Pergamon

Tetrahedron Letters, Vol. 38, No. 52, pp. 8939-8942, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10327-6

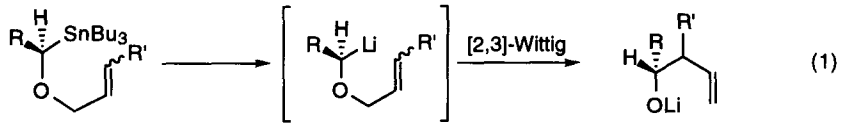
Cyclization of Enantio-enriched α-(Homoallyloxy)alkyllithiums: Evidence for Retention of Configuration at the Carbanion Center

Katsuhiko Tomooka, Nobuyuki Komine and Takeshi Nakai*

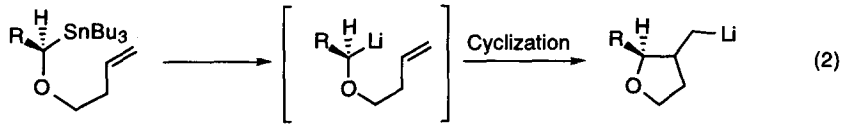
Department of Chemical Technology, Tokyo Institute of Technology, Meguro-ku, Tokyo 152, Japan

Abstract: *The titled cyclization induced by Sn-Li transmetallation of the enantio-defined stannanes is shown to proceed with complete retention of configuration at the Li-bearing sp^3-carbon to afford the enantio-enriched α,β-disubstituted tetrahydrofurans.* © 1997 Elsevier Science Ltd.

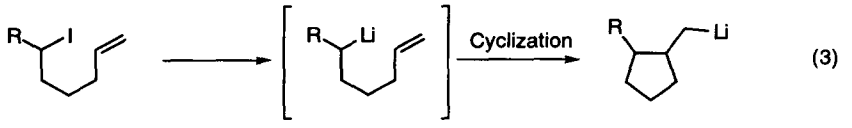
Enantiomerically defined α-(alkoxy)alkyllithiums constitute a unique and useful class of the organolithium species, since they can be generated stereospecifically (retention of configuration) from easily obtainable enantio-enriched stannanes and they are configurationally stable below -30 ℃.[1] Thus, these characteristics have been exploited as a key clue to elucidate the steric course of several organolithium reactions.[2] For instance, we have revealed that the [2,3]-Wittig rearrangement of α-(allyloxy)alkyllithium **2** generated from stannane **1** proceeds with complete inversion of configuration at the Li-bearing terminus (eq 1).[3] Taking advantage of this clue, we investigated the steric course of the cyclization of α-(homoallyloxy)alkyllithium **5** (eq 2), an oxa analogue of the well-established cyclization of the 5-hexen-1-yllithium system (eq 3).[4,5] While the steric course of the 5-hexenyllithium cyclization remains unproved, the *ab initio* calculation study[6] has suggested that the lithium might effectively interact with the olefinic π bond, thereby directing the reaction to the retentive course at the Li-bearing carbon. Disclosed herein is the experimental evidence that the titled carbanion cyclization proceeds with complete retention of configuration at the Li-bearing sp^3-carbon.[7]



1 **2** **3** (1)



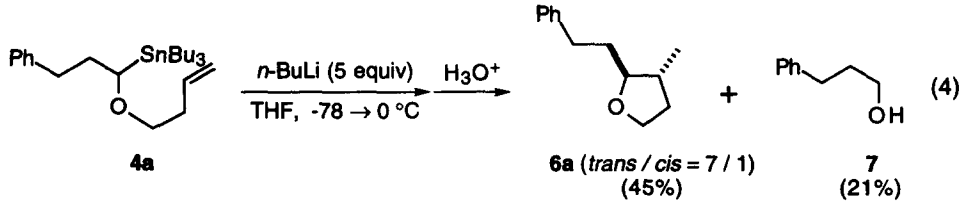
4 **5** **6** (2)

