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Use of a Conformational Radical Clock for Evaluating Alkyllithium-Mediated Cyclization Reactions

Scott D. Rychnovsky,* Takeshi Hata, Angie I. Kim, and Alexandre J. Buckmelter

Department of Chemistry, 516 Rowland Hall, University of California, Irvine, California 92697-2025

srychnov@uci.edu

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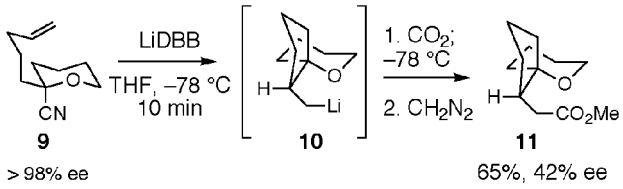
ABSTRACT



The reductive lithiation of nitrile 9 led to the cyclic product 11 as a single diastereomer in 42% ee. The intermediate radical is a conformational radical clock. The radical lifetime can be determined from the optical purity of the product 11. We show that the lifetime of the intermediate radical is too brief to allow a radical cyclization, and thus the cyclization proceeds through an alkyllithium intermediate.

Radical clock reactions are powerful tools for evaluating reaction mechanisms.[1] We recently reported a radical clock reaction based on the ring inversion of a 2-tetrahydropyranyl radical.[2] Described herein is the study of a cyclization reaction using a conformational radical clock.

Alkyllithium cyclizations with alkenes provide an interesting approach to five-membered ring synthesis. Work by Bailey and others has established that reactive alkyllithium reagents are required, and unless a leaving group is present,[3] the alkene must be terminal for efficient cyclization.[4] The mechanism is thought to be a metal−ene type cyclization,[4] and a transition state for the cyclization has been identified using ab initio methods.[5] A related cyclization of alkenyl halides catalyzed by an alkyllithium reagent has been studied.[6] In this case the cyclization was determined to proceed through a radical intermediate rather than the expected alkyllithium intermediate.[7] Unsaturated alkylmagnesium reagents have also been reported to cyclize via the corresponding radical.[8] Evaluating the mechanism of 5-hexenyl benzene sulfide reductive cyclizations[3] is particularly problematic, because the radical is an obligatory intermediate in the generation of the alkyllithium reagent and both radical and alkyllithium cyclization would produce the observed product. We report a reductive cyclization in which the alkyllithium rather than the radical is the active intermediate.

This study is predicated on determining the lifetime of an intermediate radical using a conformational radical clock reaction. An optically pure 2-tetrahydropyranyl radical can be used as a radical clock as shown in Scheme 1.[2] The optically pure radical **2**, generated by reduction of cyanohydrin **1**, racemizes by ring inversion, and we have shown that the rate of racemization is about 5.7×10^8 s^{-1} at 22 °C

(1) (a) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151−1176. (b) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317−323.

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(5) 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.

(6) Bailey, W. F.; Carson, M. W. *J. Org. Chem.* **1998**, *63*, 9960−9967.

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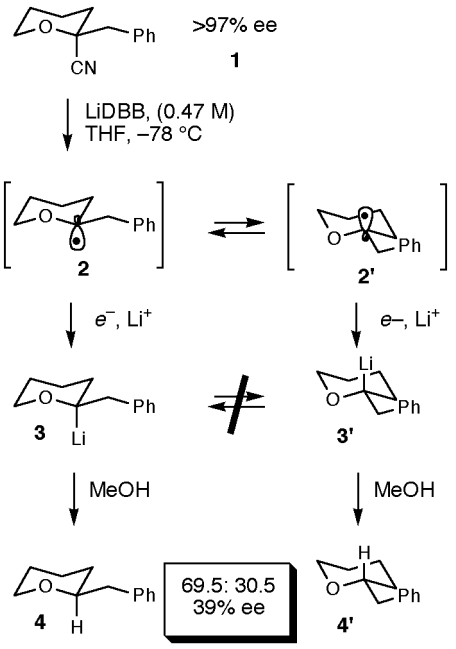
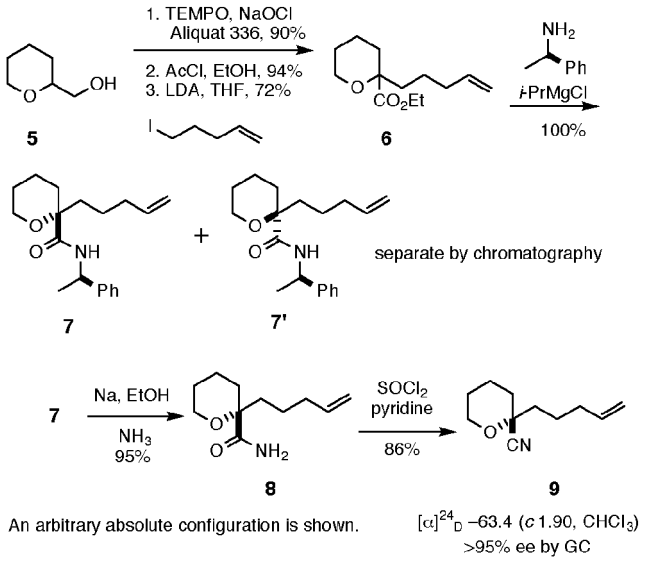
Scheme 1. Tetrahydropyranyl Radicals as Radical Clocks



