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INTRAMOLECULAR CYCLIZATIONS OF ORGANOMETALLIC COMPOUNDS
IV. HETEROATOM INFLUENCE ON CYCLIZATIONS OF ORGANOLITHIUM COMPOUNDS[1]

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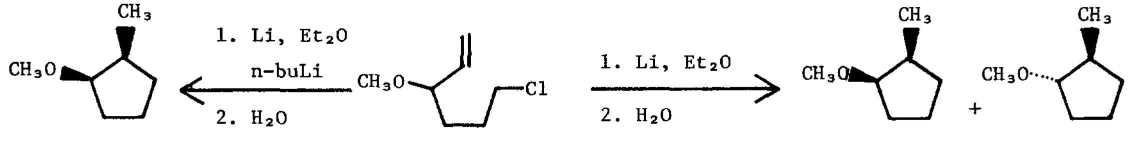
SUMMARY: Alkoxyl groups in alkenyllithiums can influence the stereochemistry of cyclization. The presence of n-butyllithium increases the stereoselectivity such that only one stereochemistry results; the presence of TMEDA negates the heteroatom's influence so that only the other stereochemistry results. Yields are 33% to 44%.

Intramolecular cyclizations of organolithium compounds containing olefinic units have been the subject of work reported by Wilson[3] and by others[4]. Reports of influence on intermolecular additions of alkenyllithiums to double bonds having proximal oxygen functions[5] encouraged us to investigate the cyclization of alkoxyl-containing alkenyllithiums, the intramolecular analogy. We felt our work could provide excellent complement to the intermolecular studies and increase the synthetic utility of the cyclization technique by providing for additional functionality in the cyclic product.

Alkoxyl influence on organolithium cyclizations is best demonstrated by comparing the reactions of alkyl- and alkoxyl-substituted systems. The cyclization[6] of the lithium reagent of 6-chloro-3-methyl-1-hexene (1) exclusively to *trans*-1,2-dimethylcyclopentane (2) provides such a basis for comparison and defines the steric course of the reaction for hexenyllithiums which have allylic substituents. Intramolecular heteroatom-metal complexation would oppose steric repulsion in allylic alkoxyl-substituted 5-hexenyllithiums. Therefore these systems provide a framework for studying alkoxyl influence on reactivity patterns and are the subject of this letter.

Compound 3, prepared by the treatment of allyl methyl ether with s-butyllithium followed by

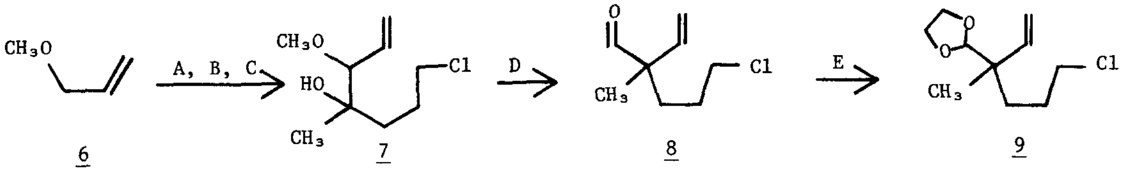


4 (40%) 3 4 (17%) 5 (17%)

SCHEME I

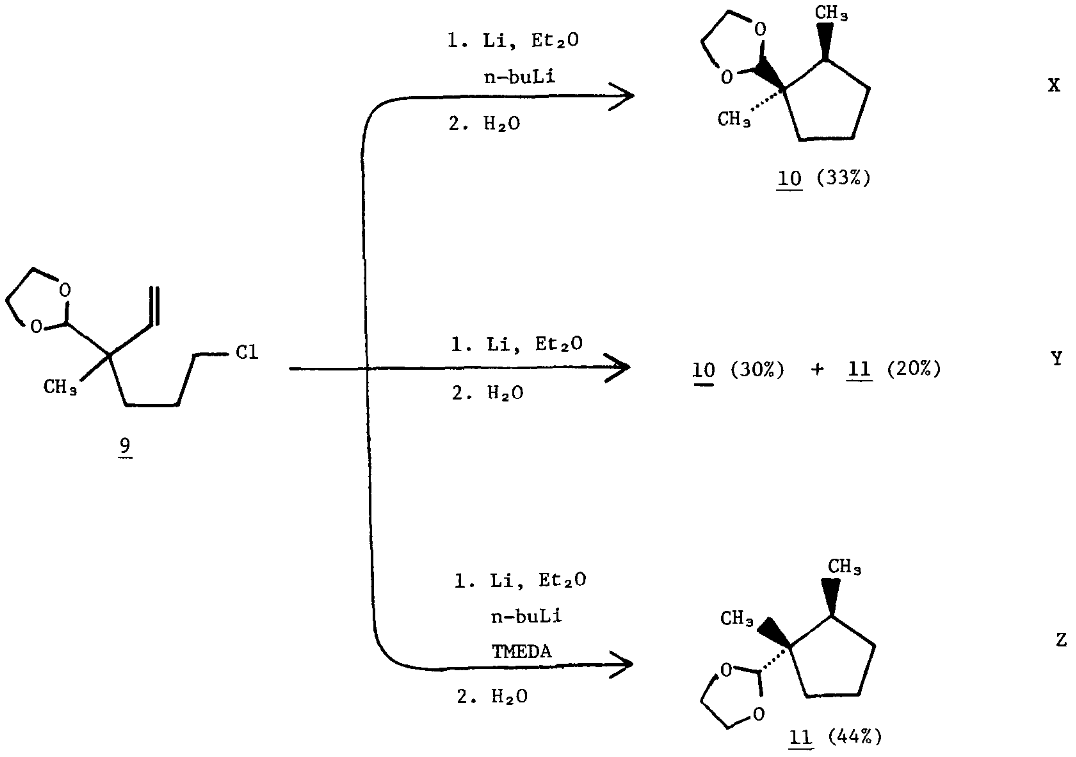
1-bromo-3-chloro-propane, can be cyclized[7] in the presence of n-butyllithium[8], as depicted in Scheme I, to give cyclic material 4, which has *cis* stereochemistry. This stereochemistry is opposite to that of 2, which is obtained for the methyl analogue. In the absence of n-butyllithium, the heteroatom seems to be less influential, and a mixture of stereoisomers[9] results.

