

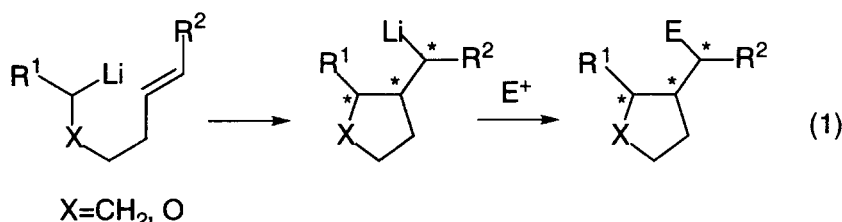
MODIFIED CYCLIZATION OF ENANTIO-ENRICHED α -HOMOALLYLOXY-
ALKYLLITHIUMS GENERATED BY Sn-Li TRANSMETALLATION:
EFFECTS OF ADDITIVES AND STRUCTURAL REQUIREMENT[#]

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Abstract– The titled cyclization, when performed in the presence of lithium chloride, afforded an improved yield of the enantio-enriched 2,3-*trans*-disubstituted tetrahydrofuran derivative in high diastereoselectivity, whereas a similar cyclization in the presence of zinc bromide gave the 2,3-*cis* isomer as the major product in lower enantiopurity.

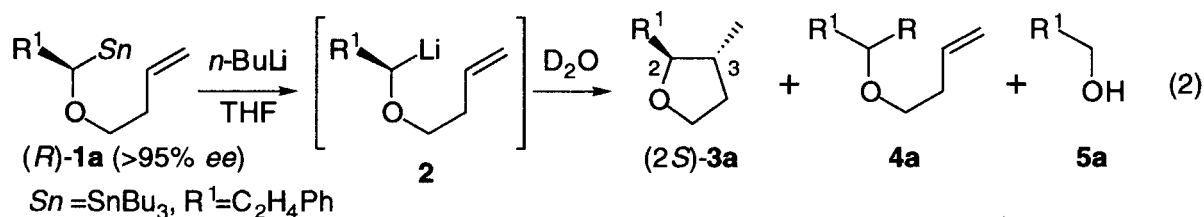
An intramolecular carbolithiation of organolithiums onto an olefinic or acetylenic bond, *i.e.*, “*carbanion cyclization*” has emerged as the useful methodology for the construction of cyclic molecules.¹ In pioneering work, Bailey and co-workers have reported the carbanion cyclization of 5-hexenyllithiums ($X=CH_2$, $R^1=H$), generated by iodine-lithium exchange, which affords the cyclopentane derivatives in highly diastereo- and regioselective fashion (eq 1).²



More recently, enantioselective carbanion cyclization of 5-hexenyl carbamates ($X=CH_2$, $R^1=R'_2NCOO$, $R^2=Ph$) has been developed which rely on asymmetric lithiation using (–)-sparteine as an external chiral ligand.³ As far as the tetrahydrofuran ($X=O$)-forming cyclization is concerned, Broka and co-workers have developed two procedures in which the organolithium is generated *via* Sn $\rightarrow$ Li transmetalation for $R^1=H$ and desulfurative lithiation ($R^1=n$ -nonyl).⁴ Recently, we have proved that the Sn $\rightarrow$ Li transmetalative cyclization proceeds complete retention of configuration at the Li-bearing carbanion center by using an enantiomerically-defined substrate.⁵ However, the synthetic utility of this type of transmetalative cyclization has been hampered by the low yield; even the use of a large excess of butyllithium leads to only moderate yields. To solve this problem, we made several attempts to improve the transmetalative cyclization protocol. Disclosed herein are the interesting modifications which provide a higher yield of the cyclization product.

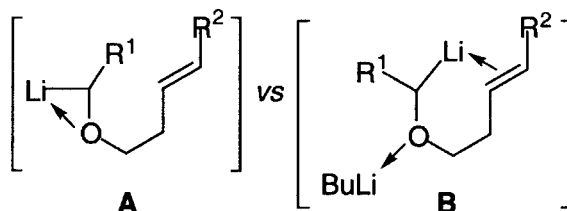
[#]Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.

First, we examined the effect of metal salts in the carbanion cyclization using the enantiomerically-defined stannane ((*R*)-**1a**) (>95% *ee*)⁶ as the organolithium precursor (eq 2). As has been reported,⁵ treatment of (*R*)-**1a** with 1.5 equiv. of *n*-BuLi in THF followed by hydrolysis with D₂O gave a trace amount (<5%) of the cyclization product (**3a**), instead producing the destannylation/deuteration product (**4a**) (R=D) in 25-30% yield, while the use of 5.0 equiv. of *n*-BuLi afforded the cyclization product ((2*S*)-**3a**) (>95% *ee*)⁷ in 45% yield as a diastereomeric mixture (*trans/cis* = 91:9), along with 21% of the α,β' -elimination product (**5a**).

