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Synthesis of Enantiomerically Enriched Tertiary 2-Cyclohexene-1-thiols via Configurationally Stable α-Thio-Substituted Allyllithium Compounds

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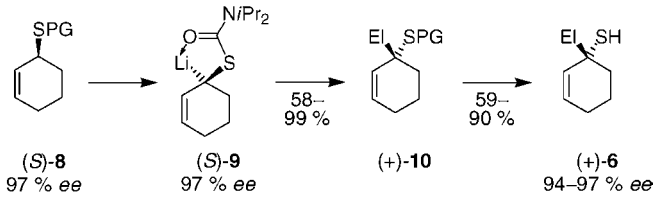
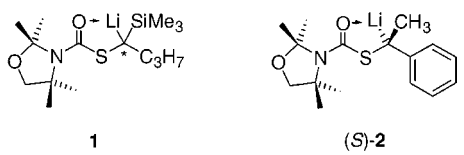
ABSTRACT



(*S*)-*S*-(2-Cyclohexenyl) *N*,*N*-diisopropylmonothiocarbamate [(−)-(*S*)-8] was deprotonated by *sec*-butyllithium/TMEDA to form a configurationally stable lithium compound (*S*)-9, which is the first example of a new class of α-thio-substituted organolithium compounds with improved properties. It is regioselectively alkylated by alkyl halides with complete stereoinversion to form the monothiocarbamates (+)-10 which afford highly enantioenriched tertiary 2-cyclohexene-1-thiols (+)-6 on reductive cleavage.

The family of α-heteroatom-substituted organolithium compounds has found widespread application in organic synthesis.[1] A number of enantioenriched, configurationally stable α-oxy-[2] and α-amino-substituted[3] organolithium compounds have been found, whereas only a few configurationally stable α-thio-substituted organolithium compounds are known. On the basis of the first two examples **1**[4] and **2**[5] (Figure 1) of this class of compounds we recently synthesized the allyllithium compounds **3a** and **3b**—showing a marked solvent dependence of their configurational stability—and applied them in stereoselective electrophilic substitution reactions (Scheme 1).[6]

Highly enantioenriched α- and γ-substitution products **4** and **5** are isolated in good yields. Their ratio depends on the reaction conditions and the employed electrophile—the



1 (*S*)-2

Figure 1. Configurationally stable α-thio-substituted organolithium compounds. Ligands (TMEDA and Et_2O) at the lithium center are omitted for the sake of clarity.

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(1) Reviews: (a) Hodgson, D. M., Ed. *Topics in Organometallic Chemistry*; Springer-Verlag: Heidelberg, Germany, 2002; in press. (b) Basu, A.; Thayumanavan, S. *Angew. Chem.* **2002**, *114*, 740; *Angew. Chem., Int. Ed.* **2002**, *41*, 717. (c) Aggarwal, V. K. *Angew. Chem.* **1994**, *106*, 185; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 175.

(2) Reviews: (a) Hoppe, D.; Marr, F.; Brüggemann, M. In Enantioselective Synthesis by Lithiation Adjacent to *O* and Electrophile Incorporation, in ref 1a. (b) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282.

(3) Review: Beak, P.; Basu, A.; Gallagher, D. J.; Park, J. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.

(4) Kaiser, B.; Hoppe, D. *Angew. Chem.* **1995**, *107*, 344; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 323.

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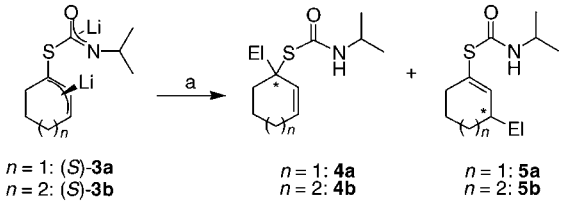
Scheme 1. Electrophilic Substitution of Dilithiated Thiocarbamates (ref 6)[a]



n = 1: (*S*)-**3a**
n = 2: (*S*)-**3b**

n = 1: **4a**
n = 2: **4b**

n = 1: **5a**
n = 2: **5b**

[a] Reagents and conditions: (a) (i) solution of ElX, −78 °C; (ii) sat. $NaHCO_3$, 0 °C.

