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A Highly Enantioenriched, Configurationally Stable α-Thioallyllithium Compound and the Stereochemical Course of Its Electrophilic Alkylation

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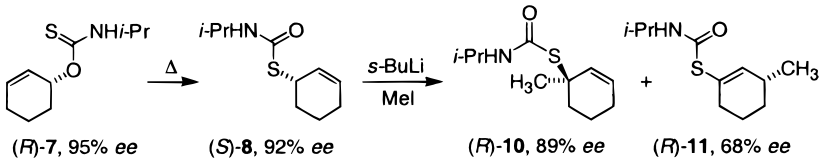
ABSTRACT



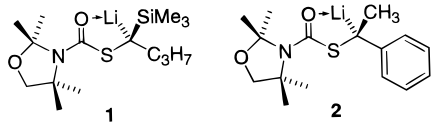
(*R*)-**7**, 95% *ee* (*S*)-**8**, 92% *ee* (*R*)-**10**, 89% *ee* (*R*)-**11**, 68% *ee*

The first highly enantioenriched, configurationally stable α-thioallyllithium compound (9) was generated by deprotonation of the *S*-cyclohex-2-enyl thiocarbamate 8. The methylation of 9 in both the α- and γ-positions proceeds antarafacially with a high degree of chirality transmission, as was elucidated by X-ray analysis of thiocarbamates 10 and 11. The optically active *S*-allyl thiocarbamate 8 was prepared by enantiospecific [3,3]sigmatropic rearrangement of the corresponding *O*-allyl thiocarbamate 7.

Enantioenriched α-heteroatom-substituted alkyllithium compounds are valuable chiral carbanion equivalents.[1] Electrophilic substitution of these chiral building blocks is generally stereospecific. Some α-oxy- and α-amino-substituted organolithium compounds have proven to be configurationally stable,[2] whereas vinylic, aryl, α-thio,[3,4] and α-seleno[5] substituents at the carbanionic center usually lead to rapid racemization even at low temperatures (e.g. −78 °C).

A configurationally stable, moderately enantioenriched α-thioalkyllithium compound (*R*)-**1** was synthesized in our laboratory, which showed no detectable racemization at −78 °C in etheral solution (Scheme 1).[6] Later we discovered the highly enantioenriched α-thiobenzyllithium compound (*S*)-**2** with unusually high configurational stability. Even warming

Scheme 1. Lithiated Monothiocarbamates[a]



[a] Ligands (TMEDA and Et_2O) at the lithium center are omitted for the sake of clarity.

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(1) Reviews: (a) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282. (b) Beak, P.; Basu, A.; Gallagher, D. J.; Park, J. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552. (c) Aggarwal, V. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 175.

(2) See references in reviews given in refs 1a−c for relevant examples.

(3) (a) Dress, R. K.; Rölle, T.; Hoffmann, R. W. *Chem. Ber.* **1995**, *128*, 673. (b) Hoffmann, R. W.; Dress, R. K.; Ruhland, T.; Wenzel, A. *Chem. Ber.* **1995**, *128*, 861. (c) Ahlbrecht, H.; Harbach, J.; Hoffmann, R. W.; Ruhland, T. *Liebigs Ann.* **1995**, 211.

(4) (a) Reich, H. J.; Dykstra, R. R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1469. (b) Reich, H. J.; Dykstra, R. R. *J. Am. Chem. Soc.* **1993**, *115*, 7041. (c) Reich, H. J.; Kulicke, K. J. *J. Am. Chem. Soc.* **1995**, *117*, 6621. (d) Reich, H. J.; Kulicke, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 273.

(5) (a) Ruhland, T.; Dress, R.; Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1467. (b) Hoffmann, R. W.; Klute, W. *Chem. Eur. J.* **1996**, *2*, 694. (c) See refs 3a,c and 4a.

(6) Kaiser, B.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 323.

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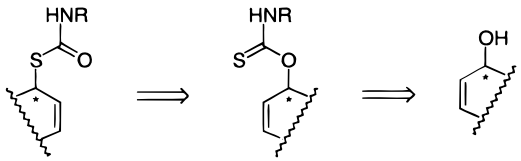
the etheral solution of (*S*)-**2** (>99% ee) to 0 °C led to unchanged high ee values in the trapping products (≥97 up to ≥99% ee).[7]

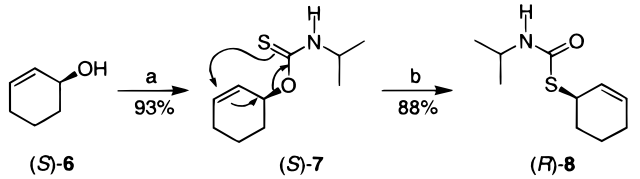
Encouraged by these results we set out to survey allylic systems wherein the double bond allows for further transformations. To avoid complications caused by *E*/*Z*-isomerization in the allylic anion, a cyclic *N*-monoalkyl thiocarbamate[8] was selected to suppress *E*/*Z*-isomerization. The required *S*-allylic thiocarbamates **3** can easily be generated from the corresponding *O*-esters **4** (Scheme 2). Rearrangement of thiocarbamates has been extensively investigated[9,10] for achiral or racemic substrates.[11] The *O*-esters **4** are prepared by the addition of isothiocyanates onto allylic alcohols **5**,[10] which are accessible in enantioenriched form via different routes.

