Ashton, R. Ballardini, V. Balzani, S. E. Boyd, A. Credi, M. T. Gandolfi, M. Gómez-López, S. Iqbal, D. Philp, J. A. Preece, L. Prodi, H. G. Ricketts, J. F. Stoddart, M. S. Tolley, M. Venturi, A. J. P. White, D. J. Williams, *Chem. Eur. J.* **1997**, *3*, 152–170; j) P.-L. Anelli, M. Asakawa, P. R. Ashton, R. A. Bissell, G. Clavier, R. Górski, A. E. Kaifer, S. J. Langford, G. Mattersteig, S. Menzer, D. Philp, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, M. S. Tolley, D. J. Williams, *Chem. Eur. J.* **1997**, *3*, 1113–1135; k) A. S. Lane, D. A. Leigh, A. Murphy, *J. Am. Chem. Soc.* **1997**, *119*, 11 092–11 093; l) H. Murakami, A. Kawabuchi, K. Kotoo, M. Kunitake, N. Nakashima, *J. Am. Chem. Soc.* **1997**, *119*, 7605–7606; m) C. Gong, T. E. Glass, H. W. Gibson *Macromolecules* **1998**, *31*, 308–313.

[6] F. Zerbetto, M. Z. Zgierski, *Chem. Phys.* **1989**, *130*, 45–54, and references therein.

[7] H. Quast, M. Seefelder, *Angew. Chem.* **1999**, *111*, 1132–1126; *Angew. Chem. Int. Ed.* **1999**, *38*, 1064–1067.

[8] a) R. C. Gilbert, S. C. Smith, *Theory of Unimolecular and Recombination Reactions*, Blackwell Scientific Publications, Oxford, **1990**; b) M. J. Pilling, P. W. Seakins *Reaction Kinetics*, Oxford University Press, Oxford, **1995**.

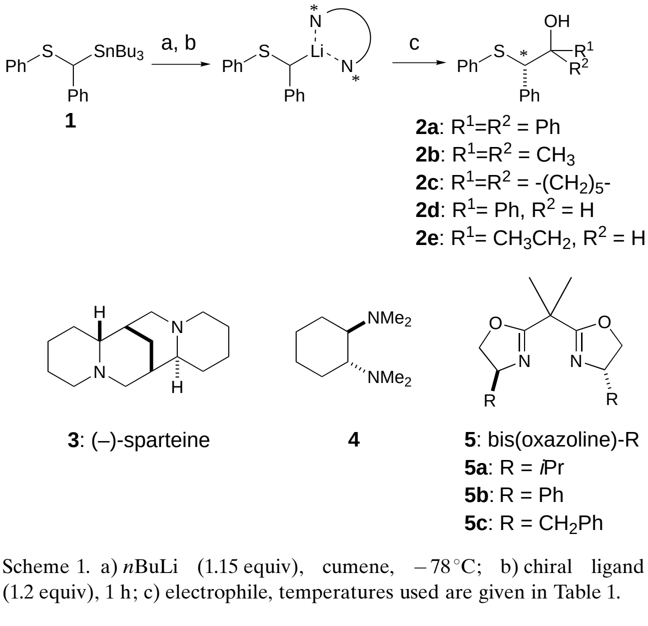
[9] a) D. A. Leigh, A. Murphy, J. P. Smart, A. M. Z. Slawin, *Angew. Chem.* **1997**, *109*, 752–756; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 728–731; b) W. Clegg, C. Gimenez-Saiz, D. A. Leigh, A. Murphy, A. M. Z. Slawin, S. J. Teat, *J. Am. Chem. Soc.* **1999**, *121*, 4124–4129.

