

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

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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.

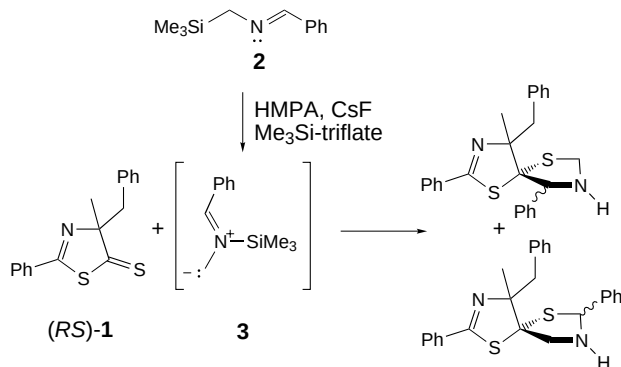
1. Introduction. – Since the first [2 + 3] cycloadditions, described by Huisgen and co-workers [1–5], azomethine ylides became a well-known class of 1,3-dipoles, and they found many applications in the synthesis of five-membered heterocycles [6–17]. The 1,3-cycloaddition with olefins and acetylenes has 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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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).

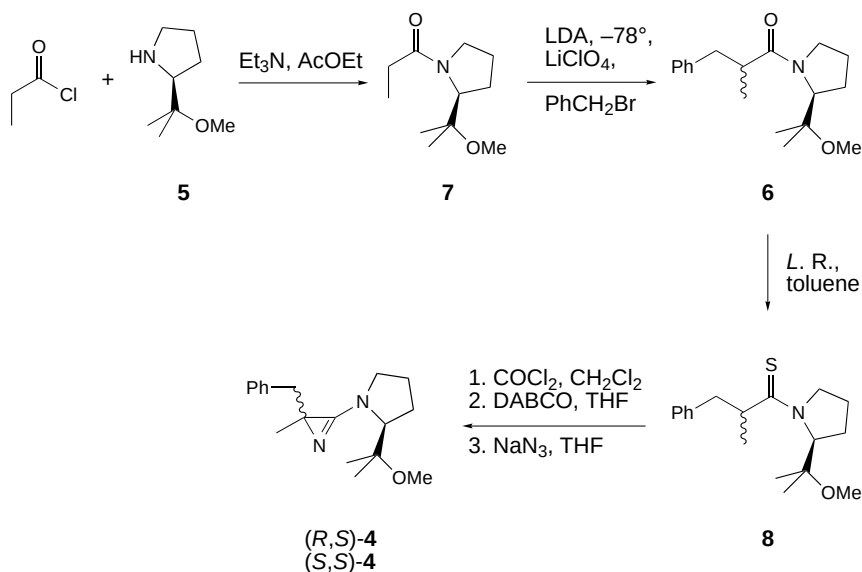
2. Results and Discussion. – A few years ago, *Bucher et al.* developed a synthesis and a preparative method for the chromatographic separation of the diastereoisomeric 2-benzyl-2-methyl-3-amino-2*H*-azirines (*R,S*)-**4** and (*S,S*)-**4** [62]. We synthesized the chiral amine **5** (Scheme 2) from (*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 diastereoisomers²⁾.

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 CHCl₃ was $[\alpha]_D^{22} = +106.4$ for (*R*)-**1** and -120.6 for the (*S*)-**1** isomer.

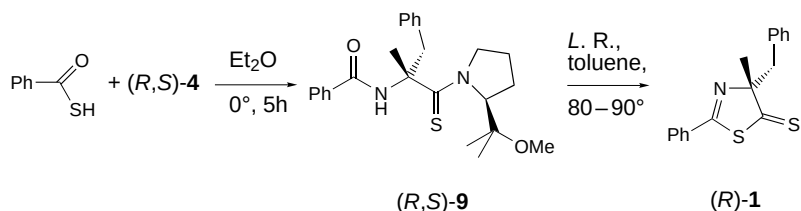
²⁾ The detour *via* **8** gave a better yield (57%) of the azirine **4** compared with the direct treatment of **6** with COCl₂. One reason is that the reaction *via* thioamide **8** is much faster, thereby suppressing the formation of side products. Another advantage is that one can use commercially available 2*M* COCl₂ solution in toluene instead of condensing COCl₂ into the reaction vessel.

