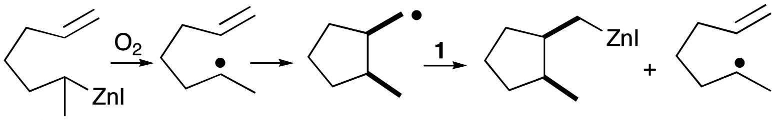
Article

Intramolecular Carbozincation of Unactivated Alkenes Occurs through a Zinc Radical Transfer Mechanism

Theodore Cohen, Heather Gibney, Roman Ivanov, Edmund A.-H. Yeh, Ilan Marek, and Dennis P. Curran

J. Am. Chem. Soc., **2007**, 129 (49), 15405-15409 • DOI: 10.1021/ja076554k



1

Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

J|A|C|S
ARTICLES
Published on Web 11/08/2007

Intramolecular Carbozincation of Unactivated Alkenes Occurs through a Zinc Radical Transfer Mechanism

Theodore Cohen,*,† Heather Gibney,† Roman Ivanov,† Edmund A.-H. Yeh,† Ilan Marek,‡ and Dennis P. Curran*,†

Contribution from the Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, and the Mallat Family Laboratory of Organic Chemistry, Schulich Faculty of Chemistry, Institute of Catalysis Science and Technology and the Lise Meitner-Minerva Center for Computational Quantum Chemistry, Technion-Israel Institute of Technology, Technion City, Haifa 32000, Israel

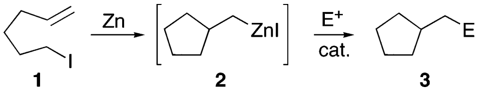
Received August 30, 2007; E-mail: cohen@pitt.edu; curran@pitt.edu

Abstract: The cyclizations of a number of terminally unsaturated alkenyl zinc iodides to cyclopentylmethylzinc iodides, formerly believed to be nonradical in nature, have been revealed as radical chain cyclizations initiated by adventitious oxygen. Five cases are presented in which the published carbozincation *cis/trans* selectivities are essentially the same as those found for the cyclizations of the unsaturated alkyl iodide precursors of the alkylzinc iodides by the iodine atom transfer method at approximately the same temperatures. In addition, it has been found that one of the organozinc cyclizations does not occur in a system in which oxygen has been rigorously excluded. The combined findings strongly suggest that these organozinc cyclizations occur by a zinc radical transfer mechanism rather than by a conventional carbometallation that is thought to occur with the analogous organolithium and organomagnesium cyclizations.

Introduction

Organozinc chemistry has enjoyed an explosion of interest, especially among synthetic chemists, largely because organozinc reagents tend to be far less reactive than the corresponding organolithium and Grignard reagents.[1] Thus, it is possible to generate organozinc reagents bearing functional groups such as esters and nitriles and, by the use of metallic or organic catalysts or promoters, to induce reactions of the functionalized organozincs with various electrophiles.

In 1993, remarkable reports by Marek, Normant, and coworkers in France described intramolecular addition or alkylzinc iodides to unactivated alkenes **1** in the absence of catalysts or additives to produce cyclopentylmethylzincs **2** (eq 1). The reactions were usually conducted at 20 °C and quenched with electrophiles to produce **3** (E = H, I, etc.).[2,3]



(1)

In addition to the surprising ability of the alkylzincs to add to unactivated alkenes despite their inability to add to carbonyl compounds without catalysis, there were two other observations that have now become significant in view of information that has been published since these earlier papers appeared. (1) Of the several stereochemical studies in the original papers of the French group, one in particular now appears startling in view of recent work from the Pittsburgh laboratory. Cyclization of the secondary alkyl iodide **4** at 20 °C in the presence of activated zinc in ether yielded cis iodide **6c** in a 4:1 ratio with its trans isomer after iodination of the intermediate cyclized organozinc **5** (Scheme 1). In contrast, cyclization of the corresponding organolithium, albeit in THF at −78 °C, gave overwhelmingly the trans product (>40:1 trans:cis)[4] and the corresponding Grignard reagent also gave predominantly the trans isomer (4:1 trans:cis) but at the far higher reflux temperature of THF.[5]

(2) Although the primary organozinc **9** did not cyclize even at 80 °C (eq 2), the organozinc derived from the secondary analogue **10** cyclized at room temperature (eq 3). This finding is significant because cyclizations of the more reactive organolithiums are notoriously foiled by the presence of an alkyl

---

† University of Pittsburgh.

