

STEREOSELECTIVE FORMATION OF A HYDRINDANE RING SYSTEM BY ANIONIC OLEFIN
CYCLIZATION. TRAPPING OF THE ALKYL LITHIUM INTERMEDIATE WITH ELECTROPHILES.

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Summary: Cyclopentane formation via the intramolecular addition of a cyclic vinyl lithium reagent to simple alkenes produces a single hydrindane alkyl lithium diastereomer that can be trapped with electrophiles.

The cyclization of reactive organometallic species is becoming an increasingly popular method of ring formation.¹ We recently reported the results of our initial studies on the cyclization of vinyl lithium reagents derived from 2,4,6-triisopropylbenzenesulfonyl hydrazones (trisyldiazones),² illustrating that the reactive vinyl lithium nucleophile could be generated cleanly in the presence of a primary halide internal electrophile (terminator). In searching for other useful terminators for this type of cyclization, the interesting mechanistic studies by Bailey³ and by Garst⁴ of the cyclization of 5-pentenyl lithium and related organometallics prompted us to investigate simple alkenes as terminators in vinyl lithium cyclization.

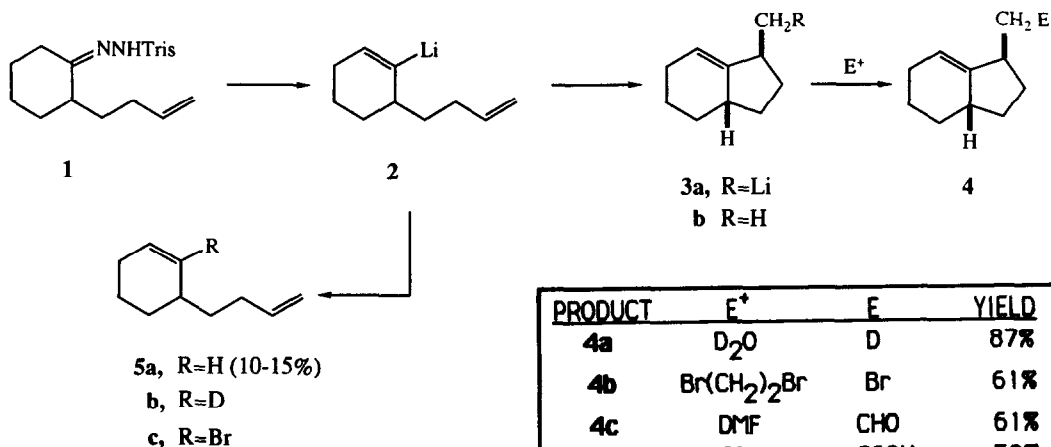


One potentially valuable aspect of this reaction drew our attention at the outset; namely, the possibility of trapping the initial cyclization product (an alkyl lithium species) with electrophiles. Despite the detection of this type of cyclized intermediate by NMR in a simple case,³ reaction with electrophiles has not been reported. This process, if successful, would be an extremely useful complement to existing methodology for functionalized cyclopentane formation, since intermolecular trapping of the corresponding intermediate in radical cyclizations is limited to a few specialized reagents,⁵ and cationic cyclization suffers from the problem that few useful terminators reliably and cleanly form 5-membered rings.⁶

Tempering our initial enthusiasm, however, was the concern that the vinyl lithium cyclization could fail because of a reduced driving force, relative to

the reported examples of alkyllithium ring closure. Specifically, literature examples involve both conversion of a C-C π bond into 2 C-C σ bonds and a primary $sp^3 + sp^3$ carbanion interchange. The proposed transformation, on the other hand, involves a much less energetically favorable $sp^2 + sp^3$ conversion, in addition to the same favorable $\pi + \sigma$ bond interconversion. For the same reason, it also was not obvious whether one would expect kinetic or thermodynamic control in cases where diastereomeric products were possible. Some cyclizations of this type were therefore attempted. The results, described in this Communication, show that cyclopentanes are indeed formed smoothly in this process; that the intermediate cyclopentylmethyl lithium intermediate can be trapped in fair overall yield; and that hydrindane formation is remarkably stereoselective.