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

Scheme 2



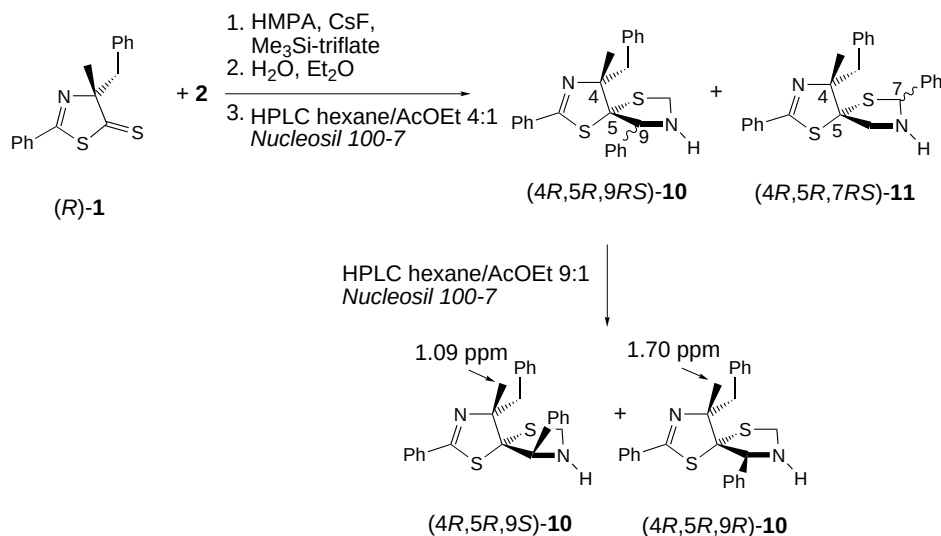
Scheme 3



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 (SiO₂). 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 **(4R,5R,9S)-10**, the Ph group is *cis*-oriented to the Me group located at C(4), whereas the relation is *trans* in **(4R,5R,9R)-10**. Therefore, the Me signal in the ¹H-NMR spectrum is shifted to higher field (1.09 ppm) in the case of **(4R,5R,9S)-10** as a consequence of the anisotropic effect of Ph, while it appears in the expected range at 1.70 ppm in **(4R,5R,9R)-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 **(4S,5S,9R)-10** and **(4S,5S,9S)-10** were obtained in 11 and 15% yield, respectively. The second regioisomer **11** was obtained in 22% yield as a mixture of the diastereoisomers **(4S,5S,7RS)-11**. The regioisomers **10** and **11** were isolated in a ratio of 1.2 : 1.

The IR, NMR and MS data of compound **(4R,5R,9S)-10** were identical to those of **(4S,5S,9R)-10**, as well as the data for **(4R,5R,9R)-10** and **(4S,5S,9S)-10**, and for the two mixtures of diastereoisomers **(4R,5R,7RS)-11** and **(4S,5S,9RS)-11**, indicating enantiomeric structures in each case. On the other hand, $[\alpha]_D$ values were opposite, *e.g.*, +52.3 (CHCl₃) in the case of **(4R,5R,9R)-10** and –52.0 (CHCl₃) for **(4S,5S,9S)-10**. The presence of enantiomers is also shown by the CD spectra of **(4R,5R,9S)-10** and **(4S,5S,9R)-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 PhCH₂ 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 **(4R,5R,9S)-10** and its enantiomer, the Ph group in the azomethine ylide **3** has to be *cis*