‡ Technion-Israel Institute of Technology.

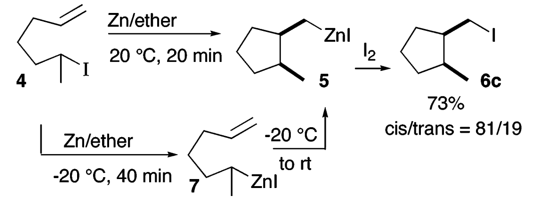
(1) (a) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC Press: Boca Raton, 1996. (b) Knochel, P.; Perea, J. J. A.; Jones, P. *Tetrahedron* **1998**, *54*, 8275−8319. (c) Knochel, P.; Millot, N.; Rodrigues, A. L. *Org. React.* **2001**, *58*, 417−731. (d) Nakamura, E. In *Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; John Wiley and Sons: New York, 2002; pp 599−664. (e) Knochel, P.; Calaza, M. I.; Hupe, E., In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; pp 619−670. (f) Knochel, P.; Leuser, H.; Gong, L.-Z.; Perrone, S.; Kneisel, F. F. In *The Chemistry of Organozinc Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, 2007; Chapter 8.

(2) (a) Meyer, C.; Marek, I.; Courtemanche, G.; Normant, J.-F. *Synlett* **1993**, 266−268. (b) Meyer, C.; Marek, I.; Courtemanche, G.; Normant, J.-F. *Tetrahedron Lett.* **1993**, *34*, 6053−56. (c) Full paper: Meyer, C.; Marek, I.; Courtemanche, G.; Normant, J. F. *Tetrahedron* **1994**, *50*, 11665−92.

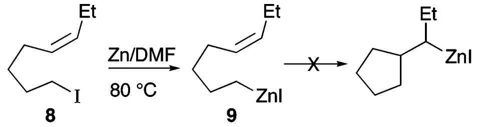
(3) Comprehensive reviews of carbozincation of alkenes and alkynes: (a) Lorthiois, E.; Meyer, C. In *The Chemistry of Organozinc Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, 2006; Chapter 19. (b) Marek, I.; Normant, J. F. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; pp 271−337.

10.1021/ja076554k CCC: $37.00 © 2007 American Chemical Society

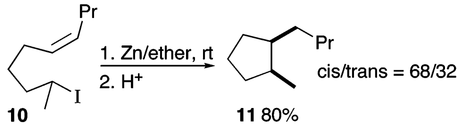
Scheme 1



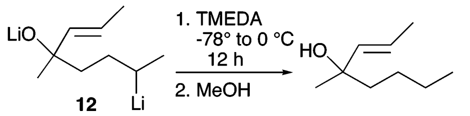
group at the terminus of the alkene.[6−8] In a very recent paper, it was reported that **12** failed to cyclize (eq 4) even though three features were present that greatly favor such cyclizations, its secondary nature, the presence of an allylic oxyanionic group, and the presence of tetramethylethylenediamine (TMEDA) which accelerates such cyclizations.[4a]



(2)



(3)

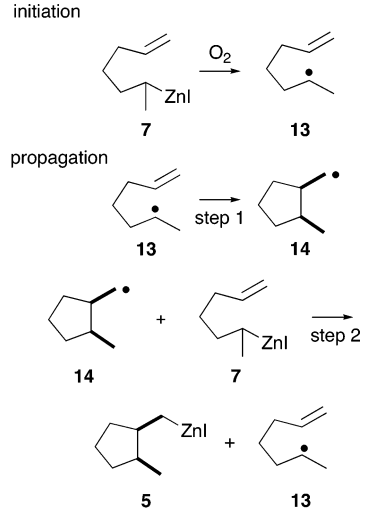


(4)