Scheme 2



Enantioenriched cyclohex-2-en-1-ol (**6**) had been prepared either by a base-mediated rearrangement of cyclohexene oxide with chiral lithium amide bases[12] [(*R*) and (*S*)] or via a kinetic resolution of a racemic cyclohexenol precursor by lipase-catalyzed enantioselective transesterfication[13] [(*R*)] with an ee up to 95%. (*R*)-*O*-(2-Cyclohexenyl) *N*-isopropylthiocarbamate (**7**, 95% ee)[14] was readily prepared in 93% yield and subjected to a thermal rearrangement in a neat state at 105 °C for 3 h. (*S*)-*S*-(2-Cyclohexenyl) *N*-isopropylthiocarbamate (**8**) was isolated in 88% yield with 92% ee, indicating a high level of chirality transfer (Scheme 3).[15,16]

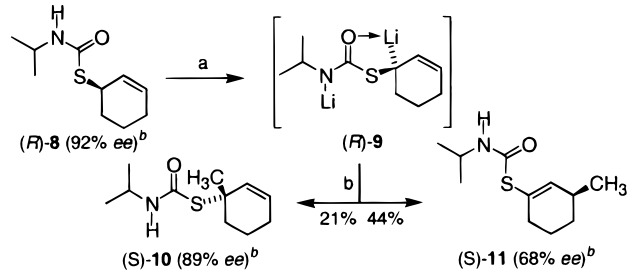
Scheme 3. Carbamoylation and Rearrangement[a]



[a] This sequence was performed with both enantiomers. Reagents: (a) (i) NaH, THF, 0 °C; (ii) *i*-PrNCS, then H_3O^+; (b) 105 °C, 3 h.

In extensive deprotonation experiments, different solvents, bases, and ligands were employed. When the deprotonation was performed in the presence of TMEDA in THF at −78 °C, formation of the dianionic species **9** was visible by the appearance of a yellow color when the addition of the second equivalent of *s*-BuLi started. The reaction was complete within 5 min. The use of a variety of electrophiles provided optically active products, fortunately the ee values of the methylation products **10** and **11** could be determined by GC and HPLC (Scheme 4).[17]

Scheme 4. Lithiation of (*R*)-**8** and Methylation[a,c]



[a] This sequence was also performed with (*S*)-**8**, see Table 1, entry 4. [b] Corrected for the enantiomeric purity of used (*S*)-**8**. [c] Reagents: (a) 2.5 equiv of *s*-BuLi/TMEDA, THF, −78 °C; (b) 1.5 equiv of 1.0 N MeI/THF, −78 °C, then H_3O^+. Ligands (TMEDA and THF) at the lithium center are omitted for the sake of clarity.

Deprotonation of **8** in toluene occurred very sluggishly; the α-product **10** isolated after methylation showed a low ee whereas the γ-product **11** was almost racemic (entry 1). Deprotonation of **8** in ether yields thiocarbamates **10** and **11** showing a remarkable loss of enantioenrichment (entry 3). Running the reaction in THF[18] yields carbamate **10** with 89% ee, what is equivalent to 97% conservation of the

(7) Hoppe, D.; Kaiser, B.; Stratmann, O.; Fröhlich, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2784.

(8) This carbamoyl moiety was chosen with the aim of smooth deprotection under mild conditions. *O*-Allyl *N*-monoalkylcarbamates were already converted to the *N*,*C*-dilithiated species and employed in synthesis, see: Hanko, R.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 127.

(9) (a) Hackler, R. E.; Balko, T. W. *J. Org. Chem.* **1973**, *38*, 2106. (b) Hayashi, T. *Tetrahedron Lett.* **1974**, *15*, 339. (c) Nakai, T.; Shiono, H.; Okawara, M. *Tetrahedron Lett.* **1974**, *15*, 3625. (d) Nakai, T.; Ari-Izumi, A. *Tetrahedron Lett.* **1976**, *17*, 2355.

(10) (a) Harayama, H.; Kozera, T.; Kimura, M.; Tanaka, S.; Tamaru, Y. *Chem. Lett.* **1996**, 543. (b) Harayama, H.; Nagahama, T.; Kozera, T.; Kimura, M.; Fugami K.; Tanaka, S.; Tamaru, Y. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 445.