Scheme 2. Synthesis of Nitrile **9**



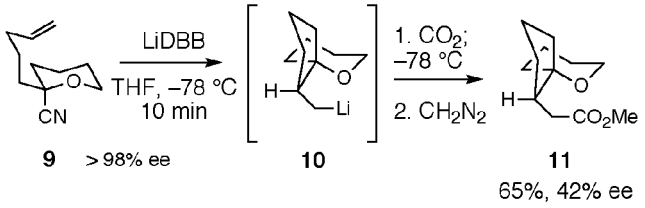
or 3.9×10^6 s^{-1} at −78 °C.[2] Note that the barrier to radical inversion is estimated to be less than 0.5 kcal/mol,[9] but the barrier to *ring inversion* of **2** is closer to 7 kcal/mol. Reduction of the radical **2** and its enantiomer **2′** lead to the configurationally stable alkyllithium reagents **3** and **3′**.[10] Most carbonyl electrophiles and protons react with α-alkoxy lithium reagents such as **3** with retention of configuration.[11] Reductive lithiation of nitrile **1** with lithium di-*tert*-butylbiphenylide (LiDBB) at −78 °C leads to a 69.5:29.5 mixture of **4** and **4′** (39% ee) on trapping with methanol. The optical purity of the product is directly related to the lifetime of the radical. The half-life of the radical under the reaction conditions is given by eq 1.[12] For the reductive lithiation of optically pure cyanohydrin **1**, the lifetime of the intermediate radical **2** under the reaction conditions was found to be 2.8×10^{-7} s using eq 1. Conformational radical clocks are useful tools for measuring the lifetimes of radical intermediates.

$$t_{1/2}=\ln 2/k_R\times(1-\text{ee})/\text{ee} \qquad (1)$$

The preparation of the substrate for the reductive cyclization, nitrile **9**, is outlined in Scheme 2. Oxidation of commercially available tetrahydropyran-2-methanol, followed by esterification, gave the expected ester. Deprotonation and alkylation with 5-iodo-1-pentene gave the unsaturated ester **6** in good overall yield. After several unsuccessful attempts to resolve the acid of **6**, we investigated the resolution of diastereomeric amides. Ester **6** was converted to amides **7** and **7′** by treatment with (*R*)-α-methylbenzylamine and isopropylmagnesium chloride.[13] The two diastereomers were easily separated by silica gel chromatography.[14] Attempts to hydrolyze the secondary amides **7** and **7′** were unsuccessful, but the secondary amide was converted to primary amide **8** by dissolving metal reduction with sodium in ammonia. Dehydration of amide **8** with thionyl chloride gave the target nitrile **9** as a single enantiomer.[15]

With nitrile **9** in hand, its reductive lithiation and cyclization was investigated, and the results are illustrated in Schemes 3 and 4. Treatment with LiDBB in THF for 10 min at −78 °C, followed by addition of CO_2 gas, aqueous workup, and diazomethane treatment, gave the spirocyclic ester **11** in 65% yield and 42% ee.[15] The relative configuration of **11** was determined by NMR analysis and subsequently confirmed by an indirect correlation.[16] When the

Scheme 3. Lithiation and Cyclization of Nitrile **9**



(9) Griller, D.; Ingold, K. U.; Krusic, P. J.; Fischer, H. *J. Am. Chem. Soc.* **1978**, *100*, 6750−6752. See ref 17.