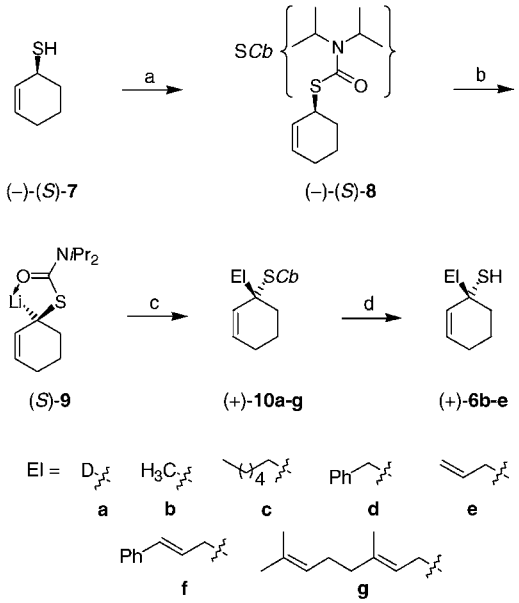
γ-products generally represent the main products, often dominating considerably (Scheme 1).[6b]

To the best of our knowledge, there is no general access to enantioenriched tertiary allylic thiols. Consequently we were interested in modifying the lithiation/substitution methodology toward an α-selective protocol.

Since we have found that the regioselectivity is influenced by the employed carbamoyl moiety,[6b] we tried different substitution patterns. The *N*,*N*-diisopropylcarbamoyl group was easily introduced to racemic cyclohex-2-enethiol (*rac*-**7**) with commercially available *N*,*N*-diisopropylcarbamoyl chloride to yield the corresponding monothiocarbamate *rac*-**8**. Enantioenriched monothiocarbamate (*S*)-**8** was synthesized from enantioenriched (*S*)-thiol (Scheme 2).[7,8]

Lithiation of **9** with *sec*-butyllithium/TMEDA occurs smoothly in toluene, ether, or THF at −78 °C.[9,10] Alkylations by alkyl halides take place with complete α-selectivity[11] in very good yields (Table 1), markedly improved in comparison to the *N*-monoalkyl-substituted, dilithiated monothiocarbamates **3**. Further, in contrast to dilithiated species (*S*)-**3a** where for synthetic application useful configurational stability is achieved in THF solution only,[12] interestingly, no solvent dependence of the configurational stability was

Scheme 2. Synthesis of Tertiary 2-Cyclohexene-1-thiols[a,b]



[a] Reagents and conditions: (a) (i) NaH, THF, reflux; (ii) Cl(C═O)N*i*Pr$_2$, THF, reflux; (iii) H_2O. (b) *s*-BuLi/TMEDA, solvent, −78 °C. (c) (i) ElX, −78→ 0 °C; (ii) NH_4Cl, rt. (d) (i) $LiAlH_4$ in ether, $ZnCl_2$ in ether, then **10** in THF, 0→ rt; (ii) HCl (aq). [b]Ligands (TMEDA and Et_2O) at the lithium center are omitted for the sake of clarity.

found for lithium compound (*S*)-**9**. Methylations in THF, diethyl ether, or toluene, respectively, lead generally to high chirality transfer of 99−100% (96−97% ee of product (+)-(*R*)-**10b**, determined on the stage of the thiol (+)-(*R*)-**6b** by GC; Table 1, entries 4−6).