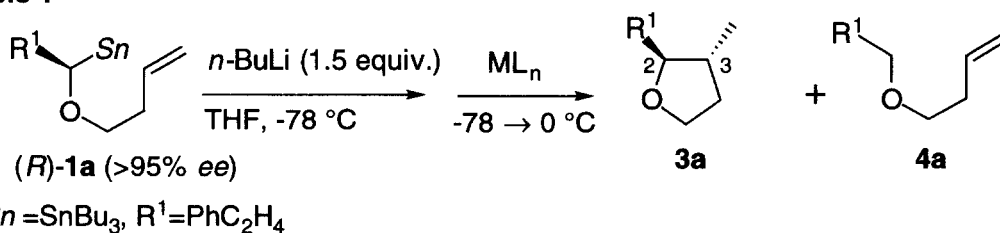


<i>n</i> -BuLi (1.5 equiv.)	-78 °C	trace	30% (R=D)	trace
(1.5 equiv.)	-78 → 0 °C	trace	25% (R=H)	trace
(5.0 equiv.)	-78 → 0 °C	45% (91% <i>dt</i>)	trace	21%

We suspected that, given the reasonable postulate that the initially generated Li-species takes the intramolecularly chelated structure (**A**), the interaction between the lithium and the olefinic π -bond required for the carbolithiation is very weak and becomes strong enough only after another butyllithium coordinates with the ether-oxygen as depicted structure (**B**).



Based on this hypothesis, we carried out the cyclization of (*R*)-**1a** with 1.5 equiv. of *n*-BuLi in the presence of lithium salts which might coordinate with the ether-oxygen. The results thus obtained are summarized in Table 1 (entries 1 and 2). Significantly enough, the addition of LiCl (3 equiv.) in particular was found to remarkably enhance the cyclization yield to give *trans*-**3a** as the major product with the same levels of enantiospecificity and diastereoselectivity as previously observed in the absence of any additive. Next, our interest was turned to the effect of other metal salts which might generate different organometallic species *via* further transmetalation of the initially formed Li-species. As shown in Table 1, magnesium bromide and cerium chloride were totally ineffective; no cyclization product was obtained (entries 3 and 4). Interestingly, however, the addition of zinc bromide was found to afford a significantly increased yield to give the opposite diastereomer (*cis*-**3a**) as the major product, but with almost complete loss of enantiospecificity (entry 5). In this case, the cyclization is likely to occur not by a zinc salt-assisted carbolithiation but by carbозincation of the organozinc species formed *via* Li→Zn transmetalation, since organozincs are known to undergo carbometalation with greater facility than organolithiums in general.^{8,9} While the exact origin of the loss of enantiospecificity is not clear at present, it might be taken into account that the Li→Zn transmetalation concerned would proceed with low stereospecificity and/or the organozinc species formed might be configurationally labile. Obviously, more detailed mechanistic studies are awaited.

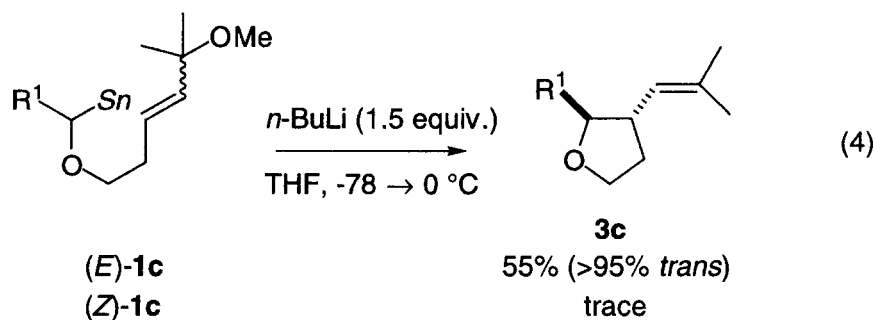
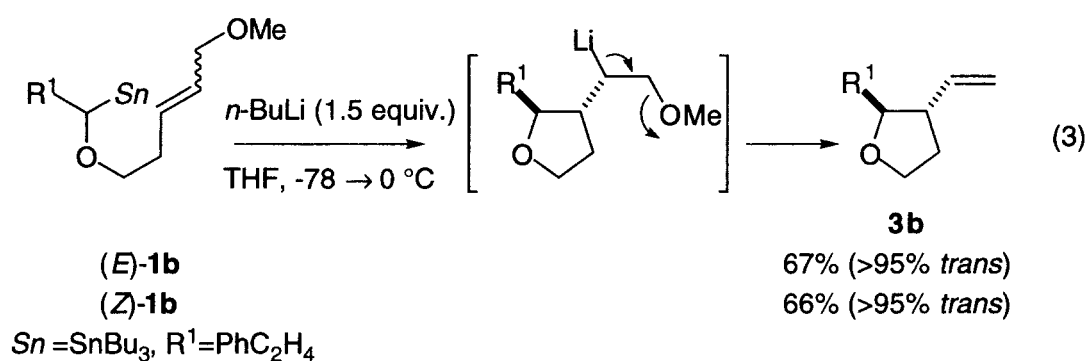
Table 1

entry	ML_n	(equiv.)	Yield of 3a (%) ^a	<i>trans</i> / <i>cis</i> ^b	<i>trans</i> - 3a ^{c,d}	<i>cis</i> - 3a ^{c,e}	Yield (%) of 4a ^a
1	LiBr	(3.0)	49	87/13	>95% <i>ee</i>	>95% <i>ee</i>	38
2	LiCl	(3.0)	63	86/14	>95% <i>ee</i>	>95% <i>ee</i>	12
3	MgBr ₂	(3.0)	trace	—	—	—	56
4	CeCl ₃	(3.0)	trace	—	—	—	48
5	ZnBr ₂	(2.0)	63	15/85	66% <i>ee</i>	2% <i>ee</i>	12
6	ZnCl ₂	(2.0)	42	27/73	59% <i>ee</i>	2% <i>ee</i>	7