The cyclization precursor **1** was prepared by standard methods,⁷ and then was treated with *t*-BuLi (2.1 equiv, THF) as described previously.² The resulting vinyl lithium species **2** underwent cyclization to **3a** at approximately the same rate as reported by Bailey for the simple parent compound,³ i.e. with

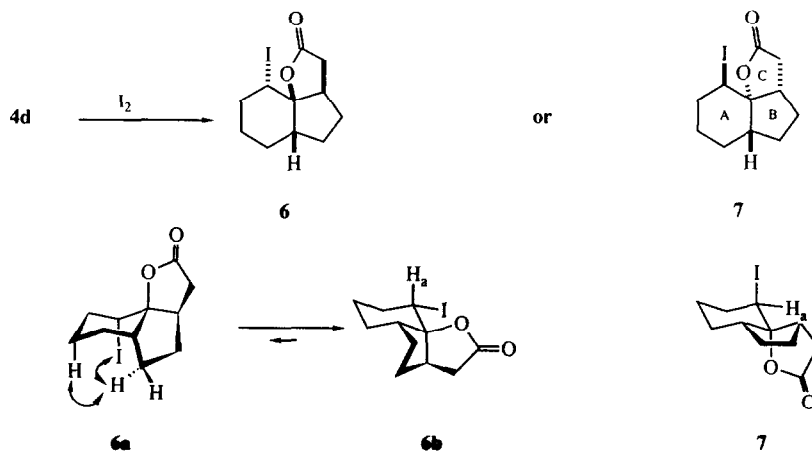


PRODUCT	E ⁺	E	YIELD
4a	D ₂ O	D	87%
4b	Br(CH ₂) ₂ Br	Br	61%
4c	DMF	CHO	61%
4d	CO ₂	COOH	50%
4e	\sqrt{O}	CH ₂ CH ₂ OH	49%

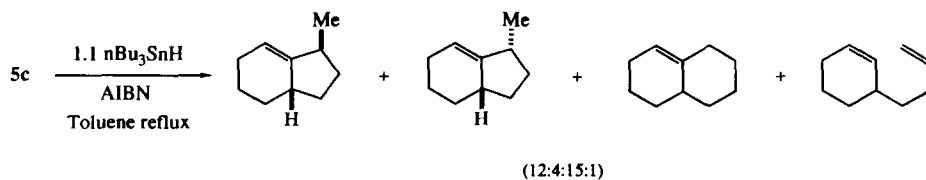
a half-life of a few minutes at 0°C. Quenching with D₂O after 15 minutes at 0°C gave an 87% yield of the monodeuterio hydrindane **4a** (~90% deuterium incorporation). Quenching at progressively shorter reaction times resulted in increasing amounts of the uncyclized deuterio alkene **5b**. Conversely, longer reaction time gave correspondingly lower deuterium incorporation in **4** due to competitive protonation (presumably by THF⁸) of the intermediate alkyllithium **3a**. Several other common electrophiles also were useful as trapping agents, including BrCH₂CH₂Br, DMF, CO₂, and ethylene oxide.⁹ Yields are modest because of competitive protonation (by solvent) of the initial vinyl lithium

species 2 (~10-15%) and of the cyclized alkyl lithium intermediate 3a (10-15%), a problem that potentially can be overcome by the use of solvents other than THF.

The most surprising aspect of this cyclization is not that the intermediate 3a can be trapped, but that a large excess of the "cis" diastereomer 4 is produced; in all cases shown, the ratio of 4 to its diastereomer is $\geq 50:1$ by 250 MHz HNMR and capillary GC. This stereoselectivity, in conjunction with other evidence, suggests a 4-center cyclic transition state ($\begin{matrix} C=C \\ C \cdots Li \end{matrix}$), a possibility that will be addressed in a later paper. The stereochemistry of the major product was deduced by ^1H NMR analysis of the γ -iodolactone (IR 1775 cm^{-1}) derived from 4d. Specifically, one of the coupling constants of H_a ($J=4$, 10Hz) is too large for the equatorial proton in the locked trans-hydrindane (A/B) ring system 7. Conversely, the larger axial-axial coupling constant (10 Hz) is consistent with the conformer 6b, expected to be the predominant form because of the indicated diaxial interactions in the alternative 6a. Note that formation of the alternative diastereomers of 6 and 7, corresponding to attack of I_2 from the opposite face of the respective double bonds, is very unlikely because of the resulting strained trans-5,5 (B/C) ring systems.¹⁰



