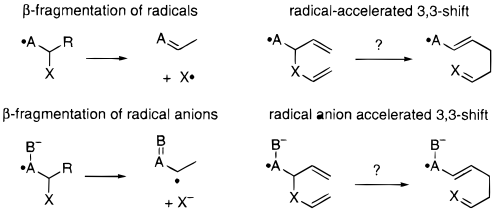
Does the Facile Reductive Rearrangement of 2-Allyloxycyclohexenone with Bu_3SnH Occur by a Radical-Accelerated Claisen Rearrangement or a Stannyloxy-Accelerated Claisen Rearrangement?

Dennis P. Curran* and Yoshinori Nishii

Department of Chemistry, University of Pittsburgh Pittsburgh, Pennsylvania 15260

Received May 19, 1999

The synthetic usefulness of 3,3-sigmatropic shifts is dramatically expanded by accelerating effects of certain substituents, and these substantial accelerating effects have challenged theory to provide satisfactory explanations and predictions.[1] Anion-accelerated 3,3-sigmatropic shifts are especially prominent, but cation-accelerated versions are also known. In contrast, we are aware of no documented radical-accelerated 3,3-sigmatropic shifts.[2] This is surprising at first glance since the energetic price of bond-breaking accounts for a significant part of the activation energy of a 3,3-sigmatropic rearrangement and since radical and radical anion substituents are well known to weaken adjacent bonds.[3] Indeed, β-fragmentation is one of the most fundamental reactions of radicals and radical anions (see eq 1).

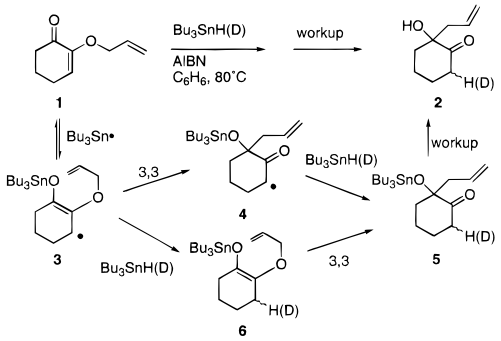


(1)

Very significant accelerations would be needed to observe a sigmatropic shift within the relatively short lifetime of a transient radical. Radical anions might hold better promise since they can persist for longer times. In this regard, we were most intrigued by a recent report by Enholm and co-workers of a "ketyl-radical anion triggered 3,3-sigmatropic shift".[4] In a key example, these workers observed that reduction of 2-allyloxycyclohexenone (**1**) with tributyltin hydride at high concentration in benzene at 80 °C with AIBN provided 2-allyl-2-hydroxylcyclohexanone (**2**) in 54% yield (Scheme 1). The generality of the reaction was demonstrated by a number of diverse examples.

Enholm and co-workers proposed the mechanism shown in the upper path of Scheme 1 to account for the facile reductive rearrangement of **1** to **2**. Addition of a tin radical to **1** provides the "ketyl radical-anion" **3**, which undergoes very rapid rearrangement to α-keto radical **4**. Abstraction of hydrogen from Bu_3SnH by **4** provides the product tin ether **5**, which hydrolyzes to the alcohol **2** (this pathway is hereafter called the "radical-Claisen mechanism"). The rearrangement of **3** to **4** is the key step of Enholm's mechanism, and this must be exceptionally rapid since the lifetime of radical **3** must be short at the high tin hydride

Scheme 1



concentrations employed.[5] An alternative mechanism for the conversion of **3** to **5** reverses the rearrangement and hydrogen-transfer steps. Reduction of **3** provides α-allyloxy stannyl enol ether **6**, which undergoes Claisen rearrangement to give **5**. In a pioneering paper in 1985, Koreeda and Luengo generated enol ethers, enol silyl ethers, and enolate intermediates related to **6** by deprotonation and showed that they underwent surprisingly facile Claisen rearrangements to products related to **5** (this route is hereafter called the "stannyloxy-Claisen mechanism").[6]

