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PhLi-initiated cycloisomerization of unsaturated organoiodides: mechanism of the isomerization of olefinic primary alkyl iodides

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Abstract

Evidence is presented indicating that the PhLi-initiated cycloisomerization of olefinic primary alkyl iodides involves a radical-mediated atom transfer process that had previously been implicated in the isomerization of secondary and tertiary substrates. © 1999 Elsevier Science Ltd. All rights reserved.

We recently reported that a variety of primary, secondary, tertiary, and aryl iodides bearing a suitably positioned carbon–carbon π-bond undergo cycloisomerization in the presence of a catalytic quantity of phenyllithium (PhLi) to give the cyclic isomers in good to excellent yields.[1,2] The mechanism of this highly atom-economical transformation[3] is substrate dependent.[2] Thus, as illustrated below, aryl iodides bearing a pendant unsaturation, exemplified by *N*,*N*-diallyl-2-iodoaniline (**1**), undergo isomerization via a three-step cascade mediated by two reversible lithium–iodine exchange equilibria bracketing an irreversible cyclization step;[2] unsaturated secondary and tertiary alkyl iodides (**2**) cyclize as the result of a rapid radical-mediated atom transfer process, depicted below,[4,5] that is apparently initiated by homolytic fragmentation of a putative 10-I-2 ate-complex generated through attack of PhLi on the iodine atom of the substrate.[2] In our initial report we had suggested that the PhLi-initiated isomerization of unsaturated primary alkyl iodides, such as 6-iodo-1-hexene, involved the three-step lithium–iodine exchange mediated mechanism.[1] The results of a more recent investigation, detailed below, require revision of this supposition: the cycloisomerization of olefinic primary alkyl iodides upon treatment with PhLi appears to be a radical-mediated atom transfer chain reaction.

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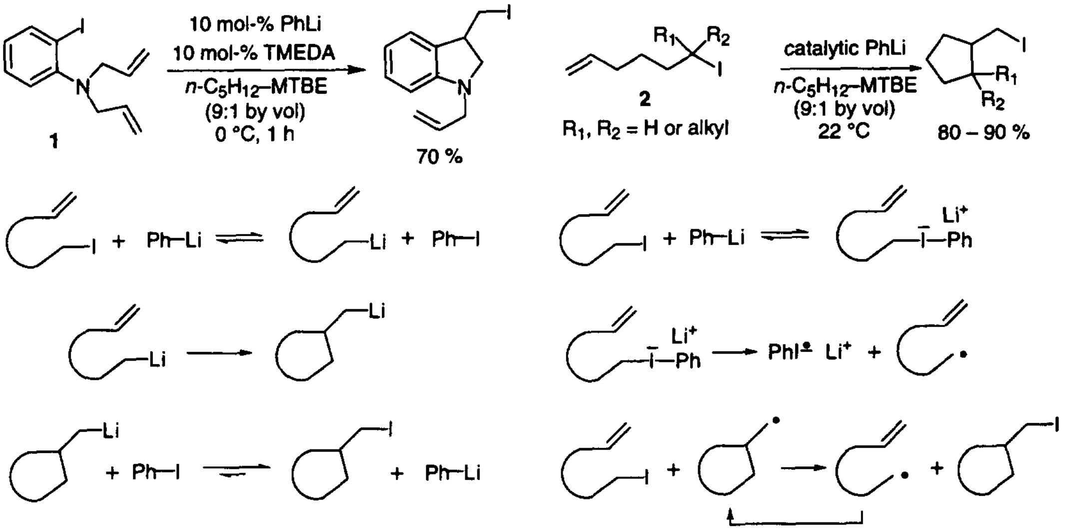
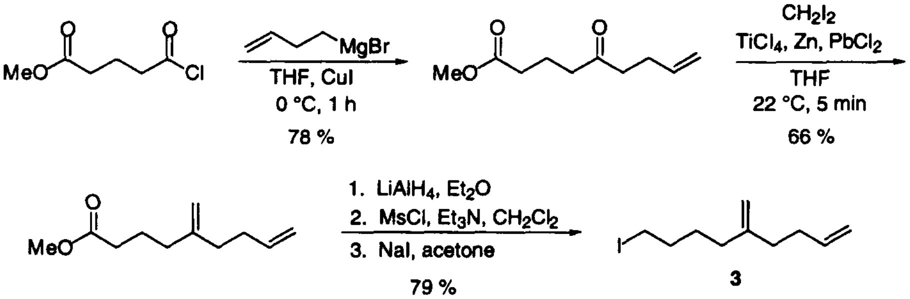
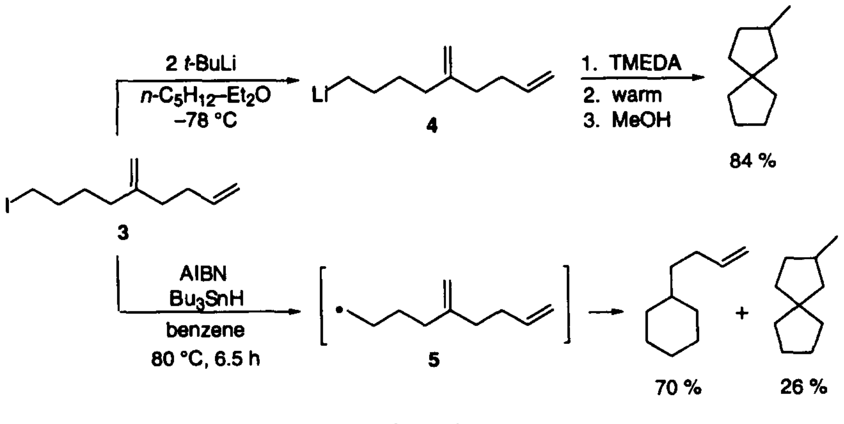