Hexylation, benzylation, and allylation of allyllithium (*S*)-**9** furnished optically active products in good yields (Table 1, entries 8, 10, and 12). The ee of allylation product (+)-(*S*)-**10e** (er ≥98:2; ≥96% ee) and hexyl-substituted thiocarbamate (+)-(*S*)-**10c** (er ≥97:3; ≥94% ee) were concluded from the corresponding thiols (all ee values were determined by GC) and are equally high, indicating an almost quantitative conservation of the enantioenrichment throughout the reaction sequence. Unfortunately, the ee of benzyl-substituted thiocarbamate (+)-(*S*)-**10d** or its corresponding thiol could not be determined because no suitable conditions for separation of enantiomers by GC or HPLC were found.[13]

Deprotection of *N*,*N*-diisopropylcarbamates is usually carried out with a large excess of diisobutylaluminum hydride (ca. 10 equiv).[14] However, this protocol suffers from the large amounts of aluminum salts formed during aqueous workup and was not useful for monothiocarbamates **10**. The *N*,*N*-

(5) (a) Hoppe, D.; Kaiser, B.; Stratmann, O.; Fröhlich, R. *Angew. Chem.* **1997**, *109*, 24, 2872; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2784. (b) Stratmann, O.; Kaiser, B.; Fröhlich, R.; Meyer, O.; Hoppe, D. *Chem. Eur. J.* **2001**, *7*, 423.

(6) (a) Marr, F.; Fröhlich, R.; Hoppe, D. *Org. Lett.* **1999**, *1*, 2081. (b) Marr, F.; Fröhlich, R.; Wibbeling, B.; Diedrich, C.; Hoppe, D. *Eur. J. Org. Chem.* **2002**, 2790.

(7) Enantioenriched (*S*)-cyclohex-2-enethiol was achieved from saponification of (*S*)-*S*-(2-cyclohexenyl) *N*-methylmonothiocarbamate, which was synthesized by Pd^0-catalyzed deracemization, see: (a) Böhme, A.; Gais, H.-J. *Tetrahedron: Asymmetry* **1999**, *10*, 2511. (b) Gais, H.-J.; Böhme, A. *J. Org. Chem.* **2002**, *67*, 1153. The *N*,*N*-diisopropylcarbamoyl group can be introduced directly by replacement of the *N*-methylmonothiocarbamoyl group in a two-step, one-pot reaction with good yield.

(8) The corresponding monothiocarbamate with the *N*,*O*-acetal type 2,2,5,5-tetramethyl-1,3-oxazolidin-3-yl-carbonyl group was synthesized analogously. This protecting group was removed quantitatively from secondary allyl thiols with a mild, acid/base-mediated two-step reaction sequence (see: Hintze, F.; Hoppe, D. *Synthesis* **1992**, 1216). However, severe problems arose in the cleavage of this group on tertiary allyl thiols.

(9) For deprotonations of achiral *S*-alkyl *N*,*N*-dimethylmonothiocarbamates with *s*-BuLi, see: Beak, P.; Becker, P. D. *J. Org. Chem.* **1982**, *47*, 3855. See also ref 4.

(10) For deprotonations of achiral *S*-allyl *N*,*N*-dimethylmonothiocarbamates with LDA, see: (a) Nakai, T.; Mimura, T.; Ari-Izumi, A. *Tetrahedron Lett.* **1977**, 2425. (b) Hoppe, D.; Hanko, R.; Brönneke, A.; Lichtenberg, F.; van Hülsen, E. *Chem. Ber.* **1985**, *118*, 2822.

(11) As the only exception, from the allylation with allyl bromide 5% of the corresponding γ-product was isolated (16:1 regioselectivity).

(12) Benzyllithium (*S*)-**2** is configurationally stable in ethereal solution; however, in contrast to the proposed racemization mechanism (see refs 5a and 6b), in THF solution some racemization is detected; see ref 5b.

(13) The enantioenrichment should be equally high, because methylation, benzylation, and allylation of the related dilithiated species **3a** take place with the constantly high stereospecificity of 96%.[6b]

(14) Tomooka, K.; Komine, N.; Sasaki, T.; Shimizu, H.; Nakai, T. *Tetrahedron Lett.* **1998**, *39*, 9715.

