shown in the third column of Table I.[19]

In conclusion, we have developed a simple procedure for the titanocene-mediated reductive cyclization of enynes. In contrast to the analogous procedure using the zirconium reagent, this procedure is tolerant of ester functionality in the substrate. We have also shown that in general the product titanacycles may be converted into highly functionalized cyclopentenones in good yield without isolation of any air-sensitive compounds. We have also discovered the first early transition-metal-mediated synthesis of iminocyclopentenes, which are easily prepared from the corresponding titanacycles (prepared in situ) and an isocyanide. We are continuing to investigate the scope of these reactions, with special regard to the functional group and substrate skeleton compatibility of the reaction. We are also conducting a mechanistic study of the isocyanide insertion and reductive elimination reaction,[20] and we are exploring conditions under which the reductive cyclization and "iminylation" of enynes may be rendered catalytic in titanium.

Acknowledgment. We thank the National Institutes of Health for support of this work. S.L.B. is a fellow of the Alfred P. Sloan foundation and a Camille and Henry Dreyfus Teacher–Scholar. We also thank Professor K. Tamao (Kyoto University) for helpful suggestions.

Supplementary Material Available: Detailed experimental procedures for the preparation of previously unreported substrates and all products in Table I and spectroscopic characterization of these compounds (23 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(19) Tamao has shown that iminocyclopentenes are easily converted into the corresponding cyclopentenones.[7]

(20) Cámpora, J.; Buchwald, S. L. Unpublished results.

Stereochemistry in Carbenoid Formation by Bromine/Lithium and Bromine/Zinc Exchange Reactions of 1,1-Dibromoalkenes: Higher Reactivity of the Sterically More Hindered Bromine Atom

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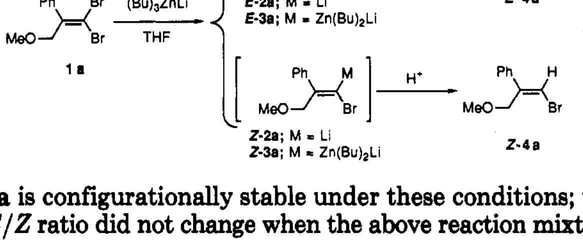
Summary: Both lithium and zincate carbenoids (R^1-(R^2)C=C(Br)M; M = Li and Zn(Bu)$_2$Li) generated by the halogen/metal exchange reaction of 1,1-dibromoalkene **1** with BuLi and (Bu)$_3$ZnLi, respectively, are configurationally stable at low temperatures, but in the presence of excess **1**, the lithium carbenoids undergo facile isomerization at the carbenoid carbons. Under kinetically controlled conditions, both the Br/Li and Br/Zn exchange reactions take place preferentially at the sterically more hindered bromine atom of **1**.

α-Haloorganometallic compounds (metal carbenoids) possessing both nucleophilic and electrophilic reactivities are versatile intermediates in carbon–carbon bond-forming reactions.[1,2] The tetravalent nature of carbenoids, if their stereochemistry is properly controlled, may endow these reactions with a high level of stereoselectivity, which is difficult to attain by using divalent free carbenes. The halogen/metal exchange reaction of *gem*-dihalo compounds is one of the most efficient and frequently employed methods of generating carbenoids. However, factors governing the stereochemistry of the reaction have not been fully elucidated.[3] We report herein an investigation of the stereochemistry in carbenoid formation by the Br/Li and Br/Zn exchange reaction of 1,1-dibromoalkenes. Observation of selective reactions at the sterically more hindered bromine atom under kinetic conditions provides information concerning the mechanism of carbenoid formation by the halogen/metal exchange reactions.