Perhaps the simplest way to distinguish between a three-step anionic mechanism and one mediated by radical intermediates is to explore the PhLi-initiated cycloisomerization of a system in which cyclization of the organolithium is known to give a different product than does ring-closure of the corresponding radical intermediate. As demonstrated by the results reported below, the previously reported diolefinic alkyl iodide, 2-(4-iodobutyl)-1,5-hexadiene (3),[6] may be used to differentiate between the two mechanistic scenarios for the cycloisomerization. Iodide 3 was easily prepared in straightforward fashion as depicted in Scheme 1.[7,8]



Scheme 1.

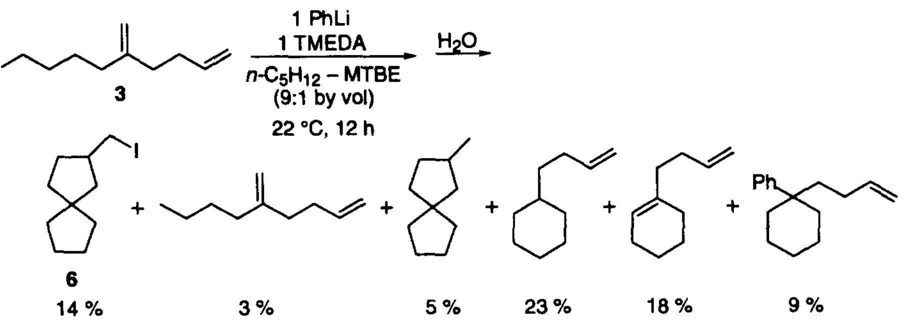
Some time ago we reported, as illustrated in Scheme 2, that the organolithium (4), derived from 3 in essentially quantitative yield by low-temperature lithium–iodine exchange,[9] cleanly undergoes two sequential 5-*exo* cyclizations when warmed to room temperature in the presence of TMEDA to deliver 2-methylspiro[4.4]nonane in 84% isolated yield following quench with methanol.[6] The balance of the reaction mixture was 2-butyl-1,5-hexadiene; there was no evidence of any other carbocyclic product in this formally anionic double-cyclization.[6] In striking contrast to the behavior of organolithium 4, the radical-mediated cyclization of 3, which to our knowledge has not been previously reported, proceeds predominantly in a 6-*endo* fashion as shown in Scheme 2 to give (3-butenyl)cyclohexane[10] as the major product (70%) along with 26% of 2-methylspiro[4.4]nonane derived from two sequential 5-*exo* closures. The observed preference for an initial 6-*endo* cyclization of the radical (5) generated from 3 was not unexpected and the approximately 2.7:1 ratio of 6-*endo*:5-*exo* closure is characteristic of product mixtures obtained from isomerization of 5-substituted-5-hexenyl radicals such as 5.[5]



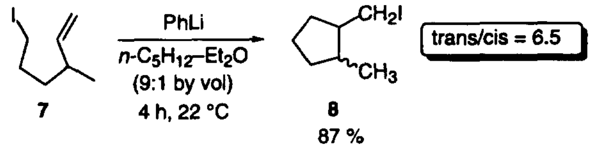
Scheme 2.

Given these preliminaries, it is clear that analysis of the product mixture generated from reaction of **3** with PhLi is indicative of mechanism: a purely anionic process involving **4** should result in two sequential 5-*exo* cyclizations to give spirocyclic product while a radical-chain process involving the 5-(3-butenyl)-5-hexenyl radical (**5**) should give an approximately 2.7:1 mixture of products derived from 6-*endo* and 5-*exo* cyclization, respectively. In the event, treatment of an approximately 0.1 M solution of **3** in dry and deoxygenated *n*-pentane:MTBE (9:1 by volume) with 1.1 molar equivalent of both PhLi and TMEDA for 12 h at room temperature afforded the mixture of products illustrated below; yields were determined by GC analysis of the crude reaction mixture using internal standards and correction for detector response.[11] Although the reaction may be run using less than stoichiometric quantities of PhLi, the mechanistic study was conducted using a full molar equivalent of the reagent so as to increase the overall rate and completely consume the iodide.