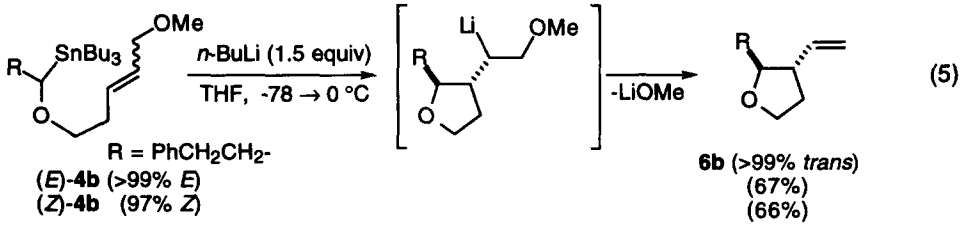


(3)

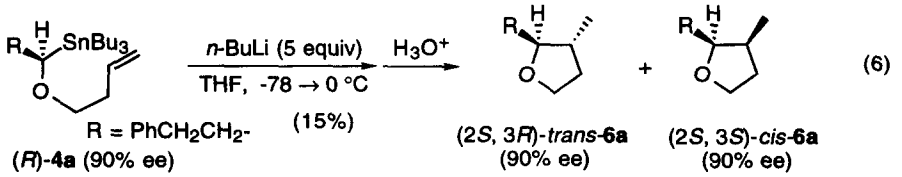
At the outset, we examined the carbanion cyclization using the *racemic* stannanes as the organolithium precursors.[8] Treatment of **4a**[9] with 1.5 equiv of *n*-BuLi in THF (-78 ℃ → rt) followed by hydrolysis gave

no cyclization product, instead producing the protiodestannylation product (*ca.* 20%). After several attempts, the use of a large excess (5.0 equiv) of *n*-BuLi (-78 → 0 °C) was found to give the cyclization product **6a** in 45% yield as a diastereomeric mixture (*trans/cis*=7:1) along with 21% of **7** (α,β'-eliminaion product) (eq 4).[10] More interestingly, treatment of the ω-methoxymethyl-substituted stannane **4b** with 1.5 equiv of *n*-BuLi gave rise to the cyclization/β-elimination product **6b** in a higher yield together with enhanced diastereoselectivity (eq 5).[9,11] These results suggest that the cyclization step would be reversible in nature and might be effectively driven by the subsequent β-elimination of lithium methanolate.

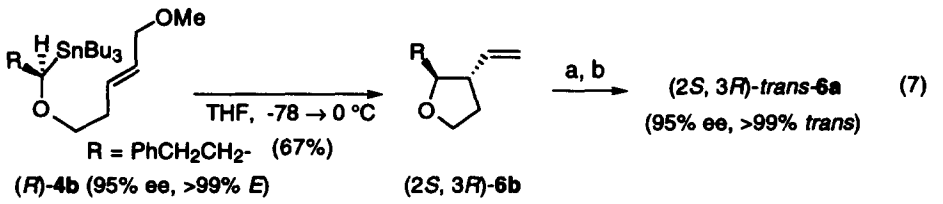




With these results in hand, our attention was focused on the steric course of the present cyclization using *enantio-enriched* substrates. The enantio-defined stannane (*R*)-**4a** was prepared from the (*S*)-stannyl alcohol (90% ee)[12] *via* mesylation and sequential S_N2 reaction with potassium homoallyl alcoholate following our previously reported procedure.[3a] Treatment of (*R*)-**4a** with *n*-BuLi (5 equiv) in THF at -78 °C followed by hydrolysis was found to afford a 7:1 mixture of the two retention products, (2*S*,3*R*)-*trans*-**6a** and (2*S*,3*S*)-*cis*-**6a** (eq 6). The absolute configurations were assigned based on chiral HPLC comparisons with authentic samples.[13] Their enantiomeric purities were determined to be both 90% ee by chiral HPLC analysis. This stereochemical outcome provides conclusive proof that the present cyclization proceeds with complete retention of configuration at the Li-bearing carbanion center, since the Sn → Li transmetalation proceeds with complete retention of configuration.