^a Isolated yield. ^b Determined by GC analysis. ^c Determined by chiral HPLC analysis.

^d (2*S*, 3*R*) isomer. ^e (2*S*, 3*S*) isomer.

Finally, another approach to improve the carbanion cyclization was investigated in which the substrate structure is modified to combine the carbanion cyclization with an irreversible β -elimination process such as extrusion of a lithium alkoxide. While the efficiency of this approach has been shown by Broka⁴ and us,⁵ more examples are now disclosed. Thus, treatment of either (*E*)- or (*Z*)-*rac*-**1b** with 1.5 equiv. of *n*-BuLi was found to give the cyclization/ β -elimination product (*trans*-**3b**) in a high yield with enhanced diastereoselectivity (eq 3). Interestingly, a similar reaction of (*E*)-*rac*-**1c** gave the cyclization product (*trans*-**3c**) in moderate yield, whereas the reaction of (*Z*)-**1c** gave no cyclization product, instead producing the protiodestannylated product in 20% yield (eq 4).¹⁰



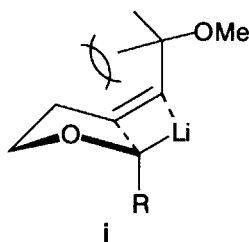
In summary, we have described three different modifications of the carbanion cyclization of α -homoallyloxy-alkyllithiums which afford a synthetically useful level of cyclization yield; (a) lithium chloride-addition approach, (b) carbozincation approach *via* Li $\rightarrow$ Zn transmetalation, and (c) β -elimination-driven approach. Moreover, both approaches (a) and (c) provide a high level of *trans*-diastereoselectivity and enantiospecificity, whereas approach (b) shows a high *cis*-diastereoselectivity with almost complete loss of enantiospecificity. Application of the newly-developed cyclization modifications to natural product synthesis is in progress.

ACKNOWLEDGMENT

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REFERENCES AND NOTES

1. Reviews on carbanion cyclization: a) W. F. Bailey and T. V. Ovaska, In *Advances in Detailed Reaction Mechanisms*, Vol. 3, 1994, pp. 251-273. b) P. Knochel, In *Comprehensive Organic Synthesis*, Vol. 4, ed. by B. M. Trost and I. Fleming, Pergamon, New York, 1991, pp. 871-872.
2. a) W. F. Bailey, J. J. Patricia, V. C. DelGobbo, R. M. Jarret, and P. J. Okarma, *J. Org. Chem.*, **1985**, *50*, 1999. b) W. F. Bailey, A. D. Khanolkar, K. Gavaskar, T. V. Ovaska, K. Rossi, Y. Thiel, and K. B. Wiberg, *J. Am. Chem. Soc.*, **1991**, *113*, 5720.
3. a) K. Tomooka, N. Komine, T. Sasaki, H. Shimizu, and T. Nakai, *Tetrahedron Lett.*, **1998**, *39*, 9715. b) M. J. Woltering, R. Fröhlich, and D. Hoppe, *Angew. Chem.*, **1997**, *109*, 1804-1805; *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 1764.
4. a) C. A. Broka, W. J. Lee, and T. Shen, *J. Org. Chem.*, **1988**, *53*, 1336. b) C. A. Broka and T. Shen, *J. Am. Chem. Soc.*, **1989**, *111*, 2981.
5. K. Tomooka, N. Komine, and T. Nakai, *Tetrahedron Lett.*, **1997**, *38*, 8939.
6. The enantio-defined stannane ((*R*)-**1a**) was prepared from the (*S*)-stannyl alcohol (>95% ee) *via* mesylation and sequential S_N2 reaction with potassium homoallyl alkoxide following our previously reported procedure: K. Tomooka, T. Igarashi, M. Watanabe, and T. Nakai, *Tetrahedron Lett.*, **1992**, *33*, 5795, and ref. 5.
7. The stereochemistry of **3a** was determined in comparison with authentic samples of (2*S*, 3*R*)- and (2*S*, 3*S*)-isomers: see ref. 5.
8. C. Meyer, I. Marek, G. Courtemanche, and J. F. Normant, *Tetrahedron*, **1994**, *50*, 11665.
9. The 2,3-*cis*-preference cyclization of 5-hexenylzinc has been reported: see ref. 8.
10. The low cyclization ability of (*Z*)-**1c** is explainable by the $A^{(1,3)}$ repulsion in the transition state (**i**).



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