(10) Rychnovsky, S. D.; Buckmelter, A. J.; Dahanukar, V. H.; Skalitzky, D. J. *J. Org. Chem.* **1999**, *64*, 6849−6860.

(11) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842−853.

(12) Here, ee is the fractional enantiomeric excess and k_R is the rate of racemization of the radical at the reaction temperature. Alternatively, the half-life of the radical can be calculated directly from the concentrations of the two enantiomers of the product: $t_{1/2} = 2 \ln 2/k_R \times$ [**4′**]/([**4**] − [**4′**]).

(13) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461−5464.

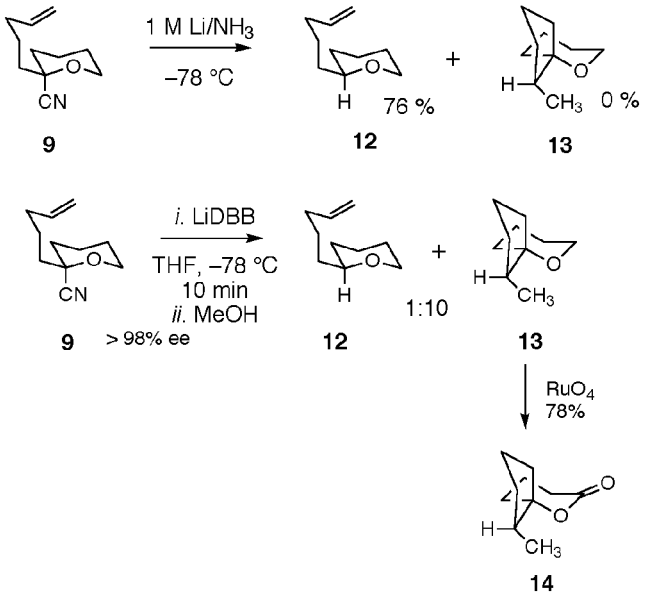
(14) The R_f values for **7** and **7′** in 20% EtOAc/hexanes are 0.34 and 0.41, respectively. The absolute configurations at the quaternary centers in **7** and **7′** were not assigned.

(15) The optical purity was directly evaluated by GC analysis on a CHIRALDEX G-TA or CHIRALDEX B-PH column.

reduction of nitrile **9** was run for 30 min at −78 °C prior to trapping, compound **11** in was isolated in similar yields and optical purities. We conclude that the cyclization was essentially complete after 10 min at −78 °C.

Reduction of **9** with lithium in ammonia gave very different results, Scheme 4. The Li/NH_3 reduction of racemic

Scheme 4. Reduction and Reductive Cyclization of Nitrile **9**



9 at −78 °C gave the uncyclized tetrahydropyran **12** in 76% yield with none of the corresponding cyclized product **13**. Lithium ammonia reductions of nitriles proceed through stepwise electron transfers and generally produce results similar to those of LiDBB reductions with the same substrates.[17] Reduction of **9** with LiDBB, followed by methanol quenching, led to **12** and **13** in a 1:10 ratio. Oxidation of **13** with RuO_4 gave the known lactone **14**.[18] Thus, nitrile **9** cyclizes rapidly and efficiently when reduced with LiDBB, but it did not cyclize at all when reduced with lithium in liquid ammonia.

The cyclization of **9** en route to **11** can be rationalized either as a radical cyclization or as an alkyllithium cyclization. These two mechanistic possibilities are illustrated in Scheme 5. In both pathways, nitrile **9** is reduced to radical **15**; radical **15** is the key branch point in each pathway. In the alkyllithium pathway, the racemization of **15** will compete with reduction to the alkyllithium reagent **16**. Alkyllithium reagents **16** and **16′** are configurationally stable at −78 °C in THF,[19] and the cyclizations of α-alkoxy alkyllithium reagents have been found to take place with retention of configuration.[20] Thus, in the alkyllithium cyclization the ratio of **16**:**16′** will determine the final ratio of **11**:**11′**.

An alternative view of the cyclization is that it proceeds via a radical cyclization. On the face of it, the fact that the cyclization of **9** is complete in 10 min at −78 °C might suggest a radical cyclization, many of which are known to be very rapid, over the alkyllithium cyclization. The radical cyclization pathway is outlined in the lower half of Scheme 5. The intermediate radical **15** is again the key branch point with cyclization and racemization reactions competing. The cyclized radicals **19** and **19′** that are produced would then be reduced to give alkyllithium reagents **17** and **17′**. Reaction with CO_2 and esterification with diazomethane generates a mixture of **11** and **11′**. In this case the ratio **11**:**11′** would be determined by competition between racemization of **15** and cyclization of **15**.