Furthermore, the retention stereochemistry was confirmed by the cyclization of stannane (*R*)-**4b** (eq 7). Thus, treatment of (*R*)-**4b** (95% ee) with 1.5 equiv of *n*-BuLi was found to afford the retention product (2*S*, 3*R*)-*trans*-**6b** as a single diastereomer with 95% ee in a much higher yield. The absolute configuration and enantiomeric purity of **6b** were determined after its conversion to (2*S*, 3*R*)-**6a**.



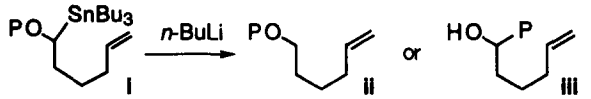
(a) (i) O_3, MeOH; (ii) $NaBH_4$ (77%); (b) (i) Ts_2O, Et_3N; (ii) $LiBEt_3H$, THF (88%).

In summary, we have demonstrated that the carbanion cyclization of α-(homoallyloxy)alkyllithium proceeds with complete retention of configuration at the Li-bearing carbanion center. This means that the lithium might coordinate with the olefinic bond in the transition state and hence the cyclization proceeds in a carbolithiative fashion, as predicted by the theoretical calculation.[6] Thus, the 5-hexenyllithium cyclization (eq 3) is likely to proceed with retention of configuration at the Li-bearing carbon as well. Of particular interest from a mechanistic point of view is that the retention stereochemistry of the present cyclization is opposite to the inversion stereochemistry of the structurally related [2,3]-Wittig rearrangement (eq 1) and the [1,2]-Wittig rearrangement.[3] Further work is underway to elucidate which factors govern the steric course of organolithium reactions in general.

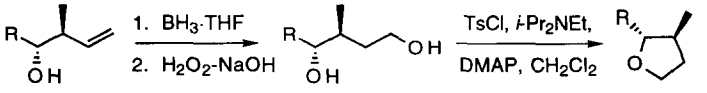
Acknowledgment: This research was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

References and Notes

1. Still, W.C.; Sreekumear, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201-1202. Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. L. *J. Am. Chem. Soc.* **1988**, *110*, 842-853.
2. Review: Tomooka, K.; Igarashi, T.; Komine, N.; Nakai, T. *J. Synth. Org. Chem., Jpn.* **1995**, *53*, 480-486.
3. a) Tomooka, K.; Igarashi, T.; Watanabe, M.; Nakai, T. *Tetrahedron Lett.* **1992**, *33*, 5795-5799; b) Tomooka, K.; Komine, N.; Nakai, T. *Synlett* **1997**, in press; c) [1,2]-Wittig rearrangement: Tomooka, K.; Igarashi, T.; Nakai, T. *Tetrahedron* **1994**, *50*, 5927-5932.
4. a) Bailey, W. F.; Patricia, J. J.; DelGobbo, V. C.; Jarret, R. M.; Okarma, P. J. *J. Org. Chem.* **1985**, *50*, 1999-2000. b) Reviews on carbanion cyclization: Bailey, W.F.; Ovaska, T. V. In *Advances in Detailed Reaction Mechanisms*, Vol. 3, 1994, 251-273. Knochel, P. In *Comprehensive Organic Synthesis*, Vol. 4; Trost, B. M.; Fleming, I., Ed.; Pergamon: New York, 1991; p 871-872.
5. For similar cyclizations of α-(homoallyloxy)alkyllithiums (racemic) generated from α-(phenylthio)ether via the reductive lithiation method: Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981-2984.
6. Bailey, W.F.; Khanolkar, A. D.; Gavaskar, K.; Ovaska, T. V.; Rossi, K.; Thiel, Y.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 5720-5727.
7. A part of this work was presented at the Annual Meeting of the Chemical Society of Japan, March, 1994, Abstr. 1K114. More recently, Coldham *et al.* have reported that the cyclization of an aza analog proceeds with retention of configuration at the carbanion center: Coldham, I.; Hufton, R.; Snowden, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 5322-5323.
8. Initially, we examined the carbanion cyclization of 1-alkoxy-5-hexenylstannanes **i** with *n*-BuLi. However, these attempts totally failed, instead yielding either the destannylated product **ii** (42% for P=$PhCH_2CH_2$ and 35% for P=MOM) or the [1,2]-Wittig product **iii** (79%, P=$PhCH_2$).