Enantioselective Reactions of Configurationally Unstable α-Thiobenzyllithium Compounds[**]

Shuichi Nakamura, Ryo Nakagawa,
Yoshihiko Watanabe, and Takeshi Toru*

Asymmetric induction that arises from organolithium substrates complexed to chiral ligands has emerged as an efficient and powerful method. Since Hoppe et al. showed a high enantioenrichment could be achieved in a lithiation reaction to provide α-oxygen-substituted dipole-stabilized carbanions,[1] the enantioselective reactions of dipole-stabilized α-heterocarbanions have been the subject of extensive studies.[2] These reactions generally afford products with high enantioselectivity through asymmetric deprotonation. However, α-thiocarbanions do not give products with such enantioselectivity,[3] possibly because these carbanions are configurationally unstable and rapidly racemize even at temperatures as low as −78 °C.[4–6] Racemization of the α-selenocarbanions also occurs,[4, 7] but Hoffmann et al. have succeeded in achieving good enantioselectivities through a dynamic thermodynamic resolution in the reactions of non-dipole-stabilized α-selenocarbanions.[8] More recently, Nakai and Tomooka's group has reported highly enantioselective reactions of α-oxyorganolithium compounds.[9] Enantioselective reactions of α-thiocarbanions using asymmetrically deprotonated η^6-arene(tricarbonyl)chromium complexes have been reported.[10] There are, however, no reports on the intermolecular enantioselective reaction of α-sulfenyl carbanions derived from primary benzyl sulfides. The α-sulfenyl carbanion may be more unstable than the α-selenocarbanion,[4] and a high level of chiral induction could be realized through the asymmetric substitution process[2a] that is controlled either by the intermediate lithium carbanion/chiral ligand complex or by the transition state of the complex–electrophile interaction. We report herein the first highly stereoselective asymmetric substitution reactions of primary α-sulfenyl carbanions.

First we examined the reaction of α-lithio aryl benzyl sulfides with various electrophiles in cumene.[11] α-Lithiobenzyl phenyl sulfide was prepared from phenyl α-(tributylstannyl)benzyl sulfide (**1**) since reactions starting with benzyl phenyl sulfide often gave products with high stereoselectivity but in yields of less than 40%. Several chiral ligands, (−)-sparteine (**3**), (1*R*,2*R*)-*N*,*N*,*N*′,*N*′-tetramethylcyclohexane-1,2-diamine (**4**), and 2,2-bis{2-[(4*S*)-substituted-1,3-oxazolinyl]}-propanes[12] **5a–c**, were examined (Scheme 1). The yields and enantioselectivities obtained in these reactions are shown in Table 1.



Scheme 1. a) *n*BuLi (1.15 equiv), cumene, −78 °C; b) chiral ligand (1.2 equiv), 1 h; c) electrophile, temperatures used are given in Table 1.

Ligands **3** and **4** provided the thio alcohol **2a** in low enantioselectivity from the reaction of lithiated **1** with benzophenone. The results are noteworthy since these chiral ligands often give high enantioselectivities in the reactions of α-heterocarbanions.[1, 2, 8] However, bisoxazolines showed excellent chiral induction. In particular, **5a** gave (*S*)-thio alcohols **2a**, **2b**, and **2c** in the reactions of lithiated **1** with

---

[*] Prof. Dr. T. Toru, S. Nakamura, R. Nakagawa, Dr. Y. Watanabe
Department of Applied Chemistry
Nagoya Institute of Technology
Gokiso, Showa-ku, Nagoya 466-8555 (Japan)
Fax: (+81) 52-735-5217
E-mail: toru@ach.nitech.ac.jp

[**] This work was partly supported by a Grant-in-Aid for Scientific Research (No. 1650890) from the Ministry of Education, Science, and Culture of Japan.

Table 1. Reaction of lithiated **1** with electrophiles in the presence of chiral ligands **3**–**5**.