Finally, it is instructive to compare the results of this anionic cyclization with the analogous radical process. To do so, the vinyl bromide 5c was prepared by "premature" trapping of vinyl lithium 2 with dibromoethane, followed by treatment with $n\text{-Bu}_3\text{SnH}$ under thermal initiation conditions.¹¹



Not only is the radical cyclization considerably less stereoselective (3:1 vs., 50:1), but it also produces a considerable amount of the 6-membered ring (~50% vs < 2%).¹² This comparison reinforces the point that the anionic process complements existing synthetically useful cyclopentane-forming reactions for 3 reasons: (1) stereoselectivity, (2) regioselectivity, and (3) ability to trap the cyclized reactive intermediate with a variety of useful electrophiles. Other aspects of this type of cyclization are being investigated, including other ring sizes, different double bond substitution patterns, and asymmetric induction of various types.

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References Notes

- For recent representative examples, see (a) Crandall, J.K.; Magaha, H.S.; Henderson, M.A.; Widener, R.K.; Tharp, G.A. J. Org. Chem. 1982, 47, 5372. (b) Crandall, J.K.; Magaha, H.S. J. Org. Chem. 1982, 47, 5368. (c) Parham, W.E.; Bradsher, C.K. Acc. Chem. Res. 1982, 15, 300. (d) Boardman, L.D.; Bagheri, V.; Sawada, H.; Negishi, E., J. Am. Chem. Soc. 1984, 106, 6105. (e) Fujikura, S.; Inoue, M.; Utimoto, K.; Nozaki, H. Tetrahedron Lett. 1984, 25, 1999. (f) Okuda, Y.; Morizawa, Y.; Oshima, K.; Nozaki, H. Tetrahedron Lett. 1984, 25, 2483. (g) Cooke, M.P. J. Org. Chem. 1984, 49, 1144. (h) Piers, E.; Friesen, R.W.; Keay, B.A. J. Chem. Soc., Chem. Commun. 1985, 809. (i) Utimoto, K.; Imi, K.; Shiragami, H.; Fujikura, S.; Nozaki, H. Tetrahedron Lett. 1985, 26, 2101. (j) Cooke, M.P.; Houpis, I.N. Tetrahedron Lett. 1985, 26, 3643. (k) Shankaran, K.; Snieckus, V. J. Org. Chem. 1984, 49, 5022. (l) For a review including earlier examples of anionic cyclizations, see Vara Prasad, J.V.N.; Pillai, C.N. J. Organomet. Chem. 1983, 259, 1.
- Chamberlin, A.R.; Bloom, S.H., Tetrahedron Lett. 1984, 25, 4901.
- Bailey, W.F.; Patricia, J.J.; DelGobbo, V.C., J. Org. Chem. 1985, 50, 1999.
- Garst, J.F.; Hines, J.B., J. Am. Chem. Soc. 1984, 106, 6443.
- For example, see Burke, S.D.; Fobare, W.F.; Armistead, D.M., J. Org. Chem., 1982, 47, 3348.
- Johnson, W.S., Bioorganic Chem., 1976, 5, 51.
- (a) Stork, G.; Dowd, S.R., J. Am. Chem. Soc., 1963, 85, 2178. (b) Chamberlin, A.R.; Stemke, J.E.; Bond, F.T. J. Org. Chem., 1978, 43, 147.
- Tombouliau, P.; Amick, D.; Beare, S.; Dumke, K.; Hart, D.; Hites, R.; Metzger, A.; Nowak, R., J. Org. Chem., 1973, 38, 322.
- Satisfactory spectroscopic data (250 MHz ¹HNMR, ¹³CNMR, IR, and HRMS) were obtained for each product.
- For a review of iodolactonization, see Dowle, M.D.; Davies, D.I., Chem. Soc. Rev., 1979, 171.
- Marinovic, N.N.; Ramanathan, H., Tetrahedron Lett., 1983, 24, 1871.
- The exact ratio of the products varied depending upon the reaction conditions employed. For related examples of sp² radical cyclizations, including 6-membered ring formation, see (a) Hart, D.J.; Tsai, Y-M., J. Am. Chem. Soc., 1982, 104, 1430. (b) Stork, G.; Baine, N.H., J. Am. Chem. Soc., 1982, 104, 2321.

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