Addition of a THF solution of dibromoalkene **1a** to a THF/hexane solution of BuLi (2 equiv) at −94 °C during a 90-s period followed by immediate treatment of the resulting lithium carbenoid **2a** with AcOH/THF gave a 73:27 mixture of (*E*)- and (*Z*)-**4a** in 84% yield (eq 1).[4] Carbenoid **2a** is configurationally stable under these conditions; the *E*/*Z* ratio did not change when the above reaction mixture



(1)

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(1) (a) Regitz, M. Carbene (Carbenoid). In Houben-Weyl, Methoden der Organische Chemie; Georg Thieme: Verlag 1989; Teil 12a,b. (b) Moss, R. A.; Jones, M., Jr. *Carbenes*; Wiley: New York, 1975; Vols. 1 and 2. (c) Kirmse, W. Carbene Chemistry, 2nd ed.; Academic Press: New York, 1971.

(2) (a) Duraisamy, M.; Walborsky, H. M. *J. Am. Chem. Soc.* **1984**, *106*, 5035. (b) Warner, P. M.; Chang, S. C.; Koszewski, N. J. *Tetrahedron Lett.* **1985**, *26*, 5371. (c) Rachon, J.; Goedken, V.; Walborsky, H. M. *J. Am. Chem. Soc.* **1986**, *108*, 7435. (d) Harada, T.; Hattori, K., Katsuhira, T.; Oku, A. *Tetrahedron Lett.* **1989**, *30*, 6035.

(3) For stereochemical aspects of carbenoid generation by halogen/metal exchange reaction, see: (a) Seyferth, D.; Lambert, R. L., Jr.; Massol, M. *J. Organomet. Chem.* **1975**, *88*, 255. (b) Kitatani, K.; Yamamoto, H.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2158. (c) Zwiefel, G.; Lewis, W.; On, H. P. *J. Am. Chem. Soc.* **1979**, *101*, 5102. (d) Smithers, R. H. *J. Org. Chem.* **1983**, *48*, 2095.

(4) Unless otherwise noted, *E*/*Z* ratios and yields of products were determined by capillary GC. All new compounds showed satisfactory spectral and/or analytical data. Stereochemical determination of products derived from **1a**–**d** is based on NOESY analyses.

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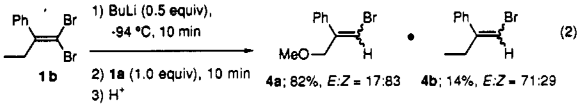
was standing for 30 min at −94 °C befor protonation (E:Z = 73:27, 83% yield).[5]

Interestingly, the ratio was reversed when BuLi was added to a THF solution of **1a**. Thus, generation of carbenoid **2a** by adding BuLi (1.1 equiv) at −94 °C during a 90-s period followed by immediate protonation gave preferentially (Z)-**4a** (Z:E = 77:23). The reversal of the stereoselectivity implies that lithium carbenoid **2a** undergoes rapid E/Z isomerization during addition of BuLi through a Br/Li exchange reaction with the unreacted dibromoalkene (i.e., (E)-**2a** + **1a** ⇄ (Z)-**2a** + **1a**).[6] Indeed, addition of BuLi to a THF solution of 2 equiv of **1a** during a 90-s period followed by standing the resulting mixture for 0, 10, and 30 min at −94 °C gave 87:13 (94%), 90:10 (102%), and 89:11 (97%) mixtures of (Z)- and (E)-**4a**, respectively. Formation of **4a** in the reaction of carbenoid **2b** (Ph(Et)C=C(Li)Br) with **1a** (eq 2) provides further support for the isomerization mechanism. Judging from the above isomerization behavior, preferential formation of (E)-**2a** in the reaction where **1a** was added to a solution of BuLi indicates kinetic selectivity of the Br/Li exchange reaction.

