

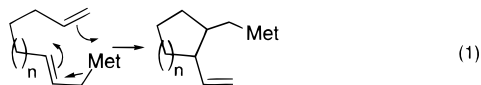
The Lithium–Ene Cyclization and the Purported Carbanion-Induced Ene Cyclization

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We provide evidence herein that the previously unstudied lithium–ene cyclization (eq 1; Met = Li) is more facile than the

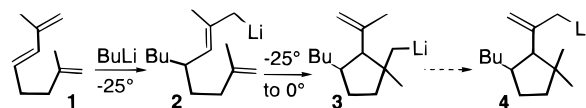


widely used Mg analogue;^{2–4} that the products, however, are unstable, accepting protons from various donors and possibly reverting to uncyclized organolithiums; that the only example of such a cyclization cited in reviews of this reaction involved a crucial misassignment of the structure of the product; and that another subsequently discovered cyclization, thought to be a carbanion-induced ene reaction, is actually a lithium–ene cyclization followed by an intramolecular proton transfer.

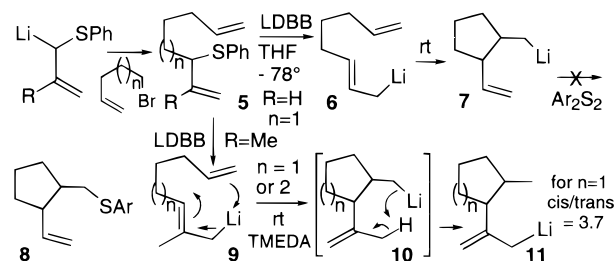
The “surprisingly smooth” lithium–ene cyclization cited in the Oppolzer reviews² refers to the addition of *n*-butyllithium to triene **1** and isolation of the products of electrophilic trapping of **3** (Scheme 1).^{5,6} However, as shown below, the actual trapped intermediate was **4**.

Our suspicions concerning the reported⁵ structure (**3**) of the cyclic organolithium arose when we were unable to detect the thioether derivative **8** of the lithium–ene cyclization product **7** (**6** readily prepared by reductive lithiation⁷ of **5** using lithium 4,4′-di-*tert*-butylbiphenylide (LDBB)) when **6** was warmed from -78 to 20 °C and the reaction mixture was treated with bis(*p*-methoxyphenyl) disulfide. The acyclic allyllithium **6** could be recovered as its thioether derivative in 40% yield (Scheme 2). On the other hand, when a methyl group was present at the 2-position of the allyllithium **9**, as was the case in Scheme 1,⁸ cyclization to five- and six-membered rings occurred partially during 1 h at 0 °C and completely at ambient temperature. However, the cyclic thioethers, isolated in yields of 77% and 64%, respectively, for $n = 1$ and 2, were not those from electrophilic capture of **10**, as expected from ref 5, but those from allyllithiums **11**. It seemed likely that these products were formed from the

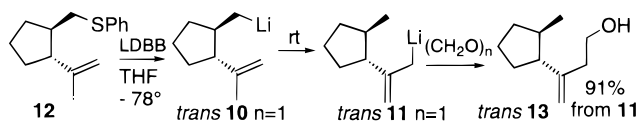
Scheme 1



Scheme 2



Scheme 3



proximate cyclization products **10** via the 1,5-proton transfer shown (Scheme 2).⁹

Indeed, the allyllithium *trans*-**11** ($n = 1$) rearranged in good yield to *trans*-**11** ($n = 1$) at ambient (Scheme 3).

After completion of this work, we became aware of a similar cyclization to an allyllithium; the report¹⁰ (see below) did not cite the cyclization in Scheme 1 and was not referenced in the reviews of metallo–ene cyclizations,² possibly because a different mechanism was invoked. The question then arose as to why **2** cyclized to **3** rather than to the allyllithium **4**. In fact, a critical reading of the paper⁵ revealed that the reported 60 MHz NMR spectrum of the product obtained upon quenching with paraformaldehyde was inadequate to distinguish between attack of formaldehyde on **3** or **4**. Our repetition of the procedure,⁵ however quenching with D_2O , delivered the deuteration product not of **3** but of **4**.

As to our failure to observe cyclized product **8** from **6** (Scheme 2), the low yield of recovered product and the methallyllithium results made us suspect that cyclization had occurred but that the cyclized allyllithium **7** removed a proton from THF¹¹ more rapidly than the less basic allyllithiums such as **11** and that the resulting volatile hydrocarbon was lost upon workup. This hypothesis was tested by reductive lithiation of **15** in THF. The cyclized organolithium, which was not trapped by added paraformaldehyde, removed a proton from solvent to deliver an excellent yield of **16**. The important conclusion can be drawn that the lithium–ene cyclization occurs at a considerably lower temperature than the magnesium analogue² but that because of the greater basicity of organolithium than organomagnesium compounds, the cyclized organolithium abstracts a proton readily, either intramolecularly to produce an allyllithium if an allylic methyl group is nearby or intermolecularly from THF.