These unusual features could be rationalized if the zinc carbometallations were radical chain processes. However, the authors of the 1993 papers convincingly demonstrated in several cases that the cyclizations did not occur during the reaction of the precursor alkyl iodides with zinc, a process believed to occur via radicals.[9,10] In these cases they were able to generate the alkylzincs at a low temperature and to subsequently observe the cyclization at a higher temperature.[2]

Nevertheless, based on reports appearing after 1993, it is now possible to conceive of a radical mechanism, proceeding from the organozincs themselves, for these intramolecular carbozincations that were previously believed to occur by an ionic or polar mechanism. In recent years it has become evident that dialkylzincs can donate an electron to O_2 and other oxidizing agents generating alkyl radicals; these alkyl radicals, or radicals generated when the alkyl radicals remove iodine atoms from isopropyl or *tert*-butyl iodide, can initiate typical radical chain reactions.[11,12]

Scheme 2



All of this suggests the mechanism in Scheme 2 for the reaction shown in Scheme 1. Oxidation of alkylzinc **7** to radical **13** initiates a chain whose propagation steps are radical cyclization (**13** → **14**) and group transfer of ZnI (**14** + **7** → **5** + **13**).[13]

This mechanism is analogous to iodine radical transfer cyclization and related reactions,[14] with the twist that the homolytic substitution (step 2) occurs at a halozinc group rather

---

(4) (a) Deng, K.; Bensari-Bouguerra, A.; Whetstone, J.; Cohen, T. *J. Org. Chem.* **2006**, *71*, 2360−2372; in this paper, evidence was presented that the alkyllithium rather than a radical precursor, generated during reductive lithiation of the corresponding alkyl phenyl sulfide, is the entity that cyclizes. In a recent report, computational studies have revealed that the main contributor to the stereochemistry of this ionic cyclization is apparent steric hindrance to production of the cis product afforded by a single molecule of solvation of the lithium ion in **4** (I = Li): (b) Liu, H.; Deng, K.; Cohen, T.; Jordan, K. D. *Org. Lett*. **2007**, *9*, 1911−1914. (c) The very largely trans product is also consistent with the cyclization of **4** when it was added to a solution of *n*-pentane/diethyl ether containing *t*-BuLi but is at odds with the cis preference when the cyclization was performed using the reverse order of addition: Bailey, W. F.; Nurmi, T. T.; Patricia, J. J.; Wang, W. *J. Am. Chem. Soc.* **1987**, *109*, 2442−48 and Ashby, E. C.; Pham, T. N. *J. Org. Chem.* **1987**, *52*, 1291−1300. The high trans:cis ratio in the presence of a large excess of *t*-BuLi was attributed by Ashby to the cyclization of the -ate complex formed between **4** and *t*-BuLi, but in view of the largely trans stereochemistry of the product formed by cyclization of the anion generated by reductive lithiation, it now seems likely that the cyclization of a secondary alkyllithium is involved.

(5) Richey, J. H. G.; Rees, T. C. *Tetrahedron Lett.* **1966**, *7*, 4297−4301.

(6) 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.

(7) Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.* **1988**, *53*, 1336−1338.

(8) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K. V. *J. Am. Chem. Soc.* **1992**, *114*, 8053−8060.

(9) Guijarro, A.; Rosenberg, D. M.; Rieke, R. D. *J. Am. Chem. Soc.* **1999**, *121*, 4155−4167.

(10) It is well established that radicals produced by the reduction of alkyl iodides by zinc metal are capable of efficient intramolecular capture by certain alkenes and alkynes. This mode of cyclization was observed in cyclizations of hexynyl iodides to vinyl radicals: (a) Crandall, J. K.; Ayers, T. A. *Organometallics* **1992**, *11*, 473−477. A similar mode of cyclization is believed to occur in an iodoalkane bearing a conjugated unsaturated ester to form a cyclopropylmethyl enolate radical that is apparently believed to be reduced to a zinc enolate by zinc: (b) Sakuma, D.; Togo, H. *Tetrahedron* **2005**, *61*, 10138−10145. An intermolecular example of this type of reaction has also been reported: (c) Yamamoto, Y.; Nakano, S.; Maekawa, H.; Nishiguchi, I. *Org. Lett.* **2004**, *6*, 799−80.