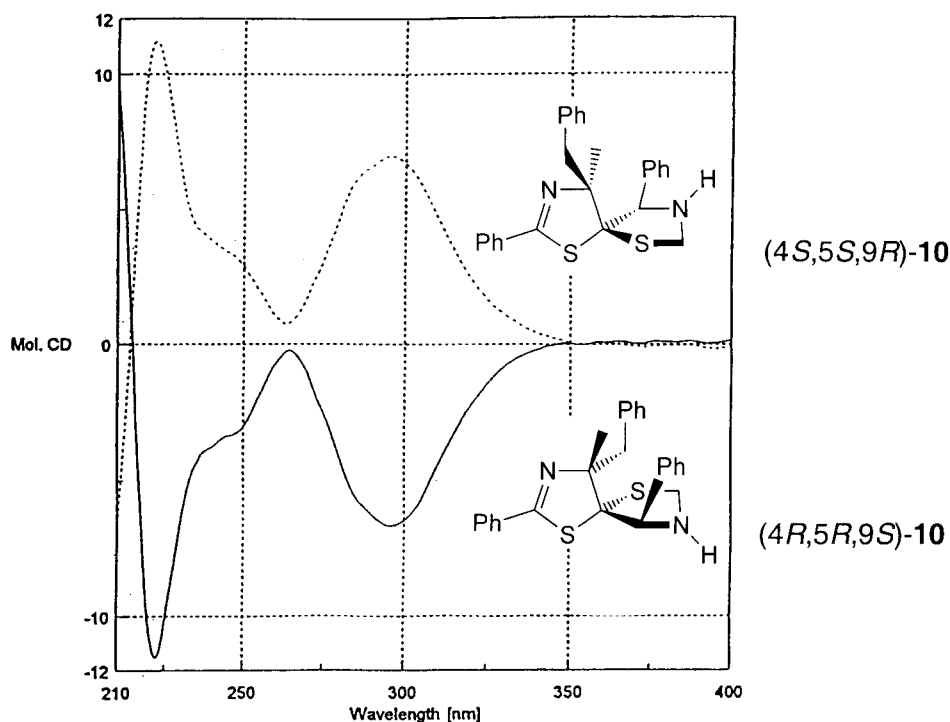


Figure. CD Spectra of the enantiomers (4R,5R,9S)-**10** and (4S,5S,9R)-**10**

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

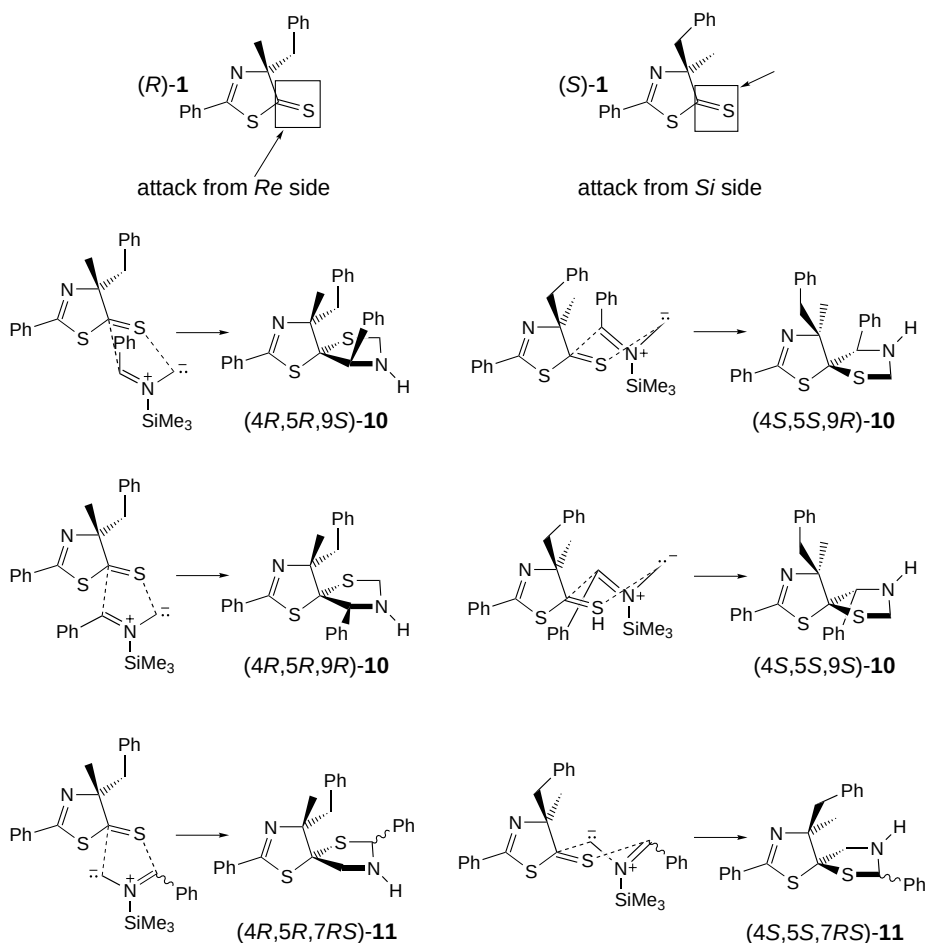
We thank the analytical units of our institute for spectra and analyses, and the Swiss National Science Foundation and F. Hoffmann-La Roche AG, Basel, for financial support.