It appears likely that this type of facile cyclization, possibly followed by 1,5-allylic proton transfer as demonstrated above, is

(9) A reviewer observed that the mainly *cis* configuration of **11** supports the metallo–ene cyclization since a *trans* configuration is generated when a nonallylic secondary organolithium cyclizes in a similar fashion: Bailey, W. F.; Nurmi, T. T.; Patricia, J. J.; Wang, W. *J. Am. Chem. Soc.* **1987**, *109*, 2442–48.

(10) Edwards, J. H.; McQuillin, F. *J. Chem. Soc., Chem. Commun.* **1977**, 838–839. See also: Cuvigny, T.; Julia, M.; Rolando, C. *J. Organomet. Chem.* **1988**, *344*, 9–28.

(11) Bates, R. B.; Kroposki, L. M.; Potter, D. E. *J. Org. Chem.* **1972**, *37*, 560–562.

(1) Taken in part from the M.S. Theses of Shirong Zhu (1997) and Xiaojun Liu (1999) and the Ph.D. Thesis of Steven H. Norton (1999) at the University of Pittsburgh.

(2) Reviews of metallo–ene reactions: Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38–52. Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, England, 1991; Vol. 5, pp 29–61.

(3) The Zn–ene cyclization, used less extensively in synthesis, has recently come into prominence. Recent references: Nakamura, E.; Kubota, K. *J. Org. Chem.* **1997**, *62*, 792–793. Lorthiois, E.; Marek, I.; Normant, J.-F. *J. Org. Chem.* **1998**, *63*, 2442–50.

(4) Cyclization of nonallylic unsaturated organolithiums: Bailey, W. F.; Ovaska, T. V. In *Advances in Detailed Reaction Mechanisms*; Coxon, J. M., Ed.; JAI Press: Greenwich, CT, 1994; Vol. 3, pp 251–273.

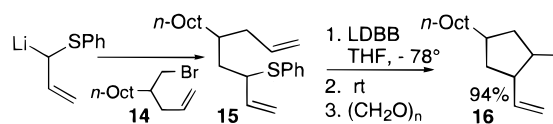
(5) Josey, A. D. *J. Org. Chem.* **1974**, *39*, 139–145.

(6) Two lithium–ene cyclizations, not included in the reviews,² may be special cases: Klumpp, G. W.; Schmitz, R. F. *Tetrahedron Lett.* **1974**, 2911–14 (strained enophile). Krief, A.; Derouane, D.; Dumont, W. *Synlett* **1992**, 907–908 (1,1,3,3-tetrasubstituted allyllithium).

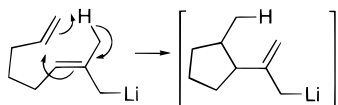
(7) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152–161.

(8) Allyllithiums are depicted here as covalent (η^1) only for simplicity and analogy with allylmagnesiums. They are known to be π (η^3) complexes. Fraenkel, G.; Cabral, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 1551–1557.

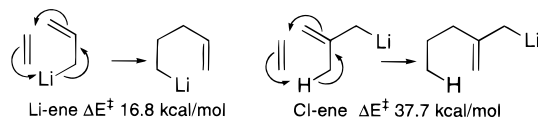
Scheme 4



Scheme 5



Scheme 6



responsible for the previously inadequately explained high degree of carbanionic cyclopolymerization of butadiene under certain conditions.¹²

For the cyclization of a terminally unsaturated methyllithium to an allyllithium analogous to **4** and **11**, Edwards and McQuillin¹⁰ suggested a very interesting carbanion-induced ene reaction (Scheme 5), which differs fundamentally from our suggestion of a lithium–ene cyclization followed by a 1,5-proton transfer. In their concept, one conjugated organolithium is converted directly to another, no nonconjugated allyllithium intervening. Whereas the Alder ene reaction usually occurs at temperatures above 200 °C,¹³ it was suggested that the carbanionic site greatly facilitates the reaction.

We examined the two mechanisms both by determining the deuterium isotope effect for the reaction **9** → **11** (Scheme 2), where **9** contains CH₃ or CD₃, and by ab initio computations. The absence of a primary isotope effect would essentially disprove the mechanism in Scheme 5 as well as that involving a reversible cyclization followed by a rate-determining proton transfer.¹⁴ An isotope effect would be revealed if allowing **9** (*n* = 1; R = CH₃ or CD₃) to cyclize for a given length of time resulted in significantly more cyclization when R = CH₃ than when it is CD₃. In the event, allowing each cyclization to occur at 0 °C for 3 h led to an 86/14 ratio of cyclized to uncyclized thioether when R = CH₃ and a ratio of 81/19 when R = CD₃; this leads to an approximate isotope effect of 1.09.¹⁵ An independent experiment involving about 90% cyclization of an equimolar mixture of labeled and unlabeled **9** and determination of the deuterium content of uncyclized **9** by ¹³C NMR revealed no isotope effect within experimental error.¹⁵