(11) Review of dialkylzincs in radical reactions: Bazin, S.; Feray, L.; Bertrand, M. P. *Chimia* **2006**, *60*, 260−265.

(12) (a) Wissing, E.; Vanderlinden, S.; Rijnberg, E.; Boersma, J.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. *Organometallics* **1994**, *13*, 2602−2608. (b) Ryu, I.; Araki, F.; Minakata, S.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 6335−6336. (c) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *Synlett* **1999**, 1148−1150. (d) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *J. Org. Chem.* **1999**, *64*, 9189−9193. (e) Bertrand, M. P.; Coantic, S.; Feray, L.; Nouguier, R.; Perfetti, P. *Tetrahedron* **2000**, *56*, 3951−396. (f) van der Deen, H.; Kellogg, R. M.; Feringa, B. L. *Org. Lett.* **2000**, *2*, 1593−1595. (g) Bazin, S.; Feray, L.; Siri, D.; Naubron, J. V.; Bertrand, M. P. *Chem. Commun.* **2002**, 2506−2507. (h) Denes, F.; Chemla, F.; Normant, J. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 4043−4046. (i) Yamamoto, Y.; Yamada, K.; Tomioka, K. *Tetrahedron Lett.* **2004**, *45*, 795−797. (j) Yamada, K.; Yamamoto, Y.; Maekawa, M.; Chen, J. B.; Tomioka, K. *Tetrahedron Lett.* **2004**, *45*, 6595−6597. (k) Cozzi, P. G. *Adv. Synth. Catal.* **2006**, *348*, 2075−2079. (l) Denes, F.; Cutri, S.; PerezLuna, A.; Chemla, F. *Chem. Eur. J.* **2006**, *12*, 6506−6513. (m) Lewinski, J.; Sliwinski, W.; Dranka, M.; Justyniak, I.; Lipkowski, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4826−4829. (n) Bazin, S.; Feray, L.; Vanthuyne, N.; Siri, D.; Bertrand, M. P. *Tetrahedron* **2007**, *63*, 77−85.

(13) Hoffmann has recently reported that magnesium -ate complexes undergo a radical chain process when subjected to certain additives, apparently due to traces of oxygen introduced at the same time: Hoffmann, R. W.; Brönstrup, M.; Müller, M. *Org. Lett.* **2003**, *5*, 313−316.

(14) (a) Byers, J. H. In *Radicals in Organic Synthesis*, 1st ed.; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, pp 72−89. (b) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1989**, *111*, 6265−6276. (c) For an excellent discussion of the behavior of radical **13**, see: Bailey, W. F.; Carson, M. W. *J. Org. Chem.* **1998**, *63*, 9960−9967.

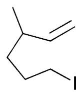
than an iodine atom. To our knowledge, the oxidation of alkyl zinc halides to radicals has not been reported, but its occurrence would not be surprising; alternatively, a Schlenk-type equilibrium might occur in which **7** could be in equilibrium with a small amount of dialkylzinc and ZnI_2.[15] Likewise, homolytic substitutions at halozinc by carbon radicals are not known, but Chemla has recently postulated a homolytic substitution in a conjugate addition of dialkylzincs.[12h,l,16]

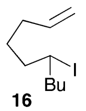
In the face of these developments, we decided that the time was ripe to reinvestigate the mechanism of the intramolecular carbozincation reaction of unactivated alkenes and in particular to determine if the cyclizations are radical in character. If so, then the work might have important synthetic as well as mechanistic implications for organozinc chemistry.