Experimental Part

1. *General.* See [64]. *N*-(Benzylidene)l(trimethylsilyl)methylamine (**2**) was prepared according to [66]. THF and toluene were dried over Na before distillation. TLC: Merck 60 F₂₅₄ SiO₂-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(4H)-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 $+5^\circ$. After further stirring for 30 min and precipitation of $\text{Et}_3\text{N} \cdot \text{HCl}$, 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. $^1\text{H-NMR}$: 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*, $J = 7.4$, MeCH_2); 2.07–2.03, 1.81–1.73 (*2m*, 4 H); 1.14 (*t*, $J = 7.45$, Me); 1.13 (*s*, 2 Me). $^{13}\text{C-NMR}$: 173.5 (*s*, CO); 78.3 (*s*, Me_2C); 62.9 (*d*, CHN); 49.1 (*q*, MeO); 47.5, 28.2, 25.1, 24.6 (*4t*, 4 CH_2); 22.7, 22.0 (*2q*, Me_2C); 9.25 (*q*, MeCH_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 ($150^{\circ}/0.004$ mbar) to yield 20.81 g (75%) **6** as a mixture of diastereoisomers (ca. 0.6:1). Colorless oil. IR (Film): 3055w, 3020w, 2970s, 2925s, 2820m, 1635s, 1450m, 1425s, 1380m, 1360m, 1320w, 1270w, 1175m, 1145m, 1085s, 1060m, 915w, 755m, 740m, 700s. $^1\text{H-NMR}$: 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 (2s, 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 (2d, 1.1:1.9, Me–C(2)); 1.04, 0.98, 0.93, 0.86 (4s, Me_2C). $^{13}\text{C-NMR}$: 176.2, 175.1 (2s, CO); 140.1, 139.9 (2s, 1 arom. C); 128.9, 128.7, 128.0, 125.9 (4d, 5 arom. CH); 78.3, 78.0 (2s, Me_2C); 64.9, 62.6 (2d, CHN); 49.0, 48.8 (2q, MeO); 47.5, 45.8 (2t, PhCH_2); 42.1, 40.6 (2t, 1 CH_2); 40.0, 39.7 (2d, C(2)); 26.2, 24.9, 24.5, 22.2 (4t, 2 CH_2); 23.0, 21.7, 21.4, 19.1, 18.1, 16.8 (6q, 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. $91.5-92.3^{\circ}$. IR (Film): 2977m, 2828w, 1444s, 1381m, 1364m, 1224m, 1178m, 1086m, 1055s. $^1\text{H-NMR}$: 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 (2s, MeO); 1.82–0.85 (m, 3.3 H); 1.41, 1.24 (2d, Me–C(2)); 1.10, 1.03, 0.97, 0.89 (4s, Me–C(2), Me_2C). $^{13}\text{C-NMR}$: 208.6 (s, C=S); 139.9 (s, 1 arom. C); 129.3, 128.7, 128.1, 126.1 (4d, 5 arom. CH); 77.9, 77.3, 76.9, 76.5 (4s, Me_2C); 68.6, 68.3 (2d, CHN); 54.2, 50.8 (2t, PhCH_2); 48.9, 48.7, 46.7, 46.4 (4q, MeO); 45.2, 44.4 (2t, 1 CH_2); 45.2 (1d, C(2)); 26.0, 24.1, 21.4 (3t, 2 CH_2); 22.7, 22.5, 21.9, 19.9 (4q, 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-2H-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 $\times$), 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 0.53; R_f 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: 3200m (br.), 2980s, 1670s, 1650m, 1580w, 1510s, 1485s, 1455s, 1430s, 1380m, 1140w, 1080s, 700m. $^1\text{H-NMR}$: 8.30 (br. s, NH); 7.75–7.02 (4m, 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 (2s, Me_2C). $^{13}\text{C-NMR}$: 204.5 (s, C=S); 165.1 (s, C=O); 136.9, 135.4 (2s, 2 arom. C); 131.1, 130.5, 128.4, 127.8, 126.8, 126.6 (6d, 10 arom. CH); 79.3 (s, Me_2C); 72.5 (d, CHN); 64.9 (s, MeOC); 52.7, 42.7 (2t, 2 CH_2); 48.7 (q, MeO); 24.6 (t, CH_2); 24.2, 22.5, 21.5 (3q, 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. $^1\text{H-NMR}$: 8.62 (br. s, NH); 7.82–7.23 (4m, 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 (2s, Me_2C). $^{13}\text{C-NMR}$: 204.6 (s, C=S); 164.6 (s, C=O); 136.5, 135.4 (2s, 2 arom. C); 131.2, 129.8, 128.5, 128.4, 127.0, 126.8 (6d, 10 arom. CH); 79.5 (s, Me_2C); 72.6 (d, CHN); 65.3 (s, MeOC); 52.9, 43.1 (2t, 2 CH_2); 48.6 (q, MeO); 27.5 (q, Me); 24.5, 22.6 (2t, 2 CH_2); 22.5, 21.9 (2q, 2 Me). CI-MS: 425 (100, $[M+1]^+$).