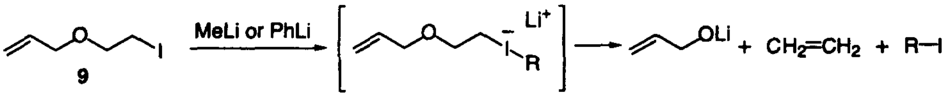
Cursory inspection of the results reveals that 2-iodomethylspiro[4.4]nonane (**6**)[11] and 2-methylspiro[4.4]nonane are minor components of the product mixture (viz., 19% of the total). Indeed, the bulk of the reaction mixture (viz., 50%) consists of cyclohexyl-containing material. Moreover, the ratio of cyclohexyl to spirocyclic products (i.e. 50:19=2.6) is virtually identical to that expected for a mechanism involving the intermediacy of the 5-(3-butenyl)-5-hexenyl radical (**5**). It is noteworthy that there is no evidence of dehydrohalogenation of the substrate upon prolonged reaction of **3** with the basic organolithium: it would appear that the PhLi serves to cleanly initiate radical-mediated chemistry.



Although the reaction of PhLi with **3** is not preparatively useful, the PhLi-initiated cycloisomerization of 6-iodo-3-methyl-1-hexene (**7**) to give the known[2] 2-iodomethyl-1-methylcyclopentanes (*trans*-**8** and *cis*-**8**) is more representative of the scope of the methodology. As shown below, allowing a solution of **7** in *n*-pentane:diethyl ether (9:1 by volume) to stand in the presence of one equivalent of PhLi for 4 h at room temperature affords **8** in 87% yield. The isomeric composition of the product (**8**, *trans/cis*=6.5) is consistent with a PhLi-initiated radical-mediated atom transfer chain reaction since the organolithium derived from **7** is known to cyclize with a much higher *trans*-selectivity (*trans/cis*=11.7)[12] than does the analogous 4-methyl-5-hexenyl radical (*trans/cis* ~5 at 80°C).[13]



The results described above indicate that the PhLi-initiated cycloisomerization of olefinic primary alkyl iodides proceeds via the radical-mediated atom transfer process previously implicated in the isomerization of secondary and tertiary substrates.[2] Our initial report that the PhLi-initiated transformation of 6-iodo-1-hexene to (iodomethyl)cyclopentane involved a lithium–iodine exchange mediated mechanism was predicated on the observation that 2-(allyloxy)ethyl iodide (**9**) afforded ethylene and the lithium salt of allyl alcohol when treated with MeLi: this observation was interpreted in terms of fragmentation of a discrete (3-oxa-5-hexenyl)lithium produced via a lithium–iodine exchange.[1] More recent studies suggest that such fragmentation may well be the result of rapid expulsion of the alloxy anion from an electron-rich 10-I-2 ate-complex generated from **9** prior to completion of the exchange reaction.[2] Indeed, the ability of PhLi to initiate radical-mediated chemistry has been attributed to homolytic cleavage of just such an ate-complex.[2]



Acknowledgements

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7. In connection with the preparation of **3**, it might be noted that methylenation of the base-sensitive methyl 5-oxo-8-nonenoate as indicated in Scheme 1, using the protocol of Takai et al.,[8] was found to be far superior to the classical Wittig methodology previously used for the preparation of this dienyl ester.[6]
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11. In addition to the products depicted, which were identified by comparison of their retention times and mass spectra with those of authentic samples, the reaction mixture also contained quantities of unidentified $C_{20}H_{34}$ hydrocarbons. An authentic sample of 2-iodomethylspiro[4.4]nonane (**6**) was prepared by addition of iodine to the spirocyclic organolithium generated upon tandem cyclization of dienyl alkyllithium **4** (Scheme 1). **6**: ^1H NMR ($CDCl_3$): δ 1.11 (a portion of ABX,

J_{AB}=12.62 Hz, J_{AX}=9.30 Hz, 1H), 1.26–1.35 (m, 1H), 1.38–1.60 (m, 11H), 1.81 (ABX, J_{AB}=12.62 Hz, J_{BX}=7.64 Hz, 1H), 1.85–1.92 (m, 1H), 3.19 (d, J=7.01 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 14.77, 24.41, 24.44, 32.66, 38.71, 39.55, 39.76, 42.01, 46.72, 51.16; HRMS calcd for $C_{10}H_{17}I$: 264.0375; found: 264.0370.

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