(11) Harayama reported low de values for the thermally activated rearrangement of *O*-6-carvyl *N*-methylthiocarbamates, see ref 10b. However, the rearrangement of *O*-allyl imidazolethiocarboxylic esters has been applied in the stereospecific synthesis of (a) ansamycin derivatives and (b) the oligosaccharide fragment of calicheamicin $\gamma_{1\alpha}$: (a) Schnur, R. C.; Corman, M. L. *J. Org. Chem.* **1994**, *59*, 2581. (b) Nicolaou, K. C.; Groneberg, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 4085.

(12) (a) Asami, M.; Ishizaki, T.; Inoue, S. *Tetrahedron: Asymmetry* **1994**, *5*, 793. (b) Bhuniya, D.; DattaGupta, A.; Singh, V. K. *J. Org. Chem.* **1996**, *61*, 6108. (c) Södergren, M. J.; Andersson, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 10760.

(13) (a) Fukazawa, T.; Hashimoto, T. *Tetrahedron: Asymmetry* **1993**, *4*, 2323. (b) Fukazawa, T.; Shimoji, Y.; Hashimoto, T. *Tetrahedron: Asymmetry* **1996**, *6*, 1649.

(14) $[\alpha]^{20}_D = +156$ (*c* 1.13 in $CHCl_3$).

(15) The slight loss of enantioenrichment is probably due to a nonconcerted rearrangement. Pd(II) catalysis of the rearrangement led here to marked loss of ee. Moreover, Pd(0) catalysis is assumed to follow a reaction pathway of dissociation, involving a stabilized allyl cation, and therefore should furnish racemic *S*-esters. See ref 13b.

(16) During the course of this research, a high-yielding protocol for the Pd(0)-catalyzed rearrangement of *rac*-*O*-allyl thiocarbamates under efficient desymmetrization by external chiral induction was published. One of three examples is the rearrangement of *O*-(2-cyclohexenyl) *N*-methylthiocarbamate. See: Böhme, A.; Gais, H.-J. *Tetrahedron: Asymmetry* **1999**, *10*, 2511.

original enantioenrichment. The electrophilic attack on the γ-carbon is less stereospecific and forms **11** with 68% ee/74% stereospecificity (Table 1, entry 4). On deprotonation in toluene, the addition of methyl iodide after a shorter reaction time leads to a marked improvement of ee (entry 2), clearly indicating that racemization takes place on the stage of carbanion **9** under these conditions. In contrast to this, prolonged reaction times in THF did not cause any decrease in the ee values (entries 5 and 6). Consequently, it is concluded that here the partial racemization is caused by incomplete stereospecificity in the alkylation step.

Table 1. Results of Methylations

			stereospecificity, %[a]	
entry	solvent	time/min	**10**	**11**
1	toluene	270	3 (41)	0 (22)
2	toluene	45	56 (6)	nd
3	Et_2O	60	61 (46)	58 (26)
4[b]	THF	5	97 (21)	74 (44)
5	THF	60	96 (19)	73 (28)
6	THF	270	96 (17)	74 (21)

[a] Carbamate (*R*)-**8** with 72−82% ee was employed as starting material. Isolated yields are given in parentheses. [b] (*S*)-**8** with 92% ee was the starting material.

The high configurational stability may be due to the branched carbanionic center, as we have found previously by comparing lithiated *S*-*n*-alkyl thiocarbamates with lithiated α-branched *S*-alkyl thiocarbamates (**1**).[6] Hoffmann et al. verified some marked steric effects on the enantiomerization rate of some racemic α-thioaryl-substituted alkyllithium compounds, wherein branching and bulky substituents at the sulfur atom cause increased configurational stability.[3b] Hence, here the steric demands of the carbon skeleton and the carbamoyl moiety are lower, and compared to species **1** and **2**, racemization in ether occurs more readily than for **1** and **2**. The observed high solvent dependence of the racemization rate matches with results by Reich et al., who reported that the enantiomerization rate of α-thio-substituted organolithium reagents decreases with increasing ion pair separation.[4a]

The stereochemical outcome of the methylation of (*R*)-**9** was elucidated by X-ray analysis (Figure 1).[19] From (*R*)-**8**, the α-product (*S*)-**10** is formed in addition to (*S*)-**11**, indicating that the methylation takes place with stereoinversion or in an *anti*-S_E'-process, respectively. Methylation proceeds, corresponding to electrophilic substitution reactions of lithiated configurationally unstable *O*-allyl *N*,*N*-diisopropylcarbamates,[20] with inversion of configuration.

