Asymmetric Induction in Intramolecular S_N2' Reaction. Enantioselective Synthesis of Cyclopenta[*b*]benzofuran with Chiral Lithium Alkoxides

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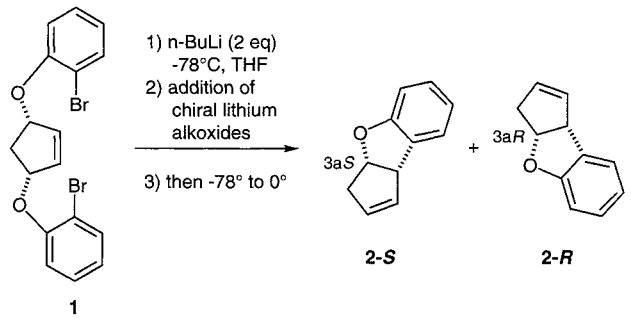
This communication is dedicated to the memory of Dr. Kiyotaka Ohno (the former director of BRC, Toray), deceased on 10 August 1995

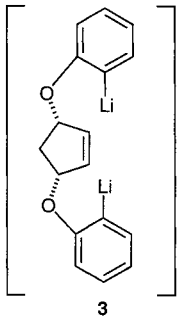
Abstract: An enantioselective intramolecular cyclization of the bis-phenyllithium species **3** was attained by addition of chiral lithium alkoxides to produce a cyclopenta[*b*]benzofuran **2** with high % ee's up to 87 %.

Desymmetric transformation of *meso*-structures has been recognized as a versatile synthetic method of optically active compounds in organic and enzymatic processes.[1] In this context, the S_N2'-intramolecular cyclization of a *cis*-di-2-bromophenoxycyclopentene **1** via a bis-phenyllithium species **3**, which was previously reported by us, includes the geometric desymmetrization giving a racemic mixture of a cyclopenta[*b*]benzofuran **2** (Scheme 1).[2] Since we have found the transformation, we have been intrigued to improve the transformation as an asymmetric reaction by aid with certain chiral auxiliaries. Here we report a novel method for the asymmetric intramolecular cyclization of phenyllithium derivatives by using chiral lithium alkoxides as additives.



Scheme 1

The bis-phenyllithium species **3** were readily generated by addition of *n*-butyllithium to a solution of the diphenoxycylcopentene **1** in absolute tetrahydrofuran (THF) at -78°C. (-)-Sparteine (1.2 eq. to **2**) was then added to the solution as a chiral auxiliary. The mixture was stirred at -78°~0°C for 2 h to give the desired benzofuran **2**[2] in 74% yield, but which proved to be a racemic form.



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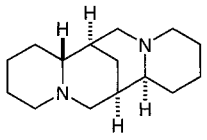
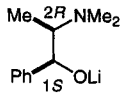
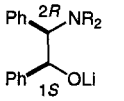
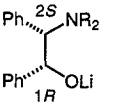
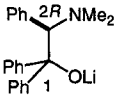
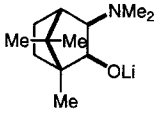
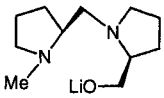
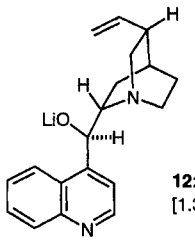
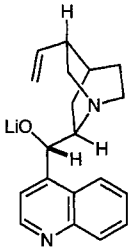


4: (-)-Sparteine

We next expected that certain chiral lithium alkoxides may strongly contact the phenyllithium skeleton of **3** rather than the neutral nitrogen ligand sparteine. Therefore, we chose several chiral lithium dialkylaminoethoxides **5-13** as chiral additives. First, the 1-phenyl-2-methyl aminoalkoxide **5** (nor-ephedrine derivative)[3] (1.3 eq. to **1**) was examined to give (3a*S*)-**2** in 77% yield accompanied with asymmetric induction of 44% (*S*). When an phenyl group was introduced in place of 2-methyl substituent on **5**, as shown in the 1,2-diphenyl derivative **6**[4], the % ee was improved to 71% (Table 1). The enantiomers **7** and **8** to **6** also gave similar results to those of **6**, 64% ee and 68%ee, respectively. However, the triphenyl derivative **9**[5] gave no asymmetric induction. (-)-DAIB **10**,[6] which was introduced as a powerful additive for asymmetric alkylation with diethyl zinc, gave only 35% ee. The above findings show that the (3a*S*)-absolute configuration of **2** may be derived from (1*S*)-configuration of the chiral auxiliaries **5**, **6**, **10**. On the other hand, the prolinyl-prolinol derivative **11**[7] afforded a good to excellent induction 62% ee as well as 56-67% ees with (-)-cinchonidine **12** and (+)-cinchonine **13**.