We have examined two aspects of the cyclizations reported by Marek, Normant, et al. that should provide information concerning the radical or ionic character of the zinc-induced cyclizations. (1) Their work is rich in stereochemical information about the cyclizations, and we have determined whether several of the stereochemical results that they report are compatible with radical cyclizations at the same temperatures. (2) If the mechanism put forth in Scheme 2 operates, then telltale mechanistic evidence should be revealed by studying the sensitivity of the rate of cyclization to the presence of oxygen.

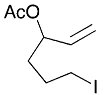
Results and Discussion

It was already known that the radical **13** cyclizes mainly to the cis radical **14**.[17] However, the published ratios were for cyclizations at temperatures other than ambient. We performed the atom transfer cyclization of the iodide **4** at ambient temperature, so that the ratio could be compared with that reported for the organozinc **7**, and at a few other temperatures, so that comparisons with some of the published data could be made. In addition, the radical cyclizations of several other iodoalkenes, **15**−**18**, whose cyclizations with zinc had been reported,[2] were studied in the same way.

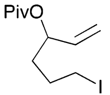

15



16



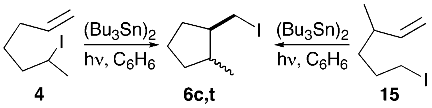
17



18

Briefly, a sample of the iodide (**4** or **15**−**18**) in benzene was warmed or cooled to the indicated temperature,[18] hexabutylditin (10 mol %) was added, and the reaction mixture was irradiated with a sunlamp. Percent conversion and stereoselectivity (indicated always as *cis/trans*) in product formation were assessed by GC or ^{1}H NMR spectroscopy. The cyclized products (**6**, **19**−**21**) were identified by comparison with authentic samples. Yields are not indicated because products generally were not isolated, but since no other products were detected by GC or ^{1}H NMR analysis, they are clearly high. Full details, including plots of the temperature dependence of the radical cyclizations, are provided in the thesis of H. Gibney.[19]

Table 1. Temperature-dependent Stereoselectivities of Alkyl-Substituted Hexenyl Radicals from **4** and **15**

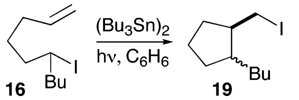


4 **6c,t** **15**

entry	iodide	temp °C	time min	% conv.	*cis/trans* **6**
1	**4**	5	90	>99	83/17
2	**4**	15	75	>99	83/17
3	**4**	25	45	>99	81/19
4	**4**	25	45	>99	81/19
5[a]	**4**	25	45	>99	81/19
6	**4**	35	45	>99	79/21
7	**4**	80	90	>99	73/27
8	**15**	5	270	>99	7/93
9	**15**	15	210	>99	8/92
10	**15**	25	150	>99	10/90
11	**15**	35	120	95	12/88
12	**15**	80	240	50	22/78

[a] This experiment was conducted in Et_2O.

Table 2. Temperature-Dependent Stereoselectivities of the Alkyl-Substituted Hexenyl Radical from **16**



16 **19**

entry	iodide	temp °C	time min	% conv.	*cis/trans* **19**
1	**15**	5	20	>99	76/24
2	**15**	20	150	>99	75/25
3	**15**	80	180	>99	70/30

Alkyl iodides **4** and **15** give cyclization products **6c,t** of the same structure but in very different stereochemical ratios, and the results for both are displayed in Table 1. It was already known[20] that the radical from **15** cyclized at elevated temperatures to yield mainly trans product, just as did the organozinc derived from **15**.

The *cis/trans* ratio, 2.7, of the products from **4** at 80 °C (entry 7) compares reasonably well with the reported values in the literature that were determined at elevated temperatures in saturated hydrocarbon solvents, 2.7 at 74 °C,[17a] 2.3 at 65 °C,[17c] and 2.7 at 90 °C.[17d] The *cis/trans* ratio, 0.28, of the products from **15** at 80 °C compares well with the reported value[20] at the same temperature in the literature. The stereochemical selectivity upon cyclization of both **4** and **15** decreases with increasing temperature; the temperature sensitivity is minimal for **4** and moderate for **15**.