Enholm and co-workers considered but dismissed the stannyloxy-Claisen mechanism on the basis of two lines of evidence: (1) they were never able to observe intermediates related to **6** (although their formation is well precedented by Enholm's prior work on enone reductions[7]) and (2) competitive experiments suggested that the allyloxy compound **1** was more reactive than a saturated propyloxy analog. The negative evidence along line 1 is unsatisfying since **6** might have rearranged faster than is was formed, and we felt that the competitive experments along line 2 were not optimally designed.[8] If Enholm's radical-Claisen mechanism is correct, then this work could be a seminal advance in radical- and radical-anion-accelerated sigmatropic shifts. We therefore designed a series of experiments that would differentate the two mechanisms. We report herein the results of these experiments, which strongly support the stannyloxy-Claisen (Koreeda) mechansim.

Stereochemical labeling experiments should be useful in differentiating the two mechanisms. For example, a reaction of **1** conducted with Bu_3SnD can give two stereoisomers of **5**. In the radical-Claisen mechanism, stereoselection is determined in the radical reduction step[9] (**4** → **5**), while stereoselection occurs in the 3,3-sigmatropic rearrangement (**6** → **5**) in the stannyloxy-Claisen mechansim. Since H and D are nearly identical in size, no stereoselection is expected in the stannyloxy-Claisen mechanism, while the level of stereoselection in the radical-Claisen mechansim is, a priori, unclear (but could only be 1/1 fortuitously).

We first conducted the reduction of **1** under Enholm's conditions with Bu_3SnD to provide alcohol **2** (48%). This was then silylated under standard conditions to provide silyl ether **7** as a 1/1 mixture of α/β stereoisomers (eq 2). To assess the stereoselectivity of stannyl ether radical **4**, we initially generated

(1) Bronson, J. J.; Danheiser, R. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 999. Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 827. Gajewski, J. J. *Acc. Chem. Res.* 1997, *30*, 219.

(2) However, radicals and radical ions are frequently postulated as intermediates (as opposed to substituents). See, for example: Bauld, N. L. In *Advances in Electron-Transfer Chemistry*; Mariano, P. S., Ed.; Jai Press Inc.: Greenwich, CT, 1992; Vol. 2, p 1.

(3) (a) Zhang, X. M. *J. Org. Chem.* **1998**, *63*, 1872. (b) Zhao, Y. Y.; Bordwell, F. G. *J. Org. Chem.* **1996**, *61*, 6623.

(4) Enholm, E. J.; Moran, K. M.; Whitley, P. E.; Battiste, M. A. *J. Am. Chem. Soc.* **1998**, *120*, 3807.

(5) Estimates for acceleration are as high as 10^{10}; see Supporting Information.

(6) Koreeda, M.; Luengo, J. I. *J. Am. Chem. Soc.* **1985**, *107*, 5573. For a recent application of this type of rearrangement, see: Wood, J. L.; Moniz, G. A.; Pflum, D. A.; Stolz, B. M.; Holubec, A. A.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1999**, *121*, 1748.

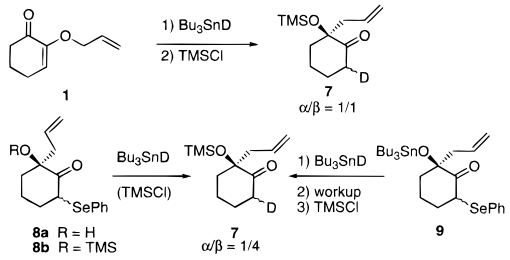
(7) Enholm, E. J.; Xie, Y. P.; Abboud, K. A. *J. Org. Chem.* **1995**, *60*, 1112. Enholm, E. J.; Whitley, P. E. *Tetrahedron Lett.* **1995**, *36*, 9157. Enholm, E. J.; Whitley, P. E. *Tetrahedron Lett.* **1996**, *37*, 559. Enholm, E. J.; Whitley, P. E.; Xie, Y. P. *J. Org. Chem.* **1996**, *61*, 5384.

