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Enantioselective Carbanion Cyclization of 5-Alkenyl Carbamates Induced by Asymmetric Lithiation with *s*-Butyllithium/(-)-Sparteine System

Katsuhiko Tomooka,* Nobuyuki Komine, Tomoya Sasaki, Hideo Shimizu and Takeshi Nakai*

Department of Chemical Technology, Tokyo Institute of Technology
Meguro-ku, Tokyo 152-8552, Japan

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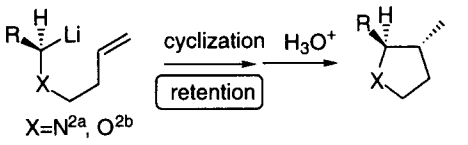
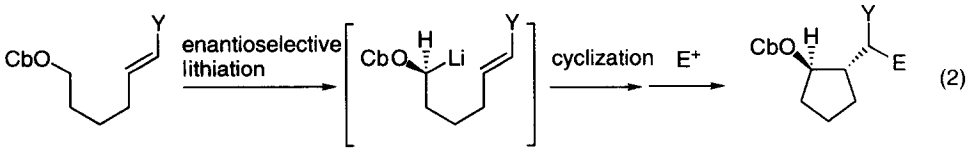
Abstract: Treatment of (*E*)-6-phenyl-5-hexenyl carbamates with *s*-BuLi / (-)-sparteine is shown to afford the *trans*-1,2-disubstituted cyclopentane derivatives in high % ee, along with the bicyclo[3.1.0]hexanes (bicyclization products).

Keyword: carbanions; cyclization; enantiocontrol; lithiation

The carbanion cyclization of 5-alkenyllithiums and their hetero-analogues has emerged as an efficient method for carbocyclization.[1] Recently, this type of carbanion cyclization has been proven to proceed with complete retention of configuration at the Li-bearing carbanion center (eq. 1).[2] Thus, this stereospecificity led us to envision that, if the Li-bearing center is generated in an *enantioselective* fashion and is configurationally stable, the cyclization product could be obtained in an enantio-enriched form. To this end, we have now investigated the feasibility of an enantioselective cyclization induced by asymmetric lithiation using (-)-sparteine as an external chiral ligand. In view of the recent remarkable progress in the sparteine-based asymmetric lithiation technology,[3] 5-alkenyl carbamates were chosen as the substrates for our study. Described herein is the successful realization of the enantioselective carbanion cyclization of (*E*)-5-alkenyl carbamates (eq 2).[4,5]





First, we examined the enantioselective cyclization of 6-phenyl-5-hexenyl carbamate (**1a**, >95% *E*)[6] prepared from δ-valerolactol with Horner-Emmons olefination, followed by reaction with *N,N*-diisopropylcarbamoyl chloride (CbCl). Thus, **1a** was treated with an ethereal solution of *s*-BuLi (5 equiv.) pre-mixed with (-)-sparteine (5 equiv.)[7] at -78 ℃ for 5 hours to afford, after standard workup, the desired