9. All the compounds were characterized by ^{1}H, ^{13}C NMR. Data for selected products are as follows. **4a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.14(m, 5H), 5.87(ddt, *J*=17.1, 10.3, 6.8 Hz, 1H), 5.10(dd, *J*=17.1, 2.0 Hz, 1H), 5.05 (dd, *J*=10.3, 2.0 Hz, 1H), 3.83(dd, *J*=8.7, 4.7 Hz, 1H), 3.41(t, *J*=6.6 Hz, 2H), 2.71(m, 2H), 2.35(dd, *J*=6.8, 6.6 Hz, 2H), 2.28-1.90(m, 2H), 1.60-1.14(m, 12H), 0.92-0.85(m, 15H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.56, 135.71, 128.56, 128.35, 125.69, 116.16, 76.46, 70.42, 36.95, 34.57, 34.10, 29.15, 27.40, 13.56, 9.16. *trans*-**6a**: ^{1}H NMR δ 7.35-7.13(m, 5H), 3.86(dd, *J*=7.5, 6.9 Hz, 1H), 3.84(dd, *J*=8.1, 5.2 Hz, 1H), 3.34(td, *J*=8.1, 3.6 Hz, 1H), 2.85(ddd, *J*=13.7, 10.8, 5.2 Hz, 1H), 2.66(ddd, *J*=13.7, 10.4, 6.3 Hz, 1H), 2.10(m, 1H), 1.96-1.66 (m, 3H), 1.54(m, 1H), 1.03(d, *J*=6.6 Hz, 3H). ^{13}C NMR δ 142.40, 128.36, 128.27, 125.65, 85.22, 66.73, 39.04, 36.23, 34.71, 32.83, 17.22. $[\alpha]_D^{25}$ -51.74 (c 0.88, $CDCl_3$; (2*S*, 3*R*)-isomer, 95% ee). *cis*-**6a**: ^{1}H NMR δ 7.35-7.13(m, 5H), 3.94(td, *J*=8.2, 6.3 Hz, 1H), 3.76(dd, *J*=11.8, 10.5 Hz, 1H), 3.74(dd, *J*=14.3, 8.5 Hz, 1H), 2.81(ddd, *J*=13.8, 10.2, 5.6 Hz, 1H), 2.63(ddd, *J*=13.8, 9.9, 6.4 Hz, 1H), 2.10(m, 1H), 1.96-1.66(m, 3H), 1.54(m, 1H), 0.92(d, *J*=7.0 Hz, 3H). ^{13}C NMR δ 142.52, 128.53, 128.40, 125.81, 80.93, 66.02, 35.32, 33.81, 33.00, 32.39, 14.18. (*E*)-**4b**: ^{1}H NMR δ 7. 35-7.13(m, 5H), 5.77(dt, *J*=15.5, 6.5 Hz, 1H), 5.64(dt, *J*=15.5, 6.4 Hz, 1H), 3.81(dd, *J*=8.9, 4.7 Hz, 1H), 3.46(d, *J*=6.4 Hz, 2H), 3.40(t, *J*=6.8 Hz, 2H), 3.33(s, 3H), 2.72(m, 2H), 2.35(dt, *J*=6.5, 6.4 Hz, 2H), 2.18(m, 1H), 2.00(m, 1H), 1.68-1.20(m, 12H), 0.92-0.85(m, 15H). ^{13}C NMR δ 142.50, 131.28, 128.54, 128.35, 128.02, 125.70, 76.43, 73.12, 70.39, 57.64, 36.92, 34.07, 33.09, 29.13, 27.38, 13.55, 9.12. $[\alpha]_D^{25}$ -22.19 (c 1.31, $CDCl_3$; (*R*)-isomer, 95% ee). (*Z*)-**4b**: ^{1}H NMR δ 7.36-7.14(m, 5H), 5.65(m, 2H), 4.02(d, *J*=5.2 Hz, 2H), 3.81(dd, *J*=8.8, 4.7 Hz, 1H), 3.38(t, *J*=6.6 Hz, 2H), 3.35(s, 3H), 2.72(m, 2H), 2.38(dt, *J*=6.6, 6.3 Hz, 2H), 2.18(m, 1H), 2.00(m, 1H), 