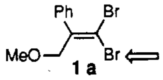
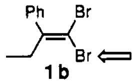
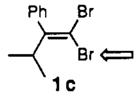
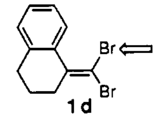
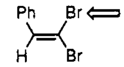
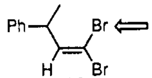
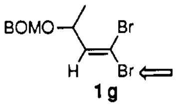


(2)

Addition of dibromoalkene **1a** to a THF solution of lithium tributylzincate ($(Bu)_3ZnLi$)[7] (1.3 equiv) at −85 °C followed by quenching with AcOH/THF after 5 min gave **4a** (100%) with high E selectivity (E:Z = 93:7).[2d,8] The E:Z ratio did not change either when a similar reaction was performed by using 2 equiv of **1a** for 24 h (E:Z = 95:5, 98%) or when $(Bu)_3ZnLi$ was added to a THF solution of 2.0 equiv of **1a** (−85 °C, 30 min) (E:Z = 94:6, 100%). Moreover, when a thermodynamic mixture of lithium carbenoids (Z)- and (E)-**2a** (90:10), prepared by adding BuLi to a THF solution of **1a** (2 equiv) at −94 °C, was treated with Bu_2Zn (1.1 equiv) and the resulting mixture of zincate carbenoid **3a** was standing, in the presence of unreacted **1a**, at −85 °C for 30 min before protonation, a 88:12 mixture of (Z)- and (E)-**4a** was obtained in 99% yield. These results indicate that zincate carbenoid **3a** is configurationally stable at −85 °C irrespective of the presence of unreacted dibromoalkene **1a**. Therefore, the observed stereoselectivity is controlled kinetically.

Stereoselectivities were investigated in generation of lithium and/or zincate carbenoids from a series of dibromoalkenes **1a–g** under the kinetically controlled conditions (Table I).[9] In the reaction of 2,2-disubstituted dibromoalkenes **1a–d**, BuLi and $(Bu)_3ZnLi$ exhibited a similar trend in the stereoselectivity while a level of the selectivity of the latter is higher than the former. The similarity in their stereoselectivites indicates that both the Br/Li and Br/Zn exchange reactions proceed through a similar reaction mechanism. Although selectivities of the Br/Li exchange reactions of monosubstituted dibromoalkenes **1e–g** were unclear due to facile Fritsch–Buttenberg–Wiechell rearrangement[10] of the resulting lithium carbenoids to alkynes, the reaction with $(Bu)_3ZnLi$ affords information on the kinetic stereoselectivities of these substrates.

Table I. Reaction of 1,1-Dibromoalkenes 1 with BuLi and $(Bu)_3ZnLi$ under Kinetic Conditions[a]

	reaction with BuLi		reaction with $(Bu)_3ZnLi$	
dibromoalkene	selectivity[b]	yield[c]	selectivity[b]	yield[c]
 1a	73:27	84%	95:5	83% (17%)
 1b	60:40	78%	80:20	30% (67%)
 1c	81:19[d]	54% (14%)	96:4	24% (74%)
 1d	82:18[d]	66% (16%)	89:11	62% (37%)
 1e			77:23	98% (2%)
 1f			69:31	61% (35%)
 1g			55:45	93% (9%)

[a] Unless otherwise noted, Br/Li exchange reaction was performed at −94 °C by adding a THF solution of 1 to a THF solution of BuLi (2.0 equiv) during a 90-s period followed by immediate protonation with AcOH/THF. Br/Zn exchange reaction was carried out by adding a THF solution of 1 to a THF solution of $(Bu)_3ZnLi$ (1.3 equiv) at −85 °C followed by protonation with AcOH/THF after 5 min. [b] Ratio of the geometrical isomers of the corresponding bromoalkenes were determined by capillary GC (PEG 20M) analysis. Major isomers are those derived from the reactions at bromine atoms indicated by arrows in the structures of **1a–g**. [c] GC yield of the corresponding bromoalkene. Recovery of the starting material is shown in parentheses. [d] The reaction was performed at −116 °C in a mixed solvent of THF and Et_2O (45:55).