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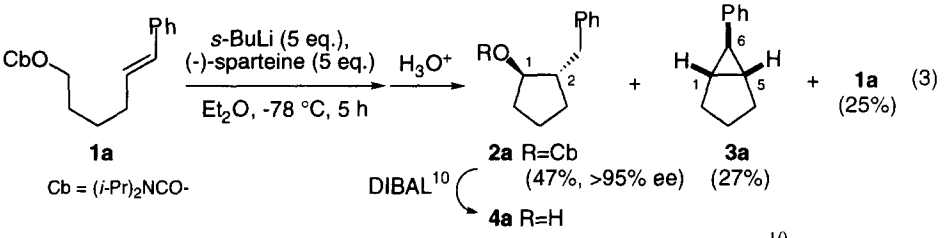
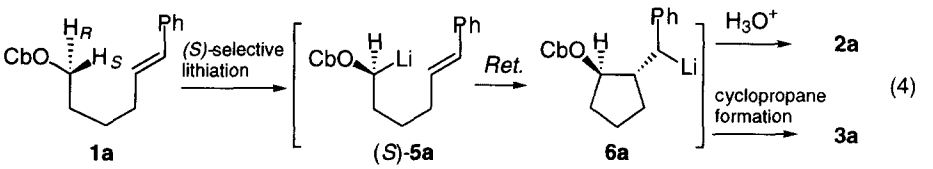
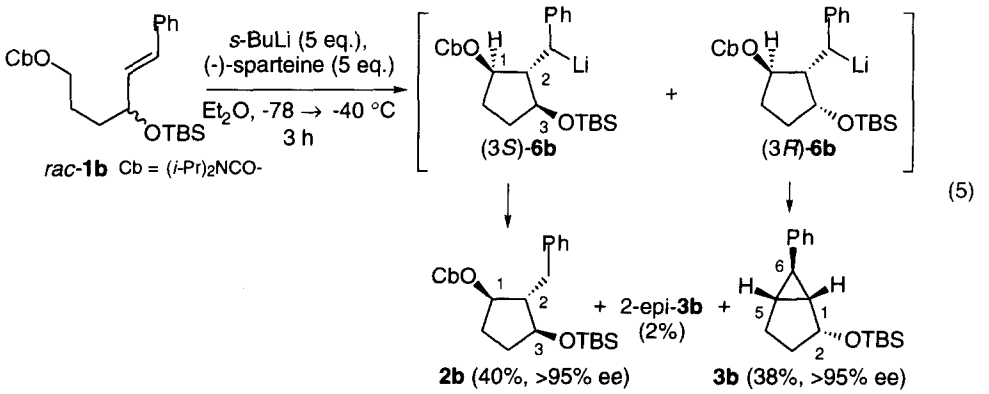
cyclopentane **2a**[8] as a single diastereomer in 47% yield, along with 27% yield of 6-phenyl-bicyclo [3.1.0]hexane **3a**[8,9] and recovered **1a** (eq 3).



The absolute stereochemistry of **2a** was assigned as (1*R*, 2*S*)-*trans* by its conversion[10] to alcohol **4a**, whose physical data (^{1}H NMR and $[\alpha]_D$) were in accord with the reported values[11] and its enantiopurity was determined to be >95% ee by ^{1}H NMR analysis of the MTPA ester of **4a**. This stereochemical outcome is rationalized as a result of the highly (*S*)-selective asymmetric lithiation[3a] forming (*S*)-**5a**, followed by the completely retentive cyclization as expected (eq 4). The formation of bicyclohexane **3a** is explained as a result of the subsequent S_N2-type cyclization of the resulting benzylic lithium **6a** which proceeds with inversion of configuration at the carbamoyloxy-carbon.[12]

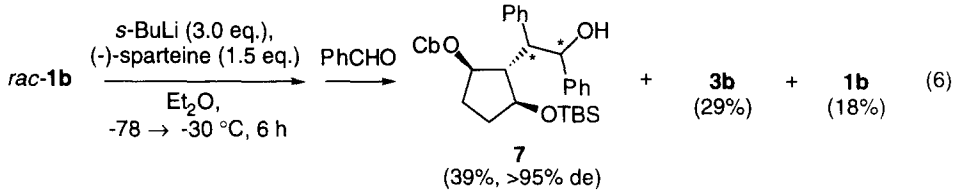


Next, our attention was turned to the asymmetric cyclization of the *racemic* 4-siloxy carbamate **1b**, wherein a kinetic resolution may occur during the initial and/or subsequent cyclization. The racemic substrate **1b** (>95% *E*) was prepared from γ-butyrolactol via reaction with lithium phenyl acetylide followed by reduction with $LiAlH_4$ and protection with CbCl and TBSCl. The cyclization of **1b**, when induced with *s*-BuLi / (-)-sparteine in a similar way, was found to give cyclopentane **2b** and bicyclohexane **3b**, both as a single stereoisomer, in a nearly 1:1 ratio (eq 5).[8] The absolute configuration of **2b** was assigned as (1*R*, 2*S*, 3*S*) by its conversions to the known compounds,[13] whereas the absolute stereochemistry of **3b** was determined as (1*R*, 2*R*, 5*S*, 6*R*) by X-ray crystallography of its derivative.[14]