(8) See Supporting Information for an evaluation of these experiments.

(9) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; VCH: Weinheim, 1996; p 283.

10.1021/ja991663n CCC: $18.00
Published on Web 09/08/1999

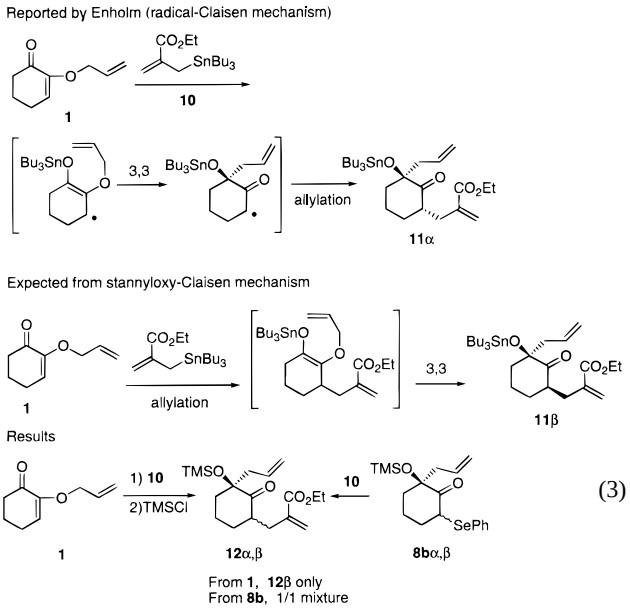
a related silyl ether analog[10] starting from a 1/1 mixture of phenylseleno ketones **8b**. Reduction of this with Bu_3SnD provided silyl ether **7** as a 1/4 mixture of α/β stereoisomers (78%). Likewise, direct reduction of the alcohol **8a** followed by silylation gave a 1/4 mixture of isomers of **7** (82%). Thus, the reductions of radicals closely related to α-keto radical **4** are moderately stereoselective, with attack of tin deuteride cis to the oxygen atom on the stereocenter adjacent to the ketone.



(2)

These results do not support Enholm's radical-Claisen mechanism but are consistent with the stannyloxy-Claisen mechanism. However, it is conceivable (although unlikely) that the stannyl ether radical **4** could give a 1/1 selectivity even though the silyl ether and alcohol precursors did not. We addressed this issue by preparing the labile stannyl ether **9** in situ from **8a**,[11] conducting the tin hydride reduction, and converting the crude product to the silyl ether **7** (eq 2). Again **7** was isolated as a 1/4 mixture of isomers (89%). Finally, it is also conceivable (although again unlikely) that the reduction of **4** by tin hydride is faster than a cyclohexane ring flip.[12] This raises the possibility that Claisen rearrangement of **3** or abstraction of phenylseleno groups from **8** or **9** could provide radicals **4** in different conformations. These could, in turn, react with different stereoselectivities. To rule out this possibility, we separated the diastereomers of **8b** and reduced them independently; each gave the same 1/4 mixture of products **7** (78% from **8b**α, 69% from **8b**β). The α and β isomers of **8b** exist predominately in different chair conformations, so the observation that they give the same ratio of isomers shows that ring flipping of **4** is faster than its reduction by Bu_3SnH.

These stereochemical experiments at once refute the radical-Claisen mechanism while supporting the stannyloxy-Claisen mechanism. However, this strong evidence in support of Koreeda's stannyloxy-Claisen mechanism is contradicted by an equally strong piece of evidence in the original Enholm paper. Rearrangement of **1** in the presence of allyl stannane **10** was reported to provide **11**α as a single stereoisomer through the mechansim shown in eq 3.[13] In 1985, Koreeda had observed high stereoselectivity in his rearrangements, but the β-isomer was obtained exclusively. Thus, **11**β is the expected isomer in the reaction in eq 3, and the formation of **11**α appears to be strong evidence in favor of the radical-Claisen mechanism. However, Enholm and co-workers did not cite this evidence, and in a footnote they commented that the configurational assignment of **11**α was tentative. We have investigated this situation, and we now propose that the configurational assignment of **11**α should be reversed.