It is clear that the exchange reaction takes place preferentially at the sterically more hindered bromine atom in dibromoalkenes **1c–f**. It is somewhat less clear which bromine atom is more hindered in **1a** and **1b**. Conformational analysis by using MM2 force field[11,12] showed that a bromine atom anti to the phenyl group is more hindered. Thus, values of torsional angles between the vinyl and phenyl groups are calculated to be near 60° for their stable conformers.[13] Substitution of the alkyl group at the

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(5) Under these reaction conditions, carbenoid **2a** did not undergo substitution reaction with BuLi.[2a]

(6) Seyferth and his co-workers[3a] have demonstrated that trans,cis isomerization of 1-bromocyclopropyllithium proceeds through a similar mechanism.

(7) (a) Isobe, M.; Kondo, S.; Nagasawa, N.; Goto, T. *Chem. Lett.* **1977**, 679. (b) Fabicon, R. M.; Parves, M.; Rchey, H. G., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 1412 and references cited therein.

(8) (a) Harada, T.; Hara, D.; Hattori, H.; Oku, A. *Tetrahedron Lett.* **1988**, *29*, 3821. (b) Harada, T.; Kotani, Y.; Katsuhira, T.; Oku, A. *Ibid.* **1991**, *32*, 1573.

(9) Under the thermodynamic conditions, E:Z ratios of 97:3 (at −97 °C), 24:76 (at −116 °C), and 97:3 (at −116 °C) were observed for lithium carbenoids generated from **1b**, **1c**, and **1d**, respectively.

(10) Köbrich, G. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 49.

(11) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

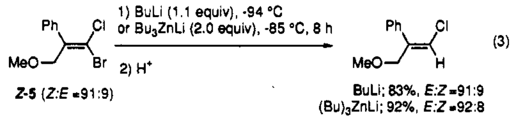
(12) Still, W. C.; Mohamadi, F.; Richards, N. G. R.; Guida, W. C.; Lipton, M.; Liskamp, R.; Chang, G.; Hendrickson, T.; DeGunst, F.; Hasel, W. MacroModel V3.0, Department of Chemistry, Columbia University, New York, NY 10027.

(13) Conformational searching by using a torsion-angle tree-search method[14] revealed that **1a** and **1b** have two and six stable conformers within 2.0 kcal/mol of the corresponding lowest energy conformers. Relative steric energy (kcal/mol) and the torsional angle (degree, the value in parentheses) for each conformer are as follows: **1a**, 0 00 (63), 0.82 (64); **1b**, 0.00 (59), 0.11 (63), 0.13 (61), 0.43 (58), 0.57 (70), 0.99 (59).

geminal position seems to render the phenyl group to rotate, resulting in reduction of its effective size against the syn bromine atom.

Judging from similar trends in stereoselectivity among **1a**, **1b**, and **1c** as well as the nonselective reaction of the (benzyloxy)methyl (BOM) derivatives **1f**, a directing effect of a metal chelation is not necessarily a major factor in the kinetically controlled reactions.[15]

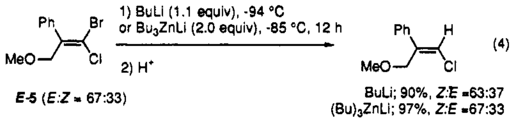
Four possible mechanisms have been proposed for the halogen/metal exchange reactions:[16] (1) a stepwise process initiated by a single electron transfer, (2) a four-centered process, (3) formation of an ate complex, and (4) an S_N2 reaction. Reaction of the pathway invoked for a single electron-transfer mechanism is less likely in the present carbenoid formation for the following reasons. Such mechanism involves a radical intermediate which could undergo *E*,*Z*-isomerization, at least partially, in the course of reaction.[17,18] The results of lithium and zincate carbenoid formation from (*E*)- and (*Z*)-bromochloroalkene **5**[19] (eq 3) clearly demonstrate that both BuLi and $(Bu)_3ZnLi$ undergo exchange reaction stereospecifically with retention of the configuration of the carbenoid carbon. Moreover, $(t\text{-}Bu)_3ZnLi$ which should be a better electron donor in comparison with $(Bu)_3ZnLi$ exhibited a lower reactivity in the Br/Zn exchange reaction: The reaction of **1a** was $(t\text{-}Bu)_3ZnLi$ at −85 °C in THF for 5 min gave **4a** (*E*:*Z* = 92:8) in 29% yield together with recovery of **1a** (68%).