Table 1. Asymmetric intramolecular cyclization of **1** with chiral lithium dialkylaminoethoxides [a]

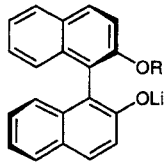
chiral lithium dialkylaminoethoxide: [equiv. of **5-13**, yield of **2** (%), % ee of **2**, abs. cofig.]	
 **5**: [1.3, 77, 44, *S*]	 **6**: R_2 = -$(CH_2)_4$- [1.2, 69, 71, *S*] [2.0, 74, 70, *S*]
 **7**: R_2 = Me_2 [1.3, 76, 64, *R*] **8**: R_2 = -$(CH_2)_4$- [1.3, 74, 68, *R*]	 **9**: [1.3, 79, 1, *S*]
 **10**: (-)-DAIB [1.3, 74, 35, *S*]	 **11**: [1.0, 64, 62, *R*] [2.0, 70, 61, *R*]
 **12**: [1.3, 59, 67, *R*] (-)-Cinchonidine	 **13**: [1.3, 72, 56, *S*] (+)-Cinchonine

[a] Substrate **1** (1.0 mmol), *n*-BuLi (2.2 mmol), THF (3 ml). The corresponding lithium salts (1.2~2.0 mmol in ca. 4~5 ml of THF) were added at -78°C. Then the mixture was stirred for 2 h at -78°~0°C

We then examined binaphthoxide derivatives **14-18** as additives. Although the dilithium binaphthoxide **14** gave a low % ee, 26%. However, use of 1.2 equivalent of the monolithium naphthoxide of mono-methyl ether **15**[8] to the substrate **1** resulted in a highest % ee,

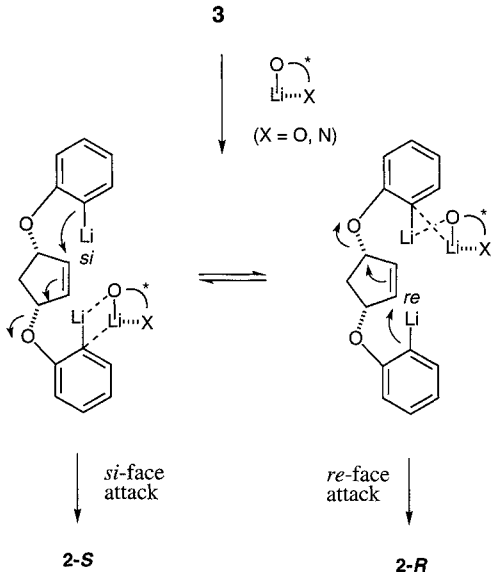
87% (*S*). Similarly, the naphthoxides of methoxymethyl ether **16** and benzyl ether **17** also gave higher results, 80-81% ee's.

Table 2. Asymetric intramolecular cyclization of **1** with chiral lithium naphthoxides **14-18** [a]

chiral lithium naphthoxide: [equiv. of **14-18**, yield of **2** (%), % ee of **2**, abs. config.]		
	**14**: R = Li	[1.2, 74, 26, *S*]
	15: R = Me	[1.2, 73, 87, *S*]
	16: R = CH_2OMe	[1.2, 81, 81, *S*]
	17: R = CH_2Ph	[1.2, 80, 80, *S*]
	18: R = $SiMe_2(t\text{-}Bu)$	[1.2, 61, 3, *S*]

[a] Substrate **1** (1.0 mmol), *n*-BuLi (2.2 mmol), THF (3 ml). The corresponding lithium salts **14~18** (1.2 mmol in ca. 4 ml of THF) were added at -78°C. Then the mixture was stirred for 2 h at -78°~0°C