These stereochemical outcomes reveal that both **2b** and **3b** arise exclusively from the initial *(S)*-selective lithiation, while their siloxy-configurations (C3 for **2b** and C2 for **3b**) are opposite to each other. Therefore, it appears unlikely that any kinetic resolution occurs during the initial 5-exo-cyclization,[15] but, significantly enough, an efficient kinetic resolution *does* occur at the subsequent cyclopropane-forming cyclization stage. In other words, the benzylic lithium (3*R*)-**6b** generated via the cyclization of (*R*)-**1b** spontaneously undergoes the second cyclization leading to **3b**, whereas the benzylic lithium (*3S*)-**6b** derived from (*S*)-**1b** does only 4%, thus permitting the isolation of **2b**.[16]

Finally, we attempted to intercept the benzylic lithium species **6b** with an external electrophile. Thus, *rac*-**1b** was treated successively with (-)-sparteine / *s*-BuLi (1.5 / 3.0 equiv.)[17] and benzaldehyde (1.0 equiv.) to afford the expected adduct **7**[8] (with five contiguous chirality centers) as a major product (eq 6).[18] Of special interest is the finding that the adduct is stereochemically homogeneous as judged from ^{1}H and ^{13}C NMR spectra,[8] although the exact stereochemistry has not been determined yet.



In summary, we have demonstrated that the carbanion cyclization of (*E*)-6-phenyl-5-hexenyl carbamates, when induced with an *s*-BuLi / (-)-sparteine system, proceeds with extremely high enantioselectivity to afford the cyclopentanol derivatives, together with the rather unexpected bicyclohexane derivatives arising from the subsequent cyclopropane-forming cyclization. Work on improvement and expansion of the substrate scope of the present enantioselective cyclization methodology is in progress.

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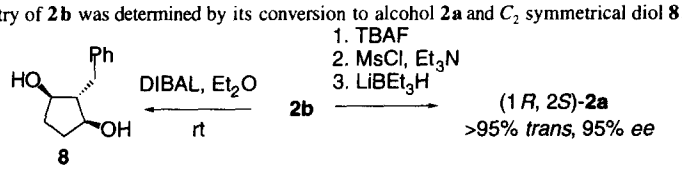
References and Notes