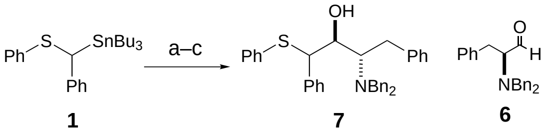
Ligand	Electrophile	T[°C]	Product	Yield[%]	ee[%][a,b]	$[\alpha]_D^T$[c]
3	Ph_2CO	−78	**2a**	93	8 (R)	–
4	Ph_2CO	−78	**2a**	8	10 (S)	–
5a	Ph_2CO	−78	**2a**	79	99 (S)	−45.1
5b	Ph_2CO	−78	**2a**	60	66 (S)	–
5c	Ph_2CO	−78	**2a**	17	59 (S)	–
5a	CH_3COCH_3	−78	**2b**	53	98 (S)	–
5a	CH_3COCH_3	−95	**2b**	71	>99 (S)	+250.0
5a	cyclohexanone	−78	**2c**	54	91 (S)	–
5a	cyclohexanone	−95	**2c**	100	98 (S)	+202.3
5a	PhCHO	−78	**2d**	99[d]	81 (syn)[e]	–
					>99 ($anti$)[e]	–
5a	CH_3CH_2CHO	−78	**2e**	51[f]	96 (syn)	–
					97 ($anti$)	–

[a] The enantiomeric excess was determined by HPLC. [b] The absolute configuration was determined by HPLC by comparison with the spectra of the authentic compounds prepared by different routes. [c] T = 20–27 °C, c = 0.29–0.52 g per 100 mL of $CHCl_3$. [d] syn:$anti$ = 61:39. [e] The enantiomeric excess was determined by HPLC after oxidation with mCPBA to give the sulfone. [f] syn:$anti$ = 38:62.

benzophenone, acetone, and cyclohexanone at −78 °C in 99, 98, and 91 % ee, respectively. The enantioselectivity increased as the reaction temperature was lowered. The reactions of **1** with benzaldehyde and propanal gave mixtures of syn and $anti$ isomers in ratios of 61:39 and 38:62, respectively, and each isomer was produced with high enantioselectivity. In all these reactions **5a** was recovered quantitatively without any loss of enantiomeric purity.

The reaction proceeded with high stereoselectivity starting not only with benzyl phenyl sulfide but also with the racemic stannyl sulfide. The Sn/Li exchange is known to occur with complete retention of configuration at the sp^3 carbanion center[13] and thus, the racemic carbanion is formed from **1**. Hence the chiral induction does not rely upon the configuration of the carbanion but occurs at a late stage of the pathway, in other words, through an asymmetric substitution, in which the enantiodetermining step is either a dynamic kinetic or dynamic thermodynamic resolution.

The configurational instability of the α-lithio benzyl phenyl sulfide/ligand complex was confirmed by the reactions with (dl)- and (S)-2-(N,N-dibenzylamino)-3-phenylpropanals[14] (**6**) in cumene according to the method reported by Hoffmann et al. (Scheme 2, Table 2).[7, 15] The reaction of the racemic carbanion with a chiral aldehyde should afford the product in a diastereoisomer ratio of 50:50 provided that the complex of anorganolithium compound and a ligand is configurationally stable. However, the reaction with the chiral aldehyde gave **7** in a ratio of 61:39, which is essentially the same as the ratio obtained in the reaction of a racemic aldehyde with N,N,N',N'-tetramethylethylenediamine (TMEDA). The diastereomer ratio was 80:20 when **5a** and the chiral aldehyde were used. These results show that the complex formed between the lithium carbanion with a ligand such as TMEDA or **5a** is configurationally unstable at −78 °C, and hence, the enantioselective outcome of the reaction with **1** should arise through a dynamic kinetic resolution. This proposal is also supported by the fact that higher enantioselectivity was attained from the reaction at lower reaction temperatures.

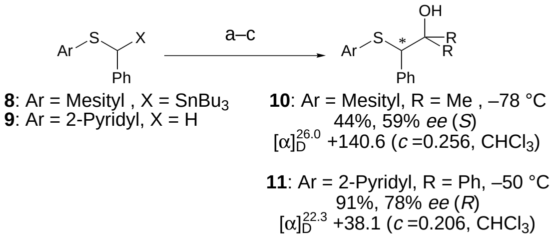


Scheme 2. a) nBuLi (1.15 equiv), cumene, −78 °C; b) ligand (1.2 equiv), −78 °C, 1 h; (dl)-**6** or (S)-**6**, −78 °C.