The results for atom transfer cyclization of **16**, a higher homologue of **4**, are shown in Table 2. Products **19c,t** are cleanly produced. As expected, the cis isomer is favored, and the selectivities are slightly lower than those with methyl analogue **4**.

---

(15) (a) Dessy, R. E.; Coe, G. R. *J. Org. Chem.* **1963**, *28*, 3592−3593. (b) Abraham, M. H.; Rolfe, P. H. *J. Organomet. Chem.* **1967**, *7*, 35−43 and references therein. (c) Charette, A. B.; Marcoux, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 4539−4549 and references therein.

(16) It has long been known that oxygen- and nitrogen-centered radicals are capable of executing an S_H2 reaction on a zinc or other metallic group of an organometallic to release an organic radical: Davies, A. G.; Roberts, B. P. *Acc. Chem. Res.* **1972**, *5*, 387−392.

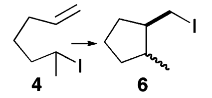
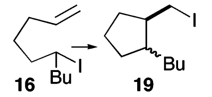
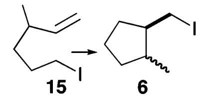
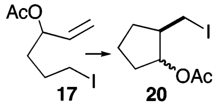
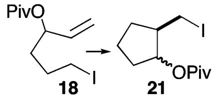
(17) (a) Brace, N. O. *J. Org. Chem.* **1967**, *32*, 2711−2718. (b) Beckwith, A. L. J.; Blair, I.; Phillipou, G. *Tetrahedron Lett.* **1974**, *15*, 2251−2254. (c) Beckwith, A. L. J.; Blair, I.; Phillipou, G. *J. Am. Chem. Soc.* **1974**, *96*, 1613−1614. (d) Lusztyk, J.; Maillard, B.; Deycard, S.; Lindsay, D. A.; Ingold, K. U. *J. Org. Chem.* **1987**, *52*, 3509−3514.

(18) Standard water or oil baths equipped with thermometers were used, so the temperature could have varied several degrees above or below the indicated temperature during the course of the experiments.

(19) Gibney, H. M.S. Thesis, University of Pittsburgh, 2006. The thesis is archived and openly available from the University of Pittsburgh Library Electronic Thesis Deposition (ETD) site at http://etd.library.pitt.edu/ETD/available/etd-08042006−085451/.

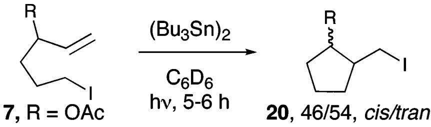
(20) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545−556.

Table 3. Comparison of Stereoselectivities in Carbozincation and Radical Reactions[a]

conversion	method	temp (°C)	*cis/trans*
 **4** **6**	zinc radical	20 25	81/19 81/19
 **16** **19**	zinc radical	20 20	73/27 76/24
 **15** **6**	zinc radical	20 25	7/93 10/90
 **17** **20**	zinc radical	25 20	42/58 45/55
 **18** **21**	zinc radical	20 25	45/55 42/58

[a] Radical stereoselectivities from this work; zinc stereoselectivities from ref 2.

The substrates **17** and **18**, precursors of 4-acyloxyl-5-hexenyl radicals, were chosen because the stereoselectivities in carbozincation were rationalized by complexation of the acyloxy group in the hexenylzinc intermediate; such complexation cannot occur in the radical cyclization. The cyclization conditions were the same as above, but only one temperature, 25 °C, was used (eq 5). The selectivities proved to be lower than in the other cases, slightly favoring the trans products.