1. Review on carbanion cyclization: Bailey, W. F.; Ovaska, T. V. In *Advances in Detailed Reaction Mechanisms*, Vol. 3, 1994, 251-273.
2. a) Coldham, I.; Hufton, R.; Snowden, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 5322-5323. b) Tomooka, K.; Komine, N.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 8939-8942.
3. Reviews: (a) Hoppe, D.; Hense, T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282-2316. (b) Beak, P.; Basu, A.; Gallageher , D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552-560.
4. This work was presented at the Annual Meeting of the Chemical Society of Japan, March, 1997, Tokyo, Abstract 3G101.
5. Quite recently, Hoppe *et al.* have already reported a similar enantioselective carbanion cyclization of a (*Z*)-5-alkenyl carbamate (with different *N*-substituents) using *s*-BuLi / (-)-sparteine: Woltering, M. J.; Frölich, R.; Hoppe, D. *Angew. Chem.* **1997**, *109*, 1804-1805; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1764-1766.
6. Initially, we attempted the carbanion cyclization of the 5-hexenol carbamate, however, no cyclization product was obtained.
7. Note that the combined use of 1.5 equiv. of *s*-BuLi and 1.5 equiv. of (-)-sparteine gave **2a** in 13% yield.
8. All the compounds were characterized by ^{1}H ($CDCl_3$, 300 MHz), ^{13}C NMR ($CDCl_3$, 300 MHz), MS and IR. Data for selected products are as follows. **2a**: ^{1}H NMR δ 7.32-7.12(m, 5H), 4.87(ddd, *J*=6.3, 5.1, 3.9 Hz, 1H), 4.07(brs, 1H), 3.69(brs, 1H), 2.92 (dd, *J*=13.2, 4.8 Hz, 1H), 2.44(dd, *J*=13.2, 9.9 Hz, 1H), 2.27(m, 1H), 2.04(m, 1H), 1.85-1.57(m, 3H), 1.45-1.08(m, 2H), 1.19(d, *J*=6.9 Hz, 12H). ^{13}C NMR δ 155.9, 141.19, 129.0, 128.3, 125.9, 81.1, 47.3, 45.6, 39.5 31.9, 29.5, 22.3, 21.3. MS m/z: 303 (M+), $[\alpha]_D^{30}$ -26.5 (c 1.48, $CHCl_3$) **3a**: ^{1}H NMR δ 7.32-7.12(m, 5H), 1.95-1.54(m, 8H), 1.28(m, 2H). ^{13}C NMR δ 142.4, 128..3, 125.7, 125.7, 125.5, 29.6, 28.0, 28.0, 23.7. MS m/z: 158 (M+). **2b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.11 (m, 5H), 4.84 (m, 1H), 3.81 (m, 1H), 2.72 (d, *J*= 6.9 Hz, 2H), 2.24 (m, 1H), 1.96 (m, 1H), 1.91-1.60 (m, 3H), 1.13 (d, *J*=6.9 Hz, 6H), 1.08 (brs, 6H), 0.85 (s, 9H), -0.05 (s, 3H), -0.09 (s, 3H). ^{13}C

NMR δ 155.5, 140.4, 129.2, 128.3, 125.9, 78.6, 76.3, 55.3, 46.0, 37.8, 33.0, 29.9, 25.9, 21.4, 18.0, -4.41, -4.87. $[\alpha]_D^{25}$ -10.2 (c 0.77, $CHCl_3$) **3b**: ^{1}H NMR δ 7.35-6.90 (m, 5H), 4.63 (td, *J*=7.7, 4.7 Hz, 1H), 2.12 (t, *J*=3.2 Hz, 1H), 1.98-1.73 (m, 2H), 1.98-1.73 (m, 2H), 1.66 (m, 1H), 1.53 (m, 1H), 1.38-1.20 (m, 1H), 0.96-0.80 (m, 1H), 0.88 (s, 9H), 0.05 (s, 6H), 0.03 (s, 3H). ^{13}C NMR δ 143.2, 128.2, 125.9, 125.2, 75.4, 34.8, 30.2, 28.3, 26.1, 25.9, 21.8, 18.3, -4.4, -4.6. MS m/z: 288 (M+) $[\alpha]_D^{27}$ 40.0 (c 1.27, $CHCl_3$) **7**: ^{1}H NMR δ 7.94-7.08 (m, 10H), 5.39 (dd, *J*= 6.0, 3.3 Hz, 1H), 5.13 (m, 1H), 4.11 (m, 2H), 3.45 (d, *J*=3.3 Hz, 1H), 3.11 (dd, *J*=7.2, 6.0 Hz, 1H), 1.25 (d, *J*=7.2 Hz, 12H), 1.03 (s, 9H) 0.25 (s, 3H), 0.21 (s, 3H). ^{13}C NMR δ 154.9, 142.4, 138.6, 130.1, 127.9, 127.8, 126.9, 126.6, 77.7, 76.7, 74.7, 55.8, 55.6, 46.0, 33.2, 30.3, 25.9, 20.7, 18.0, 3.7, 4.6. $[\alpha]_D^{26}$ -53.8 (*c* 1.11, $CHCl_3$)