A radical clock reaction would help distinguish between the alkyllithium and the radical cyclization pathways. Radical **15** is structurally similar to radical **2**, and it should have a comparable racemization rate at −78 °C. Radical **15** is the only point in either mechanism where racemization would be likely, and so the enantiomeric excess of product **11** is a direct measure of the lifetime of the radical under the reaction conditions. Using the optical purity of **11**, 42% ee, and the measured rate of racemization of radical **2** in eq 1 gives an estimated lifetime for radical **15** of 2.4×10^{-7} s.[21] How does this lifetime compare with the expected rate of radical cyclization? Extrapolating from the published Arrhenius data for a 5-hexenyl cyclization leads to a predicted cyclization rate of 4×10^2 at −78 °C.[22] Comparing the lifetime of radical **15** and the predicted rate of cyclization suggests that the rate of cyclization is approximately 5 orders of magnitude too small to allow cyclization in the lifetime of the radical.

One concern that might be raised with the foregoing analysis is that the rate of cyclization was calculated from a 5-hexenyl radical but the cyclizing radical **15** is highly substituted. Newcomb, however, has evaluated the cyclization rates of the 6,6-diphenyl-5-hexenyl radical[23] and the 1-methoxy-6,6-diphenyl-5-hexenyl radical.[24] The rate of

(16) Ester **11** was isolated as a single diastereomer, but its relative configuration was not determined easily. The ^{13}C chemical shifts for both possible diastereomers were predicted using the computational method of Forsyth and Sebag, and the ^{13}C data for **11** was more consistent with the structure shown in Scheme 3. Oxidation of **13** to lactone **14** and correlation (see ref 18) further support the assignment. Forsyth, D. A.; Sebag, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 9485−9494.

(17) (a) Rychnovsky, S. D.; Powers, J. P.; Lepage, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 8375−8384. (b) Buckmelter, A. J.; Powers, J. P.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1998**, *120*, 5589−5590.

(18) Both the cis and trans isomers of lactone **14** were reported, and NMR data for our product clearly matched the diagnostic methyl shifts for the cis isomer: trans isomer ^1H δ 0.91 ppm, ^{13}C δ 16.06 ppm; cis isomer ^1H δ 1.00 ppm, ^{13}C δ 13.00 ppm; lactone **14** ^1H δ 0.99 (d, $J = 6.6$ Hz) ppm, ^{13}C δ 12.7 ppm. However, several of the other ^{13}C peaks reported for the cis isomer did not match our data for compound **14**, and we cannot explain the discrepancy. Canonne, P.; Boulanger, R.; Bernatchez, M. *Tetrahedron* **1989**, *45*, 2525−40.

(19) Cohen, T.; Lin, M. T. *J. Am. Chem. Soc.* **1984**, *106*, 1130−1131.

