *J* = 14.3, $PhCH_2$); 3.65–3.60 (*m*, 1 H); 3.15 (*s*, MeO); 2.15–2.00 (*m*, 2 H); 2.03 (*s*, Me); 2.02–1.85 (*m*, 2 H); 1.33, 1.22 (2*s*, Me_2C). ^{13}C-NMR: 204.5 (*s*, C=S); 165.1 (*s*, C=O); 136.9, 135.4 (2*s*, 2 arom. C); 131.1, 130.5, 128.4, 127.8, 126.8, 126.6 (6*d*, 10 arom. CH); 79.3 (*s*, Me_2C); 72.5 (*d*, CHN); 64.9 (*s*, MeO*C*); 52.7, 42.7 (2*t*, 2 CH_2); 48.7 (*q*, MeO); 24.6 (*t*, CH_2); 24.2, 22.5, 21.5 (3*q*, 3 Me); 22.4 (*t*, CH_2). CI-MS: 425 (100, $[M+1]^+$).

N-*((*S*)-1-Benzyl-1-methyl-2-{2-[(*S*)-1-methoxy-1-methylethyl]pyrrolidin-1-yl}-2-thioxoethyl)benzamide* ((*S,S*)-**9**). The analogous reaction of (*S,S*)-**4** (1.9 g, 6.6 mmol) with PhCOSH yielded, after CC (hexane/AcOEt 4:1), 2.5 g (90%) of (*S,S*)-**9** as a white foam. ^{1}H-NMR: 8.62 (br. *s*, NH); 7.82–7.23 (4*m*, 10 arom. H); 5.66 (*d*, *J* = 8.5, CHN); 4.10–4.05 (*m*, 1 H); 4.05, 3.43 (*AB*, *J* = 14.4, $PhCH_2$); 3.62–3.55 (*m*, 1 H); 3.11 (*s*, MeO); 2.15–1.65 (*m*, 4 H); 2.04 (*s*, Me); 1.16, 1.02 (2*s*, Me_2C). ^{13}C-NMR: 204.6 (*s*, C=S); 164.6 (*s*, C=O); 136.5, 135.4 (2*s*, 2 arom. C); 131.2, 129.8, 128.5, 128.4, 127.0, 126.8 (6*d*, 10 arom. CH); 79.5 (*s*, Me_2C); 72.6 (*d*, CHN); 65.3 (*s*, MeO*C*); 52.9, 43.1 (2*t*, 2 CH_2); 48.6 (*q*, MeO); 27.5 (*q*, Me); 24.5, 22.6 (2*t*, 2 CH_2); 22.5, 21.9 (2*q*, 2 Me). CI-MS: 425 (100, $[M+1]^+$).

*(*R*)-4-Benzyl-4-methyl-2-phenyl-1,3-thiazole-5(4*H*)-thione* ((*R*)-**1**). A suspension of (*R,S*)-**9** (2.99 g, 7.05 mmol) and *Lawesson* reagent (3.4 g, 8.4 mmol) in toluene (80 ml) was heated to reflux for 14 h. The solvent was evaporated, Et_2O was added, the mixture was filtered through a short SiO_2 column, and washed with

Et_2O. Evaporation and CC (hexane/AcOEt 25:1) yielded 1.43 g (69%) of (*R*)-**1**. Orange oil. $[\alpha]_D = +106.4$ ($c = 0.73$, $CHCl_3$). IR: 3203*w*, 3084*m*, 3062*m*, 3030*s*, 2977*m*, 2926*m*, 2860*w*, 1608*s*, 1581*s*, 1493*s*, 1447*s*, 1364*m*, 1330*w*, 1313*m*, 1297*m*, 1258*s*, 1153*s*, 1096*s*, 1070*m*, 1029*m*, 1001*m*, 957*s*, 913*s*, 888*s*, 848*s*, 807*w*, 765*s*, 752*s*, 733*s*, 688*s*, 674*s*, 653*s*, 644*m*, 616*m*, 607*m*. ^{1}H-NMR: 7.70–7.66 (*m*, 2 arom. H); 7.46–7.35 (*m*, 3 arom. H); 7.15–7.06 (*m*, 5 arom. H); 3.44, 3.22 (*AB*, $J = 13.0$, PhCH_2); 1.68 (*s*, Me). ^{13}C-NMR: 248.8 (*s*, C=S); 162.8 (*s*, C=N); 135.5, 131.8 (2*s*, 2 arom. C); 131.9, 130.5, 128.9, 128.1, 127.7, 126.8 (6*d*, 10 arom. CH); 100.3 (*s*, C(4)); 49.3 (*t*, PhCH_2); 28.6 (*q*, Me). CI-MS: 300 (10), 299 (20), 298 (100, $[M+1]^+$), 208 (9).