Consequently, the nearly stoichiometric amount of auxiliaries **5-13** and **14-18** (1.0-1.3 eq.) to the bis-phenyllithium **3** was sufficient to obtain higher % ee's, since higher %ee's were not obtained by an addition of 2.0 equivalent of **6** and **11**. On the basis of this phenomena, we think a possible mechanism as follows: one molecule of the chiral lithium alkoxides stereoselectively associate to one lithium part of the intermediate dilithium species **3** to give a mixture of the complexes **I** and **II** in the equilibrium media (Scheme 2). The each free phenyllithium part can attack onto the *si*-face of the olefin skeleton of **I** and the *re*-face of that of **II**, respectively, to produce a mixture of **2-*S*** and **2-*R*** enantiomers. The faster cyclization from the complex **I** proceeded predominatly to afford **2-*S*** enantioselectively.



Scheme 2

Thus, we have found new method of asymmetric induction for intramolecular S_N2' cyclization on the *meso*-skeleton **1**. We are now examining scope and limitations of substrates and the mechanistic detail.

References and Notes

(1) For examples of desymmetric transformation, a) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1980**, *45*, 755. b) Asami, M. *Chem. Lett.* **1984**, 892. c) Yamashita, H.; Mukaiyama, T. *Chem. Lett.* **1985**, 1643. For reviews, d) Oguni, N. *Organic Synthetic Chemistry Japan* **1996**, *54*, 829. e) Stephenson, G. R. *Advanced Asymmetric Synthesis*; Chapman & Hall: London, 1996, Chapter 18, p 392. f) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355. g) Drauz, K.; Waldmann, H. *Enzyme Catalysis in Organic Synthesis*; VCH: Weinheim, 1995.

(2) a) Nishiyama, H.; Isaka, K.; Itoh, K.; Ohno, K.; Nagase, H.; Matsumoto, K.; Yoshihara, H. *J. Org. Chem.* **1992**, *57*, 407. b) Ohno, K.; Nishiyama, H.; Nagase, H.; Matsumoto, K.; Ishikawa, M. *Tetrahedron Lett.* **1990**, *31*, 4489. c) Nagase, H.; Matsumoto, K.; Yoshihara, H.; Tajima, A.; Ohno, K. *Tetrahedron Lett.* **1990**, *31*, 4493. The product **2** was obtained as colorless oil by silica gel column chromatography of the crude mixture with hexane as an eluent. The enantiomeric excess of **2** was determined by GC analysis with Astec Chiraldex G-TA (30 m) at 110°C under the atmosphere of He (1.5 atm): the first run was (*R*)-isomer (R_{time} = 15.5 min) and the second run was (*S*)-isomer (R_{time} = 18.5 min) [k2/k1 = 1.2, *R* = 4.0]. The (*S*)-product **2** with 87% ee exhibited $[\alpha]_D^{21}$ = -207° (c 0.86, Et_2O) and the absolute configuration (*S*) was confirmed by transformation of **2** to an authentic compound having (*S*)-configuration: lit. ref. 2c.

(3) a) Soai, K.; Niwa, S.; Yamada, Y.; Inoue, H. *Tetrahedron Lett.* **1987**, *28*, 4841. b) Soai, K.; Yokoyama, S.; Ebihara, K.; Hayasaka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1690.

(4) The pyrolidino derivatives **6** and **8** were synthesized by the reaction of (+)-(1*S*,2*R*)- and (-)-(1*R*,2*S*)-2-amino-1,2-diphenylethanol (Aldrich 33,188-0 and 33,189-9, respectively) with 1,4-diiodobutane (1.1 eq.) and $NaCO_3$ in ethanol at refluxing temperature for 10 h.

(5) **9** was prepared by phenylation of L-phenylglycine followed by dimethylation with formic acid and formaldehyde.

(6) a) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071. b) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M.; Oguni, N.; Hayashi, M.; Kaneko, T.; Matsuda, Y. *J. Organomet. Chem.* **1990**, *52*, 135. c) Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49.

(7) a) Mukaiyama, T.; Soai, K.; Kobayashi, S. *Chem. Lett.* **1978**, 601. b) Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455.

(8) Maruoka, K.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 1165.