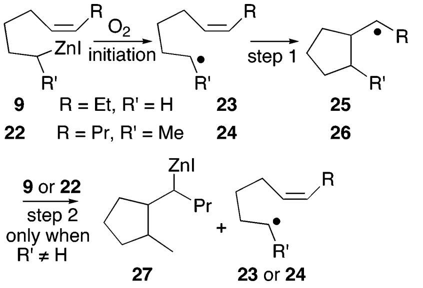
17, R = OAc
18, R = OPiv
20, 46/54, *cis/trans*
21, 48/52, *cis/trans*
(5)

The measured stereoselectivities in authentic radical cyclizations are compared with reported stereoselectivities in carbozincation reactions with Rieke zinc in ether[2] in Table 3. In each of the five cases, the radical and zinc stereoselectivities are in reasonable agreement, provided that comparisons are made at comparable temperatures. The carbozincation reactions were conducted in ether, whereas the radical cyclizations were conducted in benzene, but we assume that radical cyclizations in ether will give comparable stereoselectivities. To support this assumption, one cyclization was conducted in ether (Table 1, entry 5), and the selectivity was the same as that in benzene (entry 4).

Such a broad agreement in levels of stereoselectivity across different substituent locations with both complexing and noncomplexing substituents strongly suggests that the carbozincation reactions must involve radical cyclization.[21]

The radical chain mechanism that we suggest in Scheme 2 requires initiation, and traces of oxygen are likely to be responsible. In order to determine the sensitivity of the cyclization to oxygen, two experiments were performed on the reaction shown in eq 1. In both experiments, 6-iodo-1-hexene **1** was dissolved in diethyl ether that had been dried and distilled from sodium/benzophenone under a dry argon atmosphere and subjected at ambient temperature to the action of Riecke zinc for 24 h. Then the reactions were quenched with iodine, as in the original cyclizations.[2] The first experiment, performed under an ambient atmosphere, provided an inseparable mixture of the cyclization product **3** (E = I; 74% yield) and the starting material **1** (7% yield). Thus, the result is similar to that reported.[2] In the second experiment, the ether solvent was rigorously degassed by ultrasonication, and the atmosphere was argon. In this case, the iodination produced 85% of starting material **1**, with no trace of cyclized product **3** by NMR analysis.

Scheme 3



Both the excellent correspondence in the *cis/trans* ratios obtained in the zinc-induced and atom transfer radical cyclizations of **4** and **15**−**18** at comparable temperatures as displayed in Table 3 and the sensitivity of the zinc-induced cyclization of **1** to the presence of oxygen unequivocally show that the organozinc iodides cyclize by a radical rather than a polar mechanism. This mechanism is also consistent with the interesting cyclization of **22** (see Scheme 3), the secondary alkylzinc derived from **10**, in light of the failure of the apparently analogous primary alkylzinc **9** to cyclize. In the first propagation step after the oxidation of **22**, the putative secondary radical **24** cyclizes to a secondary radical **26**, a favorable (exothermic) step because a π bond is converted to a σ bond. The halozinc group transfer (step 2) is virtually thermoneutral because a secondary radical is converted to another secondary radical. On the other hand, in the case of **9**, while the cyclization step 1 is again favorable, step 2 is unfavorable because it would involve the conversion of a secondary radical **25** into a primary radical **23**. Presumably, the failure of this endothermic step interrupts the chain and prevents the cyclization of **9**.

As discussed above, in the original reports of these cyclizations,[2] it was convincingly demonstrated that the radical generated by the reaction of Zn with the alkyl iodide became reduced to an organozinc rather than adding to the internal alkene to produce a cyclized alkyl radical. However, there are reported examples in which this first formed radical adds to internal unsaturation more readily than it is reduced.[10] These cases differ from the cyclizations of the French group[2] in that the latter workers used highly reactive Riecke zinc that is more capable of reducing the first formed alkyl radical before it can cyclize than are other types of zinc powder. Furthermore, in one of these cases,[10b] the cyclized radical is a delocalized enolate radical that presumably forms more rapidly than the simple alkyl radical does in the work of the French group. Rieke[9] attributed

---

(21) Garst was apparently the first to use *cis/trans* ratios of cyclization products to differentiate ionic and radical mechanisms for metal-induced cyclizations in that case of the bromo and chloro analogues of **4** when subjected to sodium in various forms: Garst, J. F.; Hines, J. B., Jr. *J. Am. Chem. Soc.* **1984**, *106*, 6443−6445.

the minor amount of cyclization observed when the bromo analogue of **1** was treated with activated zinc to the radical directly formed when the alkyl bromide was reduced by zinc but in view of the results reported here one cannot rule out cyclization of the alkylzinc bromide induced by traces of oxygen.