(*R*)-4-Benzyl-4-methyl-2-phenyl-1,3-thiazole-5(4H)-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

Et₂O. Evaporation and CC (hexane/AcOEt 25 : 1) yielded 1.43 g (69%) of (*R*)-**1**. Orange oil. $[\alpha]_D = +106.4$ ($c = 0.73$, CHCl₃). IR: 3203w, 3084m, 3062m, 3030s, 2977m, 2926m, 2860w, 1608s, 1581s, 1493s, 1447s, 1364m, 1330w, 1313m, 1297m, 1258s, 1153s, 1096s, 1070m, 1029m, 1001m, 957s, 913s, 888s, 848s, 807w, 765s, 752s, 733s, 688s, 674s, 653s, 644m, 616m, 607m. ¹H-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*, $J = 13.0$, PhCH₂); 1.68 (*s*, Me). ¹³C-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*, PhCH₂); 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. $[\alpha]_D = -120.6$ ($c = 0.49$, CHCl₃).

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/H₂O and extracted with Et₂O (3 ×). The combined org. layers were dried (MgSO₄), the solvent was partially evaporated, and the crude products were filtered over a short SiO₂ column (hexane/AcOEt 5 : 1). Then, the mixture of products was separated by prep. HPLC (SiO₂, 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. $[\alpha]_D = -196.3$ ($c = 1.25$, CHCl₃). IR (KBr): 3322m, 3059m, 3025m, 2924m, 1594s, 1574s, 1492s, 1447s, 1366m, 1312m, 1255s, 1174m, 1098m, 1076m, 1029m, 960s, 842m, 763s, 740m, 702s, 690s. ¹H-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*, $J = 9.3$, CH₂(7)); 3.41, 2.64 (*AB*, $J = 13.1$, PhCH₂); 2.45 (*br. s*, NH); 1.09 (*s*, Me). ¹³C-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*, PhCH₂); 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. $[\alpha]_D = +52.3$ (CHCl₃). IR (KBr): 3299m, 3060m, 3026m, 2977m, 2931m, 1592s, 1574s, 1492s, 1446s, 1364m, 1312m, 1258s, 1234s, 1174m, 1156m, 1084m, 1029m, 1001w, 953s, 908m, 870w, 814m, 763s, 690s, 657s. ¹H-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*, $J = 9.3$, CH₂(7)); 3.80, 2.84 (*AB*, $J = 12.7$, PhCH₂); 1.70 (*s*, Me). ¹³C-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*, PhCH₂); 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): 3299w, 3059m, 3026m, 2978m, 2931m, 1592s, 1574s, 1492s, 1446s, 1365m, 1312m, 1258s, 1234s, 1175m, 1157m, 1084m, 1029m, 1001w, 953s, 908m, 870w, 814m, 763s, 740m, 690s, 657w. ¹H-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*, $J = 9.3$, CH₂(9)); 3.69, 3.44, and 3.05, 2.51 (2 *AB*, $J = 12.7$, PhCH₂); 1.29, 1.23 (2*s*, Me). ¹³C-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*, PhCH₂); 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**. $[\alpha]_D = +184.1$ (CHCl₃).

(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**. $[\alpha]_D = -52.0$ (CHCl₃).

(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**.