The computed activation energy of the Li–ene reaction of an allyllithium/ethylene complex was compared with the carbanion-induced ene (Cl–ene) reaction of a methyllithium/ethylene complex (Scheme 6), using the Gaussian program.^{16,17} The results indicate that the lithium–ene addition has a considerably lower activation energy in the gas phase than the Cl–ene process. The

(12) McElroy, B. J.; Merkley, J. H. U.S. Patent 3,678,121, July 18, 1972. Halasa, A. F., U.S. Patent 3,966,691, June 29, 1976. Quack, G.; Fetters, L. J. *Macromolecules* **1978**, *11*, 369–373.

(13) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 1–25.

(14) Melander, L.; Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; John Wiley & Sons: New York, 1980; Chapter 5.

(15) See Supporting Information for details.

(16) Gaussian 94, Revision B.2, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A.; Gaussian, Inc.: Pittsburgh, PA, 1995.

(17) Full computations concerning these and related reactions will be published separately.

ΔE^\ddagger for the lithium–ene cyclization **6** → **7** (19.4–25.8 kcal/mol,¹⁸ depending on stereochemistry) is slightly higher than that for the intermolecular version in Scheme 6, probably partly due to the enophile being substituted. When continuum models of solvation, included in Gaussian, were applied to the transition states, reactants, and products for both the Li–ene and Cl–ene reactions, the calculated energy difference between the two processes in Scheme 6 was even greater. Self-Consistent Reaction Field (SCRF) models used included the Polarized Continuum Model^{19,19} (PCM) and Isodensity Surface PCM²⁰ (IPCM) models. It is thus likely that this process is actually a lithium–ene cyclization as originally surmised.

The original putative result which is quoted in the reviews indicates not only that the lithium–ene cyclization occurs at –25 °C, which it does not (the original paper⁵ is less than clear on this point), but that the cyclization is thermodynamically favorable. Now that we know that the product structure was misassigned, the possibility exists that this is not so and that the ring closure is driven to completion by the subsequent intramolecular or intermolecular proton transfer. To test this reversibility, **7** was prepared by reductive lithiation of the corresponding phenyl thioether and an attempt was made to trap it or its retrocyclization product with paraformaldehyde. Apparently, only protonated product was generated since no trapped product could be isolated unless paraformaldehyde was added prior to warming to 20 °C, in which case the cyclic alcohol was isolated in excellent yield.

We again turned to computations. Although the intermolecular Li–ene process shown in Scheme 6 was found to have $\Delta E = -3.1$ kcal/mol, the intramolecular process **6** → **7** was found to be endergonic ($\Delta E = +11.2$ to $+11.9$ kcal/mol, depending on stereochemistry; the six-membered ring formation is only slightly endergonic). It thus appears that the incorrect assignment of **3** to the product of cyclization of **2** led to considerably incorrect conclusions about the lithium–ene cyclization. While it is a process that occurs more readily than the far more common magnesium analogue, unlike the latter it is probably thermodynamically unfavorable and observed only when the cyclization product undergoes a subsequent irreversible reaction.²¹ This concept has been utilized synthetically in a remarkably efficient, stereoselective, tandem cyclization.²² The lack of an isotope effect in **9** → **11** is consistent with the proton transfer being far more rapid than the retrocyclization, i.e., the ring closure is the rate determining step. This conclusion is also suggested by Scheme 3. If ring opening had preceded proton transfer, the resulting product would be cis as in Scheme 2.²³

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Supporting Information Available: Experimental procedures, details of compound characterization, and computational details (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(18) This and subsequent energy values are from Becke3-LYP/6-31G* calculations.

(19) Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117–129. Miertus, S.; Tomasi, J. *Chem. Phys.* **1982**, *65*, 239–245. Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.* **1996**, *255*, 327–335.

(20) Foresman, J. B.; Keith, T. A.; Wiberg, K. B.; Snoonian, J.; Frisch, M. J. *J. Phys. Chem.* **1996**, *100*, 16098–16104.

(21) The energy of the intramolecular proton transfer can be approximated by that for the transfer of an allylic proton from propene to ethyllithium, –25.7 kcal/mol at the same level of theory. Thus, $\Delta E \approx 11.5 - 25.7 = -14.2$ kcal/mol for the cyclization + proton transfer.¹⁷

(22) Cheng, D.; Knox, K. R.; Cohen, T. Manuscript in preparation.

(23) In a recent report, an intramolecular displacement of an allylic chloride by an allyllithium is represented as starting as a lithium–ene cyclization and merging into an S_N' reaction. Dieters, A.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 546–548.