Conclusions

Recent reports that dialkylzincs, when exposed to oxygen, generate alkyl radicals capable of initiating chain reactions, have opened the door to a mechanistic reinterpretation of the intramolecular addition or alkylzinc iodides to unactivated alkenes in the absence of catalysts or additives.[2] Convincing evidence that these cyclizations of unsaturated alkylzinc iodides to form cyclopentylmethylzinc iodides occur by a radical chain mechanism involving the homolytic transfer of a zinc group include the following. The stereoselectivities in five of the published cases of the organozinc cyclizations are comparable to those found for the cyclizations of the unsaturated alkyl iodide precursors of the alkylzinc iodides by the iodine atom transfer method at comparable temperatures. Furthermore, the alkylzinc cyclizations are completely inhibited when oxygen is rigorously excluded. It thus appears clear that most and probably all of these organozinc cyclizations are radical chain reactions initiated by traces of oxygen. While there are numerous recent examples of dialkylzincs producing radicals upon oxidation,[11,12] these are the first examples to our knowledge in which monoalkylzinc compounds are oxidized to alkyl radicals. Such cyclizations differ in stereochemistry, in some cases in dramatic fashion, from the corresponding cyclizations of alkyllithiums and alkylmagnesium compounds. Another important and yet to be synthetically exploited difference is the ability of certain alkylzincs to cyclize on to a 1,2-disubstituted alkene (e.g., eq 3); such cyclizations are unknown in the cases of alkyllithiums and Grignard reagents.

In the examples studied, the unsaturated alkylzincs are produced by reaction of zinc metal with the corresponding alkyl iodides (e.g., **4**). It is remarkable that these alkyl iodides, in the presence of Zn, give very satisfactory yields of cyclic product (e.g., **6c**) after electrophile quenching despite a complex series of transformations, occurring in one pot, including several radical and organometallic intermediates. These transformations include formation of an alkyl radical upon Zn reduction,[9,10] reduction of this radical, probably on the surface of the metal, to an alkylzinc **7**, oxidation of the latter to an alkyl radical **13** that is identical to the first one except for its environment, intramolecular addition of this radical to the alkene, zinc group transfer to the resulting cyclopentylmethyl radical **14** from the first-formed organozinc **7** to generate the cyclopentylmethylzincs iodide **5**, and finally capture with an electrophile, either directly as with iodine or after cuprate formation.

While the scope and limitations of this new cyclization via oxygen-induced radical carbozincation, starting from an unsaturated alkylzinc iodide, remains to be explored, it is complementary to another method of cyclization of various 6-iodo- and 6-bromo-1-hexenes in the presence of diethylzinc and a Ni or Pd catalyst, reactions that also proceed via radical intermediates and result in the formation of cyclopentylmethylzinc halides.[22] Future work will have to reveal the strengths and weaknesses of each. One advantage of the oxygen-induced cyclization is that it is presumably applicable to organozincs prepared in ways other than Zn−halogen exchange; the metal-catalyzed radical cyclization is thought not to proceed through an alkylzinc intermediate.

Acknowledgment. This research was supported by Grant 2005128 from the United States-Israel Binational Science Foundation to T.C. and I.M. and Grant CHE-0135520 from the National Science Foundation to D.P.C.

Supporting Information Available: Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

JA076554K

---

(22) (a) Vaupel, A.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 5743−5753. (b) Stadtmüller, H.; Vaupel, A.; Tucker, C. E.; Stüdemann, T.; Knochel, P. *Chem. Eur. J.* **1996**, *2*, 1204−1220. (c) Stadtmüller, H.; Lentz, R.; Tucker, C. E.; Stüdemann, T.; Dorner, W.; Knochel, P. *J. Am. Chem. Soc.* **1993**, *115*, 7027−7028. (d) Stadtmüller, H.; Tucker, C. E.; Vaupel, A.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 7911−7914.