REFERENCES

- [1] R. Huisgen, *Angew. Chem., Int. Ed.* **1963**, 2, 565.
- [2] R. Huisgen, in '1,3-Dipolar Cycloaddition Chemistry', Ed. A. Padwa, Wiley-Interscience, New York, 1984, Vol. 1, p. 1.
- [3] R. Huisgen, W. Scheer, G. Szeimies, H. Huber, *Tetrahedron Lett.* **1966**, 379.
- [4] R. Huisgen, W. Scheer, H. Huber, *J. Am. Chem. Soc.* **1967**, 89, 1753.
- [5] R. Huisgen, W. Scheer, H. Mäder, *Angew. Chem., Int. Ed.* **1969**, 8, 602.
- [6] O. Tsuge, S. Kanemasa, *Adv. Heterocycl. Chem.* **1989**, 45, 231.
- [7] A. Padwa, in 'Comprehensive Organic Synthesis', Eds. B. M. Trost, I. Fleming, Pergamon Press, Oxford, 1991, Vol. 4, p. 1085; P. A. Wade, in 'Comprehensive Organic Synthesis', Eds. B. M. Trost, I. Fleming, Pergamon Press, Oxford, 1991, Vol. 4, p. 1134.
- [8] K. Matsumoto, R. Ohta, T. Uchida, H. Nishioka, M. Yoshida, A. Kakehi, *J. Heterocycl. Chem.* **1995**, 32, 367.
- [9] I. Coldham, A. C. Collis, R. J. Mould, D. E. Robinson, *Synthesis* **1995**, 1147.
- [10] J. W. Lown, in '1,3-Dipolar Cycloaddition Chemistry', Ed. A. Padwa, Wiley-Interscience, New York, 1984, Vol. 1, p. 653.
- [11] E. Vedejs, *Adv. Cycloaddition* **1988**, 1, 33.
- [12] Y. Terao, M. Aono, K. Achiwa, *Heterocycles* **1988**, 27, 981.
- [13] R. Grigg, V. Sridharan, *Adv. Cycloaddition* **1993**, 3, 161.
- [14] H. Tanaka, S. Nagatani, M. Ohsuga, K. Mitsuhashi, *Bull. Chem. Soc. Jpn.* **1994**, 67, 589.
- [15] C. La Porta, L. Capuzzi, F. Bettarini, *Synthesis* **1994**, 287.
- [16] G. Gonzalez, M. V. Martin, M. C. Paredes, *Heterocycles* **2000**, 52, 237.
- [17] U. Obst, P. Betschmann, C. Lerner, P. Seiler, F. Diederich, V. Gramlich, L. Weber, D. W. Banner, P. Schönholzer, *Helv. Chim. Acta* **2000**, 83, 855.
- [18] R. Huisgen, K. Matsumoto, C. H. Ross, *Heterocycles* **1981**, 15, 1131.
- [19] H. W. Heine, R. Peavy, A. J. Durbetaki, *J. Org. Chem.* **1966**, 31, 3924.
- [20] A. Padwa, W. Dent, H. Nimmesgern, M. K. Venkatramanan, G. S. K. Wong, *Chem. Ber.* **1986**, 119, 813.
- [21] E. Keller, B. de Lange, T. Rispens, B. L. Feringa, *Tetrahedron* **1993**, 49, 8899.
- [22] D. M. Cooper, R. Grigg, S. Hargreaves, P. Kennewell, J. Redpath, *Tetrahedron* **1995**, 51, 7751.
- [23] D. A. Barr, M. J. Dorrity, R. Grigg, S. Hargreaves, J. F. Malone, J. Montgomery, J. Redpath, P. Stevenson, M. Thornton-Pett, *Tetrahedron* **1995**, 51, 273.
- [24] B. Alcaide, P. Almendros, J. M. Alonso, M. F. Aly, *Chem. Commun.* **2000**, 485.
- [25] P. DeShong, D. A. Kell, D. R. Sidler, *J. Org. Chem.* **1985**, 50, 2309.
- [26] T. Uchida, K. Matsumoto, *Synthesis* **1976**, 209.
- [27] E. Vedejs, G. R. Martinez, *J. Am. Chem. Soc.* **1980**, 102, 7993.
- [28] K. A. Parker, I. D. Cohen, A. Padwa, W. Dent, *Tetrahedron Lett.* **1984**, 43, 4917.
- [29] P. N. Confalone, E. M. Huie, *J. Am. Chem. Soc.* **1984**, 106, 7175.
- [30] F. Stuhlmann, D. E. Kaufmann, *J. Prakt. Chem.* **1999**, 341, 455.
- [31] G. Pandey, A. K. Sahoo, S. R. Gadre, T. D. Bagul, U. D. Phalgune, *J. Org. Chem.* **1999**, 64, 4990.
- [32] A. Padwa, Y. Y. Chen, W. Dent, H. Nimmesgern, *J. Org. Chem.* **1985**, 50, 4006.
- [33] J. Chastanet, G. Roussi, *Heterocycles* **1985**, 23, 653; J. Chastanet, G. Roussi, *J. Org. Chem.* **1985**, 50, 2910.
- [34] R. Beugelmans, J. Chastanet, G. Roussi, *Heterocycles* **1987**, 26, 3197.
- [35] R. Huisgen, V. Martin-Ramos, W. Scheer, *Tetrahedron Lett.* **1971**, 477.
- [36] A. Padwa, W. Dent, *J. Org. Chem.* **1987**, 52, 253.
- [37] G. Mlostoń, Z. Skrzypek, *Bull. Soc. Chim. Belg.* **1990**, 99, 167.
- [38] D. Planchenault, R. Wisedale, T. Gallagher, N. J. Hales, *J. Org. Chem.* **1997**, 62, 3438.
- [39] E. Vedejs, F. G. West, *Chem. Rev.* **1986**, 86, 945.
- [40] N. Imai, Y. Terao, K. Achiwa, *J. Synth. Org. Chem. Jpn.* **1985**, 43, 862.
- [41] K. Achiwa, M. Sekiya, *Tetrahedron Lett.* **1982**, 23, 2589.
- [42] O. Tsuge, S. Kanemasa, A. Hatada, K. Matsuda, *Chem. Lett.* **1984**, 801.
- [43] O. Tsuge, S. Kanemasa, K. Matsuda, *Chem. Lett.* **1983**, 1131.
- [44] K. G. Rasmussen, K. A. Joergensen, *J. Chem. Soc., Perkin Trans. 1* **1997**, 1287.
- [45] A. Padwa, F. Hornbuckle, *Chem. Rev.* **1991**, 91, 263.
- [46] A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, 96, 223.
- [47] H. Ardill, X. L. R. Fontaine, R. Grigg, D. Henderson, J. Montgomery, V. Sridharan, S. Surendrakumar, *Tetrahedron* **1990**, 46, 6449.