1.68-1.20(m, 12H), 0.92-0.85(m, 15H). ^{13}C NMR δ 142.19, 129.71, 128.03, 128.12, 127.54, 125.491, 76.40, 70.27, 68.12, 57.88, 37.06, 34.20, 29.29, 28.74, 27.56, 13.78, 9.38. *trans*-**6b**: ^{1}H NMR δ 7.34-7.13(m, 5H), 5.70(ddd, *J*=17.1, 10.1, 8.4 Hz, 1H), 5.08(ddd, *J*=17.1, 1.7, 0.9 Hz, 1H), 5.02(ddd, *J*=10.1, 1.7, 0.7 Hz, 1H), 3.90(dd, *J*=7.9, 6.8 Hz, 1H), 3.89(dd, *J*=8.3, 4.9 Hz, 1H), 3.50(dt, *J*=8.4, 3.6 Hz, 1H), 2.84(ddd, *J*=13.7, 10.7, 5.2 Hz, 1H), 2.66(ddd, *J*=13.7, 10.2, 6.2 Hz, 1H), 2.41(m, 1H), 2.13(m, 1H), 1.98-1.68(m, 3H). ^{13}C NMR δ 142.39, 138.88, 128.49, 128.39, 125.79, 115.91, 82.92, 67.05, 49.81, 35.70, 33.19, 32.69. $[\alpha]_D^{25}$ -26.3 (c 0.99, $CDCl_3$; (2*S*, 3*R*)-isomer, 95% ee).
10. The reason why such a large excess of *n*-BuLi is required is not clear at present. However, it might be considered that the excess *n*-BuLi coordinates with the ether oxygen, thereby making it possible for the counter lithium which initially coordinates with the adjacent oxygen to interact with the olefinic bond.
11. Broka *et al* have also reported the anionic cyclization of α-(homoallyloxy)alkyllithiums which involves the concomitant expulsion of an alkoxide provide a high steroselectivity and an improved chemical yield; Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.* **1988**, *53*, 1336-1338, and ref 5 .
12. The enantio-enriched (*S*)-stannyl alcohol was prepared by the literature method: Tomooka, K.; Igarashi, T.; Nakai, T. *Tetrahedron Lett.* **1994**, *35*, 1913-1916.
13. The authentic stereoisomers of **6a** were prepared from (3*S*,4*R*) or (3*R*,4*R*)-alcohol **iv** prepared by the literature method: Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339-6359.



(3*S*, 4*R*)-**iv** >99% *threo*, 90% ee R = $PhCH_2CH_2$- (2*R*, 3*S*)-*trans*-**6a** >99% *trans*, 90% ee

Chiral HPLC analysis [Chiralcel OD; eluent, hexane-*i*-PrOH (400 : 1); flow rate 0.8 mL / min] : t_R=9.2 min for (2*S*, 3*S*) -**iv**, t_R=13.9 min for (2*R*, 3*S*) -**iv**, t_R=18.1 min for (2*S*, 2*R*) -**iv**, t_R=22.3 min for (2*R*, 2*R*)-**iv**.

(*Received in Japan* 10 *September* 1997; *accepted* 3 *October* 1997)