Table 1. Results of Electrophilic Substitution Reactions of Allyllithium **9**

entry	substrate	solvent	time,[a] min	El(X)	yield
1	*rac*-**8**	Et_2O	45	D(OMe)	66% *rac*-**10a** + 34% γ-isomer
2	*rac*-**8**	THF	10	D(OMe)	28% *rac*-**10a** + 72% γ-isomer
3	*rac*-**8**	Et_2O	60	Me(I)	99% *rac*-**10b**
4	(−)-(*S*)-**8**, 97% ee	toluene	120	Me(I)	96% (+)-(*R*)-**10b**, 97% ee,[b] $[\alpha]_D$ +166[c]
5	(−)-(*S*)-**8**, 97% ee	Et_2O	60	Me(I)	95% (+)-(*R*)-**10b**, 96% ee,[b] $[\alpha]_D$ +164[c]
6	(−)-(*S*)-**8**, 97% ee	THF	30	Me(I)	87% (+)-(*R*)-**10b**, 97% ee,[b] $[\alpha]_D$ +165[c]
7	*rac*-**8**	Et_2O	60	*n*-C_6H_{13}(I)	82% *rac*-**10c**
8	(−)-(*S*)-**8**, 97% ee	toluene	120	*n*-C_6H_{13}(I)	67% (+)-(*R*)-**10c**,[d] ≥94% ee,[b] $[\alpha]_D$ +120[c]
9	*rac*-**8**	Et_2O	100	Bn(Br)	84% *rac*-**10d**
10	(−)-(*S*)-**8**, 97% ee	toluene	125	Bn(Br)	91% (+)-(*S*)-**10d**,[d] ee n.d.,[e] $[\alpha]_D$ +114[c]
11	*rac*-**8**	Et_2O	90	CH_2=CH−CH_2(Br)	78% *rac*-**10e**
12	(−)-(*S*)-**8**, 97% ee	toluene	120	CH_2=CH−CH_2(Br)	80% (+)-(*S*)-**10e**,[d] ≥96% ee,[b] $[\alpha]_D$ +153[c]
13	*rac*-**8**	Et_2O	45	PhCH=CH−CH_2(Br)	90% *rac*-**10f**
14	*rac*-**8**	Et_2O	45	geranyl(Br)	58% *rac*-**10g**

[a] Time of deprotonation at −78 °C. [b] Determined on the stage of the corresponding thiol. [c] c = 1.0−1.8 in $CHCl_3$. [d] Absolute configuration assigned in analogy to (+)-(*R*)-**10b**. [e] Not determined.

diisopropylcarbamoyl group can also be cleaved by nucleophilic attack of methyllithium; 3 equiv of MeLi are required and LDA is formed as a byproduct.[15] When using base-sensitive substrates problems have to be expected.[16] Further reducing and nucleophilic reagents have been tried for deprotection of monothiocarbamates **10**: lithium aluminum hydride in THF,[17] lithium triethylboron hydride (superhydride) in ether, and pent-1-ynyllithium in hexane.[15] In those cases no reaction or decomposition of the substrates occurred. A mixture of solutions of $LiAlH_4$ and zinc chloride, both commercially available, is superior.[18] Deprotections were achieved by adding a solution of thiocarbamates **10** in THF at 0 °C and stirring overnight at room temperature. Aqueous workup with diluted hydrochloric acid followed by flash column chromatography on silca gel under an argon atmosphere delivered the pure thiols in satisfactory yields (Table 2).

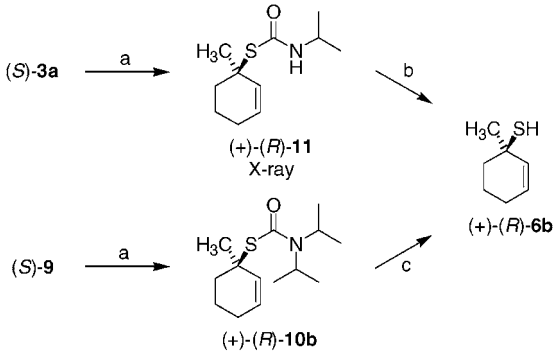
Table 2. Results of Deprotections of Monothiocarbamates **10** to Yield Tertiary Thiols **6**