Table 2. The configurational stability of lithiated **1**.

Ligand	Aldehyde	Yield[%]	Ratio
TMEDA	(dl)-**6**	90	58:42
TMEDA	(S)-**6**	88	61:39
5a	(S)-**6**	90	80:20

We also studied the enantioselective reaction of other α-lithio aryl benzyl sulfides. The reactions of benzyl mesityl sulfide (**8**) and benzyl 2-pyridyl sulfide (**9**) gave **10** and **11** in 59 and 78 % ee, respectively (Scheme 3). The enantioselectivity of the reaction starting with **8** was lower than that obtained from **1**. This is probably because the α-sulfenyl carbanion from **8** is configurationally more stable than the one from **1**.[16] Surprisingly, the enantioselective reaction of **9** with **5a** gave **11**, which has stereochemistry opposite to that obtained in the reaction of **1**. The nitrogen atom from the pyridyl group is also incorporated in the complex, such that the lithium cation is fully coordinated by the carbanion along with three nitrogen atoms from the bisoxazoline ligand and the pyridyl group. We suppose that the stereoselection is induced at this point by the energy difference of the intermediate complexes. The attack of an electrophile on the carbanion occurs from the direction opposite to the lithium cation to give the R isomer.[17]



Scheme 3. Lithiation of **8** and **9** followed by the reaction with electrophiles. a) nBuLi (1.15 equiv), cumene, −78 °C; b) **5a** (1.2 equiv), 1 h; c) electrophile, temperatures used are given in the scheme.

Experimental Section

General procedure:[18] A solution of nBuLi (0.165 mmol) in hexane was added to a solution of **1** (70.5 mg, 0.144 mmol) in cumene (1.0 mL) at −78 °C. The solution was stirred for 10 min and then **5a** (45.3 mg, 0.173 mmol) added. After the reaction mixture had been stirred for 1 h, a solution of an electrophile (0.187 mmol) in cumene (0.5 mL) was added, and the reaction mixture was stirred for an additional 1 h at −78 °C. Standard work-up and purification by column chromatography gave **2**.

Received: June 18, 1999 [Z13586]

---

[1] For a review, see D. Hoppe, T. Hense, *Angew. Chem.* **1997**, *109*, 2376–2410; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282–2316, and references therein.

[2] a) P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552–560; b) N. C. Faibish, Y. S. Park, S. Lee, P. Beak, *J. Am. Chem. Soc.* **1997**, *119*, 11561–11570; G. A. Weisen-

burger, N. C. Faibish, D. J. Pippel, P. Beak, *J. Am. Chem. Soc.* **1999**, *121*, 9522–9530, and references therein.

[3] a) B. Kaiser, D. Hoppe, *Angew. Chem.* **1995**, *107*, 344; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 323–325; b) T. Shinozuka, Y. Kikori, M. Asaoka, H. Takei, *J. Chem. Soc. Perkin Trans. 1* **1995**, 119–120.

[4] a) R. W. Hoffmann, M. Julius, F. Chemla, T. Ruhland, G. Frenzen, *Tetrahedon* **1994**, *50*, 6049–6060; b) R. W. Hoffmann, R. K. Dress, T. Ruhland, A. Wenzel, *Chem. Ber.* **1995**, *128*, 861–870.

[5] High configurational stability has been achieved only through in situ trapping or intramolecular rearrangement, see a) P. G. McDougal, B. D. Condon, M. D. Laffosse, Jr., A. M. Lauro, D. VanDerveer, *Tetrahedron Lett.* **1988**, *29*, 2547–2550; b) P. G. McDougal, B. D. Condon, *Tetrahedron Lett.* **1989**, *30*, 789–790; c) H. J. Reich, M. D. Bowe, *J. Am. Chem. Soc.* **1990**, *112*, 8994–8995; d) K. Brickmann, R. Brückner, *Chem. Ber.* **1993**, *126*, 1227–1239.