9. The stereochemistry of **3a** was assigned as (1,5-*cis*, 1,6-*trans*) by ^{1}H NMR analysis: *cf.* Lit. Casey, P.; Polichnowski, W.; Shusterman, J.; Jones, R. *J. Am. Chem. Soc.* **1979**, *101*, 7282-92.
10. Recently we have found that treatment of alkyl *N,N*-diisopropyl carbamates with DIBAL in ether affords the corresponding alcohol in high yields: Unpublished results (Shimizu, H. MS Thesis, Tokyo Institute of Technology, 1997).
11. Seemayer, R.; Schneider, M. P. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 171-174.
12. For similar cyclopropane formations in organolithium reactions, see: Paetow, M.; Kotthaus, M.; Grehl, M.; Frölich, R.; Hoppe, D. *Synlett* **1994**, 1034-1036. Krief, A.; Hobe. M.; Dumont, W.; Badaoui, E.; Guittet, E.; Evard, G. *Tetrahedron Lett.* **1992**, *33*, 3381-3384. Krief, A.; Hobe. M. *Tetrahedron Lett.* **1992**, *33*, 6527-6530, 6529-6532.
13. The stereochemistry of **2b** was determined by its conversion to alcohol **2a** and C_2 symmetrical diol **8**, as depicted below.



14. The stereochemistry of **3b** was determined by X-ray crystallography of its phthalate **9**. Lit. for the chiral phthalate preparation, see: Harada, N.; Nehira, T.; Soutome, T.; Hiyoshi, N.; Kido, F. *Enantiomer*, **1996**, *1*, 35. Crystal data for **9** ($C_{30}H_{33}NO_5S$): orthorhombic, $P2_12_12_1$ (#19), a=11.903(2) Å, b=19.630(10) Å, c=11.685(2) Å, V= 2730.4 Å^3, Z=4. A total of 3906 reflections (*h,k,±l*) were collected in the range $2\theta_{max}$ 60.1° being used in the structural refinement by full-matrix least-squares techniques (334 variables) using the TEXSAN crystallographic package from Molecular Structures Corporation Final *R*=0.053, R_w=0.052 (Fig.1).

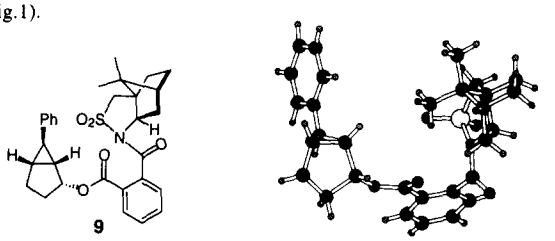
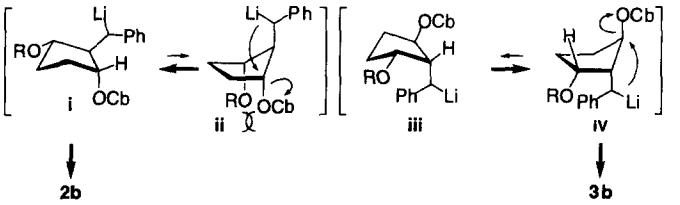


Fig. 1 ORTEP representation of **9**

15. Quite recently, Hoppe's group has reported that an appreciable level of kinetic resolution is not observed in the *s*-BuLi / (-)-sparteine-induced cyclization of a 4-substituted 5-hexynyl carbamate: Oestreich, M.; Fröhlich, R.; Hoppe, D. *Tetrahedron Lett.* **1998**, *39*, 1745-1748.
16. The exact origin of the observed kinetic resolution is not clear at present. A possible explanation is that conformer **i** sterically preferred for the benzylic lithium (3*S*)-**6b** is not capable of the S_N2-type cyclization, whereas conformer **i v** preferred for (3*R*)-**6b** is well suited for the cyclopropane formation.



17. It is worth noting that, the yield and stereopurity of **7** were highly dependent on the amounts of (-)-sparteine and *s*-BuLi.
18. Similar 5-exo cyclization / substitution reaction was reported by Hoppe's group: see ref. 5.