The cyclization of compound 9, prepared[10] as indicated in Scheme II, provides an example of heteroatom influence exerted by an alkoxyl group homoallylic to the double bond. Reactions X, Y, and Z in Scheme III show the cyclization chemistry. The relative stereochemistries of 10 and 11



SCHEME II: A. s-buLi B. $ZnCl_2$ C. 5-chloro-2-pentanone D. HCOOH, reflux E. HO⌒OH, H^+

SCHEME III



were not proven by independent synthesis. Rather, they are assigned on the basis of the structures proven for the products of the cyclizations of 3 under conditions analogous to those in reactions X and Y. And based on our observation that in lithium cyclizations of other alkoxyl-containing systems, n-butyllithium's presence invariably leads to an increase in heteroatom influence.[11] Reaction Z provides further support for the stereochemical assignments and offers an interesting extention of the method's synthetic utility. As we had hoped, a single cyclic product, assigned structure 11, is afforded; it can be explained as a result of TMEDA's monopolizing of the metal's coordination site, which eliminates the possibility of acetal-metal interaction and sends the reaction on the sterically-influenced pathway to 11.

At this time, the basis for n-butyllithium's accentuation of the alkoxyl's influence is not clear, especially since less than a full equivalent is required. A control experiment (treatment of 9 with 2.5 equivalents of n-butyllithium under typical reactions leaves starting material unchanged) seems to rule out metal-halogen exchange as the source of the effect.

In conclusion, we have described alkoxyl influence on organolithium cyclizations. In the presence of n-butyllithium, the reaction has the attractive feature of being stereoselective to either of two isomers, by the inclusion or exclusion of TMEDA. This capacity might compensate for the unattractive yields[12] reported here. The heteroatom influence we observed in lithium cyclizations and the attractive yields we had obtained for the cyclizations of alkenylaluminums[13] prompted us to look for heteroatom influence in the latter case. That work shows that the two features can be combined successfully and will be the subject of an upcoming report.

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Notes and References:

1. The work described here is taken from the PhD dissertation of Michael J. Smith, Oregon State University, 1978.
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4. B. Wakefield, "The Chemistry of Organolithium Compounds," Pergamon Press, New York, 1974.
5. (a) H. G. Richey, Jr. and C. W. Wilkins, Jr., J. Org. Chem., 1980, 45, 5042.
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6. S. E. Wilson, Unpublished Results.

7. An experimental procedure for the cyclization is as follows: The reaction is done under inert atmosphere. Lithium dispersion (0.5 g, 50% in mineral oil, containing 2% Na) is washed with dried (sodium benzophenone) diethyl ether. Dry ether solvent (50 mL) is added, and the metal is activated with a drop of 1,3-dibromopropane. If desired, n-butyllithium (1.0 equivalent[8] relative to the alkenyl halide), TMEDA (1.1 equivalent per organolithium), and an internal standard are added. The stirred reaction mixture is cooled to 0°C, and the alkenyl halide (1 to 2 mmole) is added in one portion. The reaction mixture is brought to room temperature over one hour and stirred for an additional two hours. The contents of the reaction vessel are cooled to -22°C, and the liquid contents are removed from the supernatant lithium metal by pipet and quenched by squirting onto ice/NH_4Cl. The organic layer is dried, vacuum transferred, and analyzed for product distribution and yield by glc (20% SE-30 on Chromosorb P).

8. The presence of as little as 0.1 equivalent of n-butyllithium enhances heteroatom influence such that the "steric control" product comprises <10% of the products, with >90% being of "heteroatom influenced" stereochemistry, e.g., 4 and 10. In order to increase that stereoselectivity, a full equivalent of n-butyllithium was normally used.

9. Compounds 4 and 5 were independently prepared by the methylation of the commercially available *cis* and *trans* alcohols, respectively.

10. D. Evans, and C. Simms, *J. Amer. Chem. Soc.*, 1977, 99, 5453.

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12. Yields are not optimized and likely are low due to formation of dimers and other high molecular weight species which are left behind in the vacuum transfer or have excessively long retention times. No starting material is left unreacted, and the cyclic products indicated are the only nonsolvent peaks in the gc trace. Yields could probably be raised by more involved methods of formation of the lithium reagent (e.g., see P. Freeman and L. Hutchinson. *Tetrahedron Lett.*, 1976, 1849).

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14. Acceptable elemental analyses were obtained for compounds 3, 7, 8, 9, 10, and 11.

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