*(*S*)-4-Benzyl-4-methyl-2-phenyl-1,3-thiazole-5(4*H*)-thione* ((*S*)-**1**). The analogous reaction of (*S*,*S*)-**9** (2.5 g, 5.89 mmol) with *Lawesson* reagent (2.8 g, 7.07 mmol) gave 1.13 g (65%) of (*S*)-**1**. Orange oil. $[\alpha]_D = -120.6$ ($c = 0.49$, $CHCl_3$).

3. *Cycloaddition of* **1** *with* **2**. *General Procedure*. A soln. of **1** (238 mg, 0.8 mmol) and **2** (153 mg, 0.8 mmol) in HMPA (5 ml) was added dropwise to a soln. of trimethylsilyl triflate (TMS-triflate; 45 mg, 0.04 ml) and CsF (30 mg, 0.2 mmol) in HMPA (5 ml). The mixture was stirred for 3 d at r.t., poured into 150–200 ml of ice/H_2O and extracted with Et_2O (3×). The combined org. layers were dried ($MgSO_4$), the solvent was partially evaporated, and the crude products were filtered over a short SiO_2 column (hexane/AcOEt 5:1). Then, the mixture of products was separated by prep. HPLC (SiO_2, *Nucleosil 100-7*). First run (hexane/AcOEt 4:1) yielded two fractions, each as a mixture of diastereoisomers. The more-polar fraction was separated in a second run with hexane/AcOEt 9:1 yielding pure isomers.

*(4*R*,5*R*,9*S*)-4-Benzyl-4-methyl-2,9-diphenyl-1,6-dithia-3,8-diazaspiro[4.4]non-2-ene* ((4*R*,5*R*,9*S*)-**10**). Less-polar fraction of second HPLC separation: 63 mg (19%). White foam. $[\alpha]_D = -196.3$ ($c = 1.25$, $CHCl_3$). IR (KBr): 3322*m*, 3059*m*, 3025*m*, 2924*m*, 1594*s*, 1574*s*, 1492*s*, 1447*s*, 1366*m*, 1312*m*, 1255*s*, 1174*m*, 1098*m*, 1076*m*, 1029*m*, 960*s*, 842*m*, 763*s*, 740*m*, 702*s*, 690*s*. ^{1}H-NMR: 7.78–7.74 (*m*, 2 arom. H); 7.61–7.58 (*m*, 2 arom. H); 7.47–7.35 (*m*, 3 arom. H); 7.30–7.25 (*m*, 3 arom. H); 7.32–7.01 (*m*, 3 arom. H); 6.99–6.97 (*m*, 2 arom. H); 4.84 (*s*, H–C(9)); 4.61, 4.53 (*AB*, $J = 9.3$, CH_2(7)); 3.41, 2.64 (*AB*, $J = 13.1$, PhCH_2); 2.45 (br. *s*, NH); 1.09 (*s*, Me). ^{13}C-NMR: 162.8 (*s*, C=N); 138.5, 138.1, 133.6 (3*s*, 3 arom. C); 131.1, 129.1, 128.4, 128.3, 128.1, 128.0, 127.4, 126.0 (8*d*, 15 arom. CH); 95.5, 80.7 (2*s*, C(4), C(5)); 76.6 (*d*, C(9)); 52.8 (*t*, C(7)); 44.5 (*t*, PhCH_2); 17.6 (*q*, Me). ESI-MS: 439 (12, $[M+Na]^+$), 417 (100, $[M+1]^+$), 388 (20), 298 (40), 280 (39).

*(4*R*,5*R*,9*R*)-4-Benzyl-4-methyl-2,9-diphenyl-1,6-dithia-3,8-diazaspiro[4.4]non-2-ene* ((4*R*,5*R*,9*R*)-**10**). More-polar fraction of the second HPLC separation: 57 mg (17%). White foam. $[\alpha]_D = +52.3$ ($CHCl_3$). IR (KBr): 3299*m*, 3060*m*, 3026*m*, 2977*m*, 2931*m*, 1592*s*, 1574*s*, 1492*s*, 1446*s*, 1364*m*, 1312*m*, 1258*s*, 1234*s*, 1174*m*, 1156*m*, 1084*m*, 1029*m*, 1001*w*, 953*s*, 908*m*, 870*w*, 814*m*, 763*s*, 690*s*, 657*s*. ^{1}H-NMR: 7.37–7.23 (*m*, 5 arom. H); 7.21–7.03 (*m*, 7 arom. H); 6.98–6.85 (*m*, 3 arom. H); 4.41 (*s*, H–C(9)); 4.32, 4.19 (*AB*, $J = 9.3$, CH_2(7)); 3.80, 2.84 (*AB*, $J = 12.7$, PhCH_2); 1.70 (*s*, Me). ^{13}C-NMR: 166.2 (*s*, C=N); 137.3, 135.7, 132.6 (3*s*, 3 arom. C); 131.3, 130.9, 128.8, 128.0, 127.8, 127.6, 127.5, 127.2, 126.2 (9*d*, 15 arom. CH); 93.4, 81.5 (2*s*, C(4), C(5)); 76.5 (*d*, C(9)); 52.0 (*t*, C(7)); 46.0 (*t*, PhCH_2); 17.9 (*q*, Me). ESI-MS: 417 (100, $[M+1]^+$), 298 (61), 266 (17).