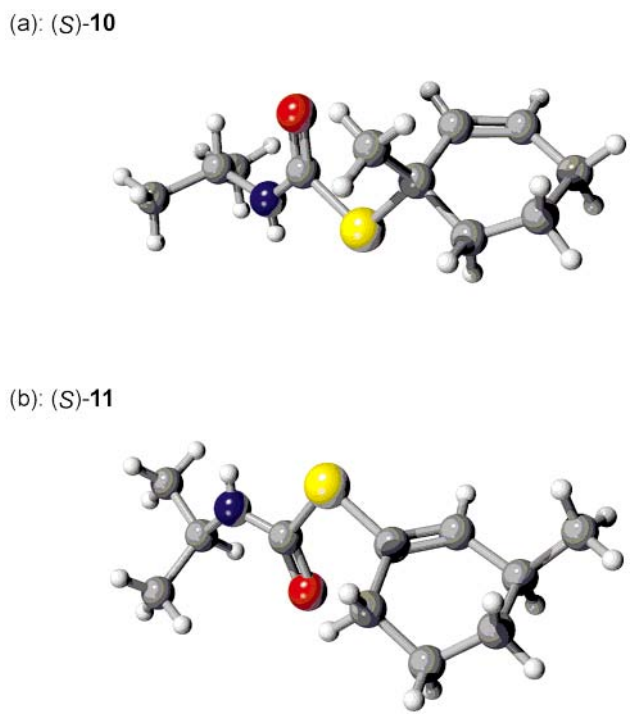


Figure 1. Crystal structures of carbamates (*S*)-**10** and (*S*)-**11**, achieved from starting material (*R*)-**8**. O: red. N: blue. S: yellow.

In summary we have found the first configurationally stable, highly enantioenriched α-thioallyllithium compound, showing a marked solvent dependence of its racemization rate. Both the α- and γ-methylation of the dianionic species by methyl iodide take place with inversion of configuration.

The work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie by a grant for F.M.

Supporting Information Available: Crystal data for compounds **10** and **11** and detailed experimental procedures with spectroscopic data for compounds **7**, **8**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL991134O

(17) All compounds were characterized by ^1H NMR, ^{13}C NMR, IR, MS, and elemental analysis.

(18) **Representative Procedure (Table 1, entry 4):** A solution of (*S*)-**8** (100 mg, 0.50 mmol, 92% ee (determined by GC on a β-DEX 120 column [Supelco]), $[\alpha]^{20}_D = -194$ (*c* 1.01 in $CHCl_3$), mp = 92 °C (petroleum ether)), and TMEDA (151 mg, 1.30 mmol, 2.59 equiv) in dry THF (5.0 mL) under Ar in a flask, sealed with a rubber septum, was cooled to −78 °C. *s*-BuLi (1.02 mL, 1.25 mmol, 2.50 equiv, 1.23 N) was added dropwise over a period of 5 min through a precooled needle. The yellow reaction mixture was stirred for additional 5 min, and MeI/THF (0.76 mL, 0.76 mmol, 1.5 equiv, 1.0 N) was added dropwise over a period of 3 min through a precooled needle. The flask was sealed, and after an additional 12 h of stirring, HOAc/Et_2O (1.25 mL, 1.25 mmol, 2.50 equiv, 1.00 N) was added. The reaction mixture was brought to approximately 0 °C, and a saturated $NaHCO_3$ solution (3 mL) and Et_2O (10 mL) were added. The phases were separated, and the aqueous phase was extracted with Et_2O (2 × 5 mL). The combined organic phases were washed with brine (3 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford a pale yellow oil which was subjected to column chromatography (silica gel, EtOAc/cyclohexane gradient). (*R*)-**10** (22 mg) (89% ee (determined by GC on a α-DEX 120 column [Supelco]), $[\alpha]^{20}_D = +159$ (*c* 0.615 in $CHCl_3$), mp = 103 °C (cyclohexane)) and 47 mg of (*R*)-**11** (68% ee (determined by HPLC on a ZWE−805 column [Bayer], $[\alpha]^{20}_D = +5.6$ (*c* 0.970 in $CHCl_3$), mp = 79 °C (cyclohexane)) were isolated as white crystals.

(19) Crystals suitable for X-ray diffraction analyses were grown by vapor diffusion of pentane into an etheral solution of **10** or **11**.

(20) First example: (a) Hoppe, D.; Zschage, O. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 67. (b) Revised configuration: Zschage, O.; Hoppe, D. *Tetrahedron* **1992**, *48*, 5657. (c) Paulsen, H.; Graeve, C.; Hoppe, D. *Synthesis* **1996**, 141. (d) Behrens, K.; Fröhlich, R.; Meyer, O.; Hoppe, D. *Eur. J. Org. Chem.* **1998**, 2397.