

STEREOCHEMISTRY OF SULFUR-LITHIUM AND TIN-LITHIUM EXCHANGE REACTIONS OF FUNCTIONALIZED CYCLOPROPANES

Kazuhiko Tanaka,* Keizaburo Minami, Ikuo Funaki, and Hitomi Suzuki
Department of Chemistry, Faculty of Science, Kyoto University,
Sakyo, Kyoto 606, Japan

Summary: Sulfur-lithium exchange reaction of 2-substituted-2-(phenylthio)-cyclopropanecarboxamides by LDMAN in THF at -50°C proceeded with inversion of configuration, leading to the predominant formation of trans-2-substituted cyclopropanes, while in tin-lithium exchange, the configuration was maintained at -78°C .

Stereoselective synthesis of functionalized cyclopropanes are of great importance since these cyclopropanes are frequently found in natural products and are synthetically useful intermediates for construction of other complex molecules.¹ We have previously reported the new synthetic method for functionalized cyclopropanes via β -lithiation-cyclization procedure of 3-phenylthio-2-[(phenylthio)methyl]propanecarboxamide.² This method also provided optically pure 2-(phenylthio)cyclopropanecarboxamides, which could be further metalated to furnish carbon-carbon bond formation with high stereoselectivity.³

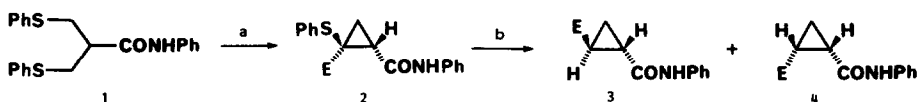


If the phenylthio moiety utilized in the cyclization can be stereoselectively removed or replaced by another electrophile via sulfur-lithium exchange reaction, this cyclopropanation reaction will be more efficient for the preparation of a wide variety of optically pure cyclopropane derivatives which are difficult to prepare by conventional methods.

Cohen⁴ and Shiner⁵ have recently found that lithium 1-(dimethylamino)naphthalenide (LDMAN) and lithium *p,p'*-di-tert-biphenylide (LDBB) are effective reagents for reductive lithiation of phenylthio-substituted cycloalkanes and acetals. However, the stereochemistry of this reductive lithiation is still unclear, owing to

the lack of studies on the substrates with well-defined configurations.

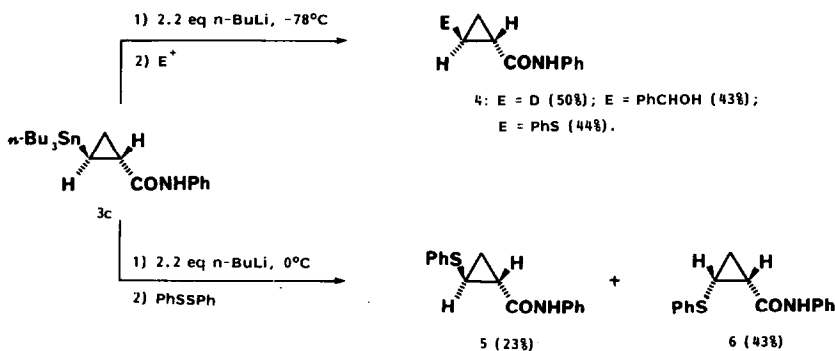
We now wish to report the first study of the stereochemical course of sulfur-lithium and tin-lithium exchange reactions using the stereodefined 2-substituted-2-(phenylthio)cyclopropanecarboxamides (**2**). When **2** was treated with 3 eq of LDMAN⁶ at -50 °C in THF for 3 h, trans-substituted cyclopropanes **3** was obtained predominantly as shown in Table.



Reagents; (a) *n*-BuLi (2.2eq), electrophile;
(b) LDMAN, -50°C, THF.

Compound (2)	Yield of 3+4	3:4
2a E = H	92%	-
2b E = SiMe ₃	96	95:5
2c E = SnBu ₃	79	95:5
2d E = CH ₂ OH	58	70:30
2e E = CH=CH ₂	42	a

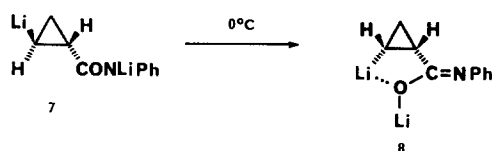
a: not determined.



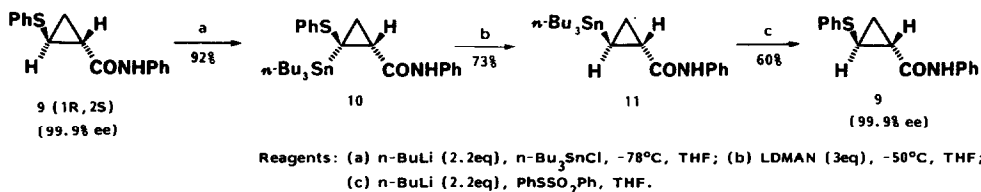
These results indicate that the sulfur-lithium exchange reaction proceeds with inversion of configuration of the cyclopropyl radical⁷ formed by an electron transfer from LDMAM followed by homolytic cleavage⁴ in order to minimize the steric hindrance between *N*-phenylcarbamoyl group and the substituent (E). The cyclopropyl carbanion produced by reduction of the carbon radical is then stabilized by intramolecular chelation.⁸