entry	substrate	El	yield[a]
1	*rac*-**10b**	Me	59% *rac*-**6b**
2	(+)-(*R*)-**10b**	Me	83% (+)-(*R*)-**6b**, ≥96% ee[b]
3	*rac*-**10c**	*n*-C_6H_{13}	85% *rac*-**6c**
4	(+)-(*R*)-**10c**[c]	*n*-C_6H_{13}	90% (+)-(*R*)-**6c**,[c] 94% ee[b]
5	*rac*-**10d**	Bn	86% *rac*-**6d**
6	*rac*-**10e**	CH_2=CH−CH_2	86% *rac*-**6e**
7	(+)-(*S*)-**10e**[c]	CH_2=CH−CH_2	76% (+)-(*S*)-**6e**,[c] 96% ee[b]
8	*rac*-**10f**	PhCH=CH−CH_2	78% *rac*-**6f**

[a] Isolated yields. [b] Determined by GC. [c] Absolute configuration assigned in analogy to (+)-(*R*)-**10b**.

The ee values of enantioenriched thiols (+)-(*R*)-**6b**,**c** and (+)-(*S*)-**6e** could be determined by GC. The determined ≥96% ee values for thiols (+)-(*R*)-**6b**,**e** are indicating ≥99% stereospecificity for the reaction sequence deprotonation/alkylation/deprotection—this is evidence for an enantiospecific reaction pathway and deprotection without loss of enantiomeric purity (Table 2, entries 2 and 7).

Scheme 3. Stereochemical Correlation[a]



[a] Reagents and conditions: (a) MeI, −78 °C. (b) (i) 1.0 N NaOH (aq), rt; (ii) 2.0 N HCl (aq), rt. (c) (i) $LiAlH_4$ in ether, $ZnCl_2$ in ether, then **10b** in THF, 0→ rt; (ii) HCl (aq).

The stereochemical course of the alkylations was elucidated by chemical correlation: Methylation of dilithiated monothiocarbamate (*S*)-**3a** leads to thiocarbamate (*R*)-**11**, as

(15) Madec, D.; Henryon, V.; Férézou, J.-P. *Tetrahedron Lett.* **1999**, *40*, 8103.

(16) An excess of MeLi here led to deprotonation of allylic positions whereas deprotection failed with less than 3 equiv of MeLi.

(17) (a) Paetow, M.; Kotthaus, M.; Grehl, M.; Fröhlich, R.; Hoppe, D. *Synlett* **1994**, 1034. (b) Marko, I. E.; Leroy, B. *Tetrahedron Lett.* **2000**, *41*, 7225.

(18) This mixture presumably forms alane; see: (a) Ashby, E. C.; Sanders, J. R.; Claudy, P.; Schwartz, R. *J. Am. Chem. Soc.* **1973**, *95*, 6485. (b) Brower, F. M.; Matzek, N. E.; Reigler, P. F.; Rinn, H. W.; Roberts, C. B.; Schmidt, D. L.; Snover, J. A.; Terada, K. *J. Am. Chem. Soc.* **1975**, *98*, 2450.

was determined by X-ray crystal structure analysis.[6] Saponification furnished the tertiary thiol (+)-(*R*)-**6b**. Methylation of allyllithium (*S*)-**9** forms monothiocarbamate (+)-**10b**, which was deprotected to yield thiol (+)-(*R*)-**6b** (Scheme 3). Consequently, the (*R*) configuration is assigned to *N*,*N*-diisopropylmonothiocarbamate (+)-**10b**. Thus alkylation of (*S*)-**9** with methyl iodide proceeded with stereoinversion of configuration as was found previously for the *N*-isopropyl species (*S*)-**3a**.[6]

In summary we have found a convenient access to tertiary allyllic thiols. This synthesis of highly enantioenriched thiols employs a configurationally stable α-thioallyllithium compound, which is alkylated with essentially complete regio- and stereoselectivity in high yield, taking place with stereoinversion of configuration. Smooth deprotection of the intermediary monothiocarbamates with lithium aluminum hydride/zinc chloride occurs without loss of enantiomeric purity and provides the thiols in good yield.

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Supporting Information Available: Detailed experimental procedures with spectroscopic data for monothiocarbamates **10** and thiols **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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