(3)

Z-5 (*Z*:*E* = 91:9)

BuLi; 83%, *E*:*Z* = 91:9
$(Bu)_3ZnLi$; 92%, *E*:*Z* = 92:8

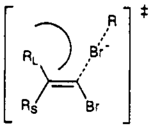


(4)

E-5 (*E*:*Z* = 67:33)

BuLi; 90%, *Z*:*E* = 63:37
$(Bu)_3ZnLi$; 97%, *Z*:*E* = 67:33

The observation of the higher reactivities of the more hindered bromine atom is not compatible with a sterically demanding four-centered transition-state model. The selectivities are most reasonably explained by a linear transition state **6** of either an ate complex[20] or S_N2[21] reaction where strain relief due to elongation of the carbon–bromine bond is expected in the reaction at the more hindered bromine atom.



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Acknowledgment. This work was supported partially by grants from the Ministry of Education, Science, and Culture, Japanese Government [Grant-in-Aid for Scientific Research on Priority Areas No. 03233216 (Unusual Valency) and Grant-in-Aid for Scientific Research Relating to JSPS Fellowships for Japanese Junior Scientist (for T.K.)] and from the Japan Science Society [Sasakawa Scientific Research Grant (for T.K.)].

Supplementary Material Available: General experimental procedures and characterization data of new compounds including NOESY spectra of (*E*)- and (*Z*)-bromoalkenes derived from **1a–d** (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(15) (a) Lau, K. S. Y.; Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595. (b) Meyers, A. I.; Spohn, R. F. *J. Org. Chem.* **1985**, *50*, 4872.

(16) (a) Review; Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1 and references cited therein. (b) Beak, P.; Allen, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 3420.

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(18) Walborsky, H. M. *Acc. Chem. Res.* **1990**, *23*, 286.

(19) **5** was prepared by the reaction of lithium carbenoid **2a** with $ClCF_2CCl_2F$.

(20) (a) Reich, H. J.; Philips, N. H.; Reich, I. L. *J. Am. Chem. Soc.* **1985**, *107*, 4101. (b) Reich, H. J.; Green, D. P.; Philips, N. H. *Ibid.* **1989**, *111*, 3444.

(21) Farnham, W. B.; Calabrese, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 2449.

Enantiopure 2,3-Dihydro-4-pyridones as Synthetic Intermediates. Asymmetric Syntheses of the Quinolizidine Alkaloids (+)-Myrtine, (−)-Lasubine I, and (+)-Subcosine I[†]

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Summary: The first asymmetric syntheses of three quinolizidine alkaloids, (+)-myrtine, (−)-lasubine I, and (+)-subcosine I, were accomplished with a high degree of stereocontrol from readily available 4-methoxy-3-(triisopropylsilyl)pyridine in three, four, and five steps, respectively.

The indolizidine and quinolizidine skeletons comprise the backbone of many biologically and structurally interesting alkaloids.[1] We have been exploring methods for the enantioselective preparation of these ring systems via chiral 1-acyl-2,3-dihydro-4-pyridone intermediates. Using this strategy, we recently accomplished short, enantioselective syntheses of the indolizidine alkaloids (+)-elaeokanine A and (+)-elaeokanine C.[2] In this paper we report a three-step preparation of the quinolizidine alkaloid (+)-myrtine and the first asymmetric syntheses of the

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[†] Dedicated to Professor A. I. Meyers on the occasion of his 60th birthday.

(1) Elbein, A. D.; Molyneus, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1987; Vol. 5, Chapter 1.

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