Since the stereoselective synthesis of trans-2-(tributylstannyl)-cyclopropanecarboxamide (**3c**) has been established, we next examined the

stereochemistry of tin-lithium exchange reaction. Treatment of **3c** with 2.2 equiv of butyllithium at $-78\text{ }^{\circ}\text{C}$ and subsequent addition of electrophiles afforded exclusively trans cyclopropanes (**4**). In contrast, the reaction at $0\text{ }^{\circ}\text{C}$ produced a mixture of cis and trans cyclopropane derivatives (**5** and **6**). These results suggest that the tin-lithium exchange reaction proceeds with retention of configuration at low temperatures⁹ and the trans lithiocyclopropane (**7**) isomerizes at $0\text{ }^{\circ}\text{C}$ to thermodynamically more stable, chelated cis-lithiospecies (**8**).⁸

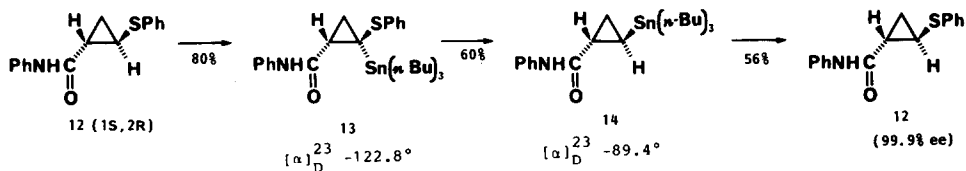


The possibility of racemization during these manipulations was finally investigated by using optically pure (1*R*,2*S*)-*N*-phenyl-2-(phenylthio)cyclopropanecarboxamide (**9**, $[\alpha]_{\text{D}}^{23} +79.8^{\circ}$ (c 0.93, dioxane)) as a candidate, because cis- and trans-2-(phenylthio)cyclopropanecarboxamides could be easily separated by silica gel chromatography and the enantiomeric excess of the trans isomer could be determined by HPLC using a chiral stationary phase.³ Lithiation of **9** and subsequent addition of Bu_3SnCl gave **10** ($[\alpha]_{\text{D}}^{25} +122.4^{\circ}$ (c 0.96, dioxane)) in high yield. Sulfur-lithium exchange produced (1*R*,2*S*)-*N*-phenyl-2-(tributylstannyl)cyclopropanecarboxamide (**11**, $[\alpha]_{\text{D}}^{23} +90.0^{\circ}$ (c 1.03, dioxane)), which was then converted to **9** via tin-lithium exchange at $-78\text{ }^{\circ}\text{C}$. The optical purity of **9** was determined to be 99.9% by analysis of HPLC. These results indicate that no racemization took place during these reaction sequences.



A similar transformation of enantiomerically pure cyclopropane

(1S,2R)-12 ($[\alpha]_D^{25} -79.0^\circ$) proceeded without any racemization.



The present method provides an efficient route to the synthesis of both the enantiomers of cyclopropane derivatives free from phenylthio moiety by using the newly devised chiral reagent (1R,2S)-11 and its antipode (1S,2R)-14.

Acknowledgement: This work was supported by Grant-in-aid for Scientific Research on Priority Area No. 01607005. K. T. thanks the Kurata Foundation for financial support.

References and Notes

- For a recent review, see: J. Salaün, *Chem. Rev.*, **89**, 1247 (1989).
- K. Tanaka, K. Minami, and A. Kaji, *Chem. Lett.*, **1987**, 809.
- K. Tanaka, I. Fumaki, A. Kaji, K. Minami, M. Sawada, and T. Tanaka, *J. Am. Chem. Soc.*, **110**, 7185 (1988).
- (a) T. Cohen and J. R. Mats, *Synth. Commun.*, **10**, 311 (1980).
(b) T. Cohen, W. M. Daniewski, and R. B. Weinsensfeld, *Tetrahedron Lett.*, **1978**, 4665.
(c) T. Cohen and J. R. Mats, *J. Am. Chem. Soc.*, **102**, 6902 (1980).
(d) T. Cohen and B.-S. Guo, *Tetrahedron*, **42**, 2803 (1986).
(e) C. S. Shiner, T. Tsunoda, B. A. Goodman, S. Ingham, S. Lee, and P. E. Vorndam, *J. Am. Chem. Soc.*, **111**, 1381 (1989).
- C. S. Shiner, T. Tsunoda, B. A. Goodman, S. Ingham, S. Lee, and P. E. Vorndam, *J. Am. Chem. Soc.*, **111**, 1381 (1989).
- LDBB was ineffective in this sulfur-lithium exchange reaction. Reduction by potassium and dicyclohexyl-18-crown-6 in toluene was also fruitless. For a reference of this reduction, see: T. Ohsawa, T. Takagaki, A. Haneda, and T. Oishi, *Tetrahedron Lett.*, **22**, 2583 (1981).
- L. A. Paquette and M. Hoppe, *Tetrahedron Lett.*, **27**, 411 (1986).
- P. Beak, J. E. Hunter, Y. M. Jun, and A.P. Wallin, *J. Am. Chem. Soc.*, **109**, 5403 (1987).
- M. P. Periasamy and H. M. Walborsky, *J. Am. Chem. Soc.*, **99**, 2631 (1977).

(Received in Japan 7 February 1990)