- [48] C. Wittland, M. Arend, N. Risch, *Synthesis* **1996**, 367.
- [49] R. Grigg, S. Thianpatanagul, *J. Chem. Soc., Chem. Commun.* **1984**, 180; M. Joucla, J. Mortier, *J. Chem. Soc., Chem. Commun.* **1985**, 1566.
- [50] O. Tsuge, S. Kanemasa, M. Ohe, S. Takenaka, *Bull. Chem. Soc. Jpn.* **1987**, 60, 4079.
- [51] H. Heimgartner, *Croat. Chim. Acta* **1986**, 59, 237.
- [52] M. Kägi, A. Linden, G. Mlostoń, H. Heimgartner, *Helv. Chim. Acta* **1996**, 79, 855.
- [53] M. Kägi, A. Linden, G. Mlostoń, H. Heimgartner, *Helv. Chim. Acta* **1998**, 81, 285.
- [54] G. Mlostoń, J. Romański, H. Heimgartner, *Pol. J. Chem.* **1996**, 70, 437.
- [55] G. Mlostoń, J. Romański, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1998**, 81, 66.
- [56] K.-R. Meier, A. Linden, G. Mlostoń, H. Heimgartner, *Helv. Chim. Acta* **1997**, 80, 1190.
- [57] A. Gebert, A. Linden, H. Heimgartner, *Heterocycles* **2001**, 54, 691.
- [58] G. Mlostoń, K. Urbaniak, H. Heimgartner, *Helv. Chim. Acta* **2002**, 85, 2056.
- [59] G. Mlostoń, A. Linden, H. Heimgartner, *Pol. J. Chem.* **1997**, 71, 32.
- [60] G. Mlostoń, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1998**, 81, 558.
- [61] A. Gebert, A. Linden, G. Mlostoń, H. Heimgartner, *Heterocycles* **2002**, 56, 393.
- [62] C. B. Bucher, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1995**, 78, 935.
- [63] D. Wipf, Dissertation, Universität Zürich, 1987.
- [64] K. Brun, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2001**, 84, 1754.
- [65] C. Jenny, P. Wipf, H. Heimgartner, *Helv. Chim. Acta* **1989**, 72, 838.
- [66] M. Letellier, D. J. McPhee, D. Griller, *Synthetic Commun.* **1988**, 18, 1975.

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