[6] An example of a dipole-stabilized α-thiobenzyllithium compound that is configurationally stable in diethyl ether is known, see D. Hoppe, B. Kaiser, O. Stratmann, R. Fröhlich, *Angew. Chem.* **1997**, *109*, 2872–2874; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2784–2786.

[7] T. Ruhland, R. Dress, R. W. Hoffmann, *Angew. Chem.* **1993**, *105*, 1487; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1467–1468.

[8] a) W. Klute, R. Dress, R. W. Hoffmann, *J. Chem. Soc. Perkin Trans. 2* **1993**, 1409–1411; b) R. W. Hoffmann, W. Klute, R. K. Dress, A. Wenzel, *J. Chem. Soc. Perkin Trans. 2* **1995**, 1721–1726; c) R. W. Hoffmann, W. Klute, *Chem. Eur. J.* **1996**, *2*, 694–700.

[9] For enantioselective reactions of nondipole-stabilized α-oxycarbanions in the presence of bisoxazolines, see a) N. Komine, L. Wang, K. Tomooka, T. Nakai, *Tetrahedron Lett.* **1999**, *40*, 6809–6812; b) K. Tomooka, L. Wang, N. Komine, T. Nakai, *Tetrahedron Lett.* **1999**, *40*, 6813–6816. We are grateful to Prof. K. Tomooka for helpful discussions.

[10] a) S. E. Gibson (nèe Thomas), P. Ham, G. R. Jefferson, M. H. Smith, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2161–2162; b) A. Ariffin, A. J. Blake, R. A. Ewin, N. S. Simpkins, *Tetrahedron: Asymmetry* **1998**, *9*, 2563–2566. For α-oxycarbanions see also: c) R. A. Ewin, N. S. Simpkins, *Synlett* **1996**, 317–318; d) S. E. Gibson (nèe Thomas), P. C. V. Potter, M. H. Smith, *Chem. Commun.* **1996**, 839–840; e) S. E. Gibson (nèe Thomas), P. C. V. Potter, M. H. Smith, *Chem. Commun.* **1996**, 2757–2578; f) R. A. Ewin, A. M. MacLeod, D. A. Price, N. S. Simpkins, A. P. Watt, *J. Chem. Soc. Perkin. Trans 1* **1997**, 401–415.

[11] Reactions in diethyl ether or THF gave **2** with much lower stereoselectivity.

[12] For enantioselective reactions using bis-oxazolines, see a) A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1–45; b) S. E. Denmark, N. Nakajima, O. J.-C. Nicaise, *J. Am. Chem. Soc.* **1994**, *116*, 8797–8798; c) M. Nakamura, M. Arai, E. Nakamura, *J. Am. Chem. Soc.* **1995**, *117*, 1179–1180; d) D. M. Hodgson, G. P. Lee, *Tetrahedron: Asymmetry*, **1997**, *8*, 2303–2306. e) K. Tomooka, N. Komine, T. Nakai, *Tetrahedron Lett.* **1998**, *39*, 5513–5516; f) V. Schulze, R. W. Hoffmann, *Chem. Eur. J.* **1999**, *5*, 337–344; g) T. Kambara, K. Tomioka, *Chem. Pharm. Bull.* **1999**, *47*, 720–721.

[13] a) W. C. Still, C. Sreekumar, *J. Am. Chem. Soc.* **1980**, *102*, 1201–1202; b) J. S. Sawyer, A. Kucerovy, T. L. Macdonald, G. J. McGarvey, *J. Am. Chem. Soc.* **1988**, *110*, 842–853. There is a reaction with partial inversion, see J. Clayden, J. H. Pink, *Tetrahedron Lett.* **1997**, *38*, 2565–2568.