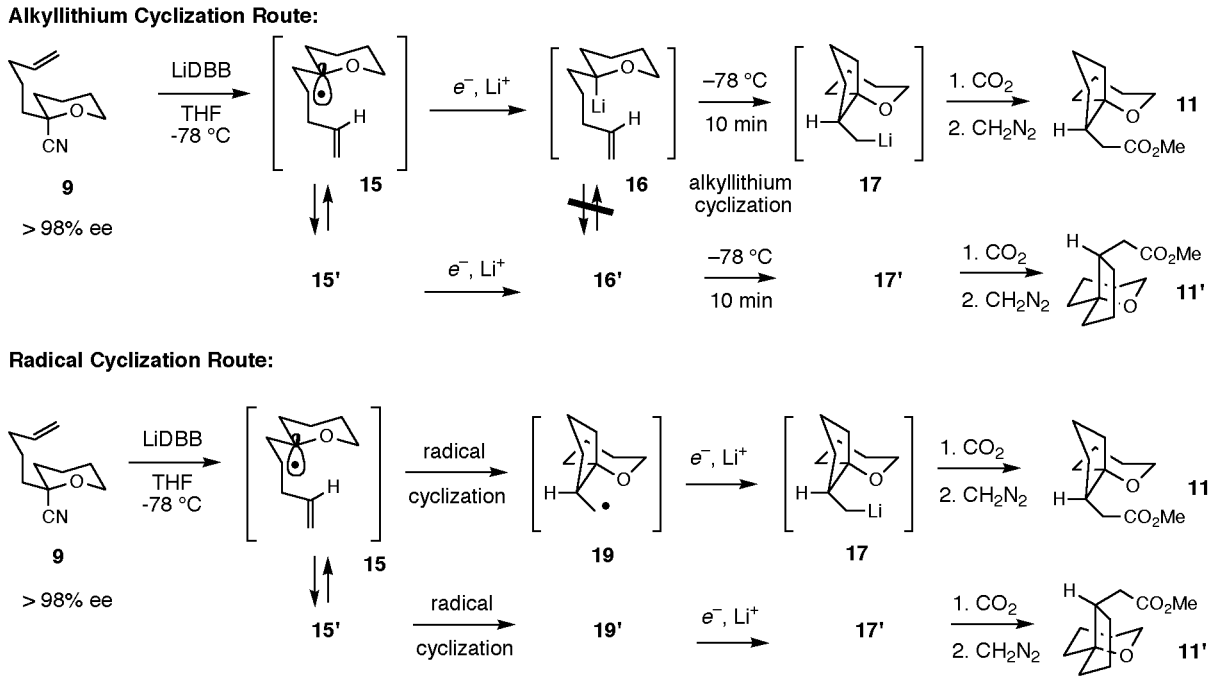
(20) (a) Tomooka, K.; Komine, N.; Nakai, T. *Tetrahedron Lett* **1997**, *38*, 8939−8942. (b) Woltering, M. J.; Frohlich, R.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1764−1766.

(21) The reviewer noted that the rate of reduction of a radical with LiDBB can be estimated, in principle, from electrochemical data. Unfortunately, neither the self-exchange rate nor the solvent reorganization energy for DBB reduction has been reported. For an insightful discussion, see: (a) Andrieux, C. P.; Gallardo, I.; Savéant, J.-M. *J. Am. Chem. Soc.* **1989**, *111*, 1620−1634. (b) Gonzalez, J.; Hapiot, P.; Konovalov, V.; Savéant, J.-M. *J. Am. Chem. Soc.* **1998**, *120*, 10171−10179.

(22) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317−323.

(23) Ha, C.; Horner, J. H.; Newcomb, M.; Varick, T. R.; Arnold, B. R.; Lusztyk, J. *J. Org. Chem.* **1993**, *58*, 1194−8.

Scheme 5. Radical and Alkyllithium Cyclization Pathways for the Formation of Esters **11** and **11′**



cyclization for the α-alkoxy radical does differ from that of the primary radical, but only by about a factor of 2 over the extrapolated range from −70 to 80 °C. Variations of this magnitude do not change the conclusions of the analysis.

A final piece of evidence is the absence of cyclization products in the reduction of **9** under Li/NH_3 conditions (Scheme 3). We were not able to measure the optical purity of **12** directly,[25] but one might expect that it would have an optical purity of about 30% on the basis of the Li/NH_3 reduction of nitrile **1** under comparable conditions (Scheme 1). Similar enantiomeric excesses between acyclic product **12** and cyclic product **11** would dictate a similar lifetime of the radical **15** in each reaction. Since one product is cyclic and the other is not, the cyclization cannot be attributed to the radical intermediate **15**. Only in the reduction of **9** with LiDBB, where intermediate alkyllithium reagents **16** and **16′** would have long lifetimes, is cyclization observed.

Conformational radical clocks are useful for determining the lifetime of radical intermediates. For the reductive lithiation of nitrile **9**, the optical purity of the product **12**, 42% ee, implies a lifetime for radical **15** of 2.4×10^{-7} s. This lifetime is too brief for a radical cyclization to take place. Thus, the reduction of **9** to **11** proceeds via cyclization of the alkyllithium **16**.

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Supporting Information Available: Experimental procedures for the preparation and reduction of nitrile **9**. Data and analysis for the structural assignment of ester **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006866R

(24) Johnson, C. C.; Horner, J. H.; Tronche, C.; Newcomb, M. *J. Am. Chem. Soc.* **1995**, *117*, 1684−7.

(25) We were not able to determine the optical purity of **12** or any of a number of derivatives by GC analysis on chiral columns. The optical rotation of **12** has not been reported in the literature.