*(4*R*,5*R*,7*R*)- and (4*R*,5*R*,7*S*)-4-Benzyl-4-methyl-2,7-diphenyl-1,6-dithia-3,8-diazaspiro[4.4]non-2-ene* ((4*R*,5*R*,7*RS*)-**11**). Less-polar fraction of the first HPLC separation. Mixture of diastereoisomers (*ca.* 1:1): 76 mg (23%). White foam. IR (KBr): 3299*w*, 3059*m*, 3026*m*, 2978*m*, 2931*m*, 1592*s*, 1574*s*, 1492*s*, 1446*s*, 1365*m*, 1312*m*, 1258*s*, 1234*s*, 1175*m*, 1157*m*, 1084*m*, 1029*m*, 1001*w*, 953*s*, 908*m*, 870*w*, 814*m*, 763*s*, 740*m*, 690*s*, 657*w*. ^{1}H-NMR (2 diastereoisomers): 7.74–6.83 (*m*, 15 arom. H); 4.88, 4.49 (2*s*, H–C(7)); 4.54, 4.47, and 4.31, 4.21 (2 *AB*, $J = 9.3$, CH_2(9)); 3.69, 3.44, and 3.05, 2.51 (2 *AB*, $J = 12.7$, PhCH_2); 1.29, 1.23 (2*s*, Me). ^{13}C-NMR (2 diastereoisomers): 165.3, 165.1 (2*s*, C=N); 138.8, 138.5, 138.2, 137.2, 136.1, 133.2 (6*s*, 3 arom. C); 131.5, 131.3, 131.1, 131.0, 130.7, 129.1, 128.9, 128.8, 128.6, 128.4, 128.2, 127.9, 127.8, 127.6, 127.4, 126.8, 126.3, 126.1 (18*d*, 15 arom. CH); 94.1, 93.3, 81.4, 81.1 (4*s*, C(4), C(5)); 75.0, 71.8 (2*d*, C(7)); 64.4, 63.2 (2*t*, C(9)); 52.5, 51.8 (2*t*, PhCH_2); 18.6, 17.9 (2*q*, Me). ESI-MS: 417 (95, $[M+1]^+$), 388 (16), 298 (100), 280 (89), 266 (40).

*(4*S*,5*S*,9*R*)-4-Benzyl-4-methyl-2,9-diphenyl-1,6-dithia-3,8-diazaspiro[4.4]non-2-ene* ((4*S*,5*S*,9*R*)-**10**). According to the *General Procedure*, (*S*)-**1** (227 mg, 0.77 mmol) was reacted with **2** (147 mg, 0.77 mmol). The second HPLC separation yielded 35 mg (11%) of (4*S*,5*S*,9*R*)-**10** as the less-polar fraction. White foam. The IR, NMR, and MS data are identical with those of (4*R*,5*R*,9*S*)-**10**. $[\alpha]_D = +184.1$ ($CHCl_3$).

*(4*S*,5*S*,9*S*)-4-Benzyl-4-methyl-2,9-diphenyl-1,6-dithia-3,8-diazaspiro[4.4]non-2-ene* ((4*S*,5*S*,9*S*)-**10**). More-polar fraction of the second HPLC separation: 48 mg (15%). White foam. The IR, NMR, and MS data are identical to those of (4*R*,5*R*,9*R*)-**10**. $[\alpha]_D = -52.0$ ($CHCl_3$).

*(4*S*,5*S*,7*R*)- and (4*S*,5*S*,7*S*)-4-Benzyl-4-methyl-2,7-diphenyl-1,6-dithia-3,8-diazaspiro[4.4]non-2-ene* ((4*S*,5*S*,7*RS*)-**11**). Less-polar fraction of the first HPLC separation. Mixture of diastereoisomers (*ca.* 1:1): 70 mg (22%). White foam. The IR, NMR, and MS data are identical to those of (4*R*,5*R*,7*RS*)-**11**.

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