[14] M. T. Reetz, M. W. Drewes, A. Schmitz, *Angew. Chem.* **1987**, *99*, 1186–1188; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1141–1143.

[15] a) R. Hirsch, R. W. Hoffmann, *Chem. Ber.* **1992**, *125*, 975–982; b) R. W. Hoffmann, M. Bewersdorf, *Liebigs Ann. Chem.* **1992**, 643–653. Configurational instability of the α-lithiobenzyl phenyl sulfide in THF has been verified, see R. W. Hoffmann, T. Ruhl, J. Harbach, *Liebigs Ann. Chem.* **1992**, 725–730.

[16] The barrier to racemization for the α-seleno- and α-thiocarbanions having a bulky aryl group such as the duryl or mesityl group is known to be significantly higher than for those with a phenyl group, see refs.[3b, 5d]

[17] This hypothesis relies on several reactions involving the Hoffmann test as well as MO calculations and will be discussed in detail in due course.

[18] All complexes formed from the carbanions and the chiral ligands were soluble in cumene.

Hydroxy-Directed, SmI$_2$-Induced Conversion of Carbohydrates into Carbocycles[**]

Toshiyuki Kan, Shinji Nara, Takashi Ozawa,
Haruhisa Shirahama, and Fuyuhiko Matsuda[*]

Recently, we established that the configuration of the hydroxy groups in a starting material has a powerful influence in facilitating the reductive couplings promoted by samarium(II) iodide[1] and in controlling the stereochemical outcome.[2, 3] All of these hydroxy-directed carbon–carbon bond formation reactions proceed in good yields and provide access to highly funtionalized molecules with excellent stereocontrol. Furthermore, the sense of the diastereoselectivity was in full accordance with a chelation-control model. We have now discovered that this new methodology allows the stereoselective construction of polyoxygenated six-membered carbocycles from carbohydrate templates. During the last decade, organic chemists have been very interested in the transformation of carbohydrates to carbocycles.[4] Although most current approaches involve a radical methodology, only a limited number of SmI$_2$-mediated annulations of five-membered ring carbocycles from carbohydrates have been reported.[5]

As shown in Scheme 1, the six-membered ring carbocycles can be accessed from the allyl sulfides **1** and **4**, which are prepared from methyl β-D-glucopyranoside and β-D-galactopyranoside by simple carbohydrate manipulations.[6] When **1** was allowed to react directly with SmI$_2$ (2.5 equiv) at room temperature in THF/MeOH (5/1), the ring-closing reaction proceeded with complete stereochemical control to furnish the *cis*-1,3-cyclohexanediols **2** and **3** in a 75:25 ratio and in excellent yield. Similarly, the *cis*-1,3-cyclohexanediols **5** and **6** (27:73) were exclusively obtained through the SmI$_2$-mediated reaction of **4**.[9] Apparently, the corresponding δ-hydroxy aldehydes **7** and **8** must be generated in equilibrium processes before the self-terminating 6-*exo-trig* ketyl–olefin cyclization mediated by SmI$_2$ (Scheme 2).[10] This new annulation process is of considerable synthetic utility not only because of the observed high diastereoselectivity but also because of the exceptional synthetic versatility of the cyclization products.

---

[*] Prof. Dr. F. Matsuda,[+] Dr. T. Kan, Dr. S. Nara, T. Ozawa,
Prof. Dr. H. Shirahama
Department of Chemistry, Faculty of Science
Hokkaido University
Sapporo 060-0810 (Japan)
E-mail: fmatsuda@ees.hokudai.ac.jp

[+] Current address:
Division of Material Science
Graduate School of Environmental Earth Science
Hokkaido University
Sapporo 060-0810 (Japan)
Fax: (+81) 11757-5995

[**] The present work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (no. 09231201) from The Ministry of Education, Science, Sports and Culture of the Japanese Government. The authors are greatly indebted to Professor Dennis P. Curran (University of Pittsburgh) for helpful discussions.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.