(3)

Consistent with Enholm's results, upon reaction of **10** with **1**, we obtained a single stereoisomer of **12** after silylation (40%). Its configurational assignment was indeed not straightforward since very few diagnostic cross-peaks were observed in its NOE spectrum. However, reaction of **8b** with **10** now provided both diastereomers of **12** as a 1/1 mixture (80%). These were readily separated, and NOE experiments clearly showed that the new diastereomer was **12**α. Accordingly, the structure obtained from the allylation experiments must be **12**β. Once again, the stereochemical probes refute the radical-Claisen mechanism (because different ratios of **12**α/β are observed in the experiments in eq 3) and are fully consistent with the stannyloxy-Claisen mechanism (the expected single isomer **12**β is formed from **8b** in eq 3). Accordingly, we propose that the reductive conversion of **1** to **2**, and by extension all the related examples in Enholm's paper, occur by Koreeda's mechanism (eq 1): enone **1** is hydrostannated to provide intermediate **6**, which then suffers rapid 3,3-sigmatropic rearrangement to give **5**. That **6** cannot be observed (Enholm's results) suggests that it rearranges faster than it is formed. This requires a half-life of **6** on the order of minutes or less at 80 °C, which we feel is consistent with Koreeda's results for different but related enol derivatives.[6]

In summary, the reductive rearrangement of **1** to **2** does not occur through open-shell intermediates by a radical (or ketyl) accelerated Claisen rearrangement. Instead, closed-shell enol ether intermediates are generated by radical hydrostannation, and these undergo stannyloxy-accelerated Claisen rearrangements. Similar intermediates have previously been generated by deprotonation by Koreeda.[6] That Enholm's reductive rearrangement does not occur by a radical-Claisen mechanism has no bearing on the obvious synthetic utility of this new process. Hydrometalation of enones has frequently been used in synthesis as a complementary strategy to deprotonation for the generation of enol intermediates, and in this sense Enholm's method is a powerful complement to Koreeda's for these types of transformations. The viability of radical- and radical-anion-accelerated sigmatropic rearrangements remains an open problem.

Acknowledgment. We thank the National Science Foundation for funding this work. Y.N. thanks JSPS for a postdoctoral fellowship.

Supporting Information Available: Experimental details and characterization of all reported products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA991663N

(10) We choose to model the stannyl ether group with a silyl ether because stannyl ethers are hydrolytically sensitive and are difficult to form from tertiary alcohols. See: Davies, A. G. *Organotin Chemistry*; VCH: Weinheim, 1997; p 327. After many failures, the tin ether from **9** was ultimately generated in situ (see text). That it provides the same results as the silyl ether and alcohol supports the validity of this model.

(11) Jones, K.; Lappert, M. F. *J. Chem. Soc.* **1965**, 1944.

(12) For representative examples where the rates of radical reactions exceed those of relatively rapid conformation processes, see: (a) Snieckus, V.; Cuevas, J. C.; Sloan, C. P.; Liu, H.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 896. (b) Sauer, S.; Schumacher, A.; Barbosa, F.; Giese, B. *Tetrahedron Lett.* **1998**, *39*, 3685. (c) Buckmelter, A. J.; Powers, J. P.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1998**, *120*, 5589. (d) Musa, O. M.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1999**, *64*, 1022.

(13) It was also reported that reductive rearrangement of 2-allyloxy-3-methylcyclohexenone provided the opposite stereosiomer, as would be expected from both the Enholm and Koreeda mechanisms.