A Ketyl Radical-Anion “Triggered” [3,3]-Sigmatropic Shift

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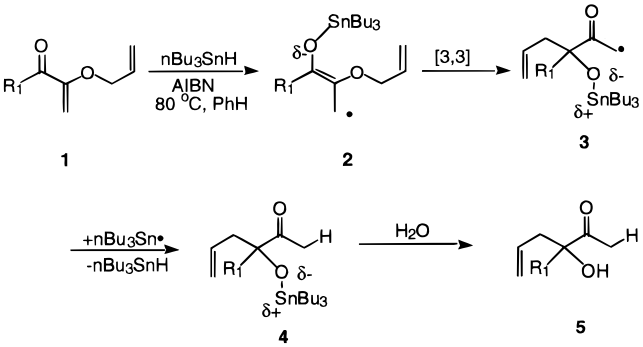
One of the most important pericyclic reactions in organic synthesis involves an internal allyl transfer in the [3,3]-sigmatropic shift.[1] A very useful modification of this reaction involves incorporating anionic charge in the substrate which accelerates the rearrangement; thus, greatly reduced temperatures are now used extensively. Metal alkoxides, enolates, and silyl ketene acetals are often used to accelerate sigmatropic reactions such as the Cope and Claisen rearrangements.[1a,c] Reagents which are one-electron donors, such as samarium(II) iodide and tributyltin hydride, have the potential to induce a radical-anion into the array of atoms undergoing rearrangement.[2−4] A metal-associated ketyl radical-anion, readily obtained by partial reduction of a ketone by a one-electron donor, could initiate or “trigger” a [3,3]-sigmatropic process; however, these intermediates have not been studied in this capacity.[3]

Resonance-stabilized allylic *O*-stannyl ketyls can be readily prepared from an α,β-unsaturated ketone and tributyltin hydride.[5,6] For example, if dienone **1** is reacted with tributyltin hydride, as shown in Scheme 1, an allylic *O*-stannyl ketyl intermediate forms and can be represented by the tin(IV) enolate and allylic radical species **2**. Formed under neutral free radical conditions, these delocalized bifunctional intermediates possess both radical and anionic character.[6] Intermediate **2** has two ether-tethered olefins in a 1,5-diene orientation; therefore, the electron-rich tin enolate in the allylic *O*-stannyl ketyl is now a potentially reactive partner in an anion-accelerated [3,3]-sigmatropic shift. This should “trigger” a [3,3]-Claisen rearrangement to prepare the tin(IV) alkoxide and radical species **3**.[7] After hydrogen atom transfer from $^{n}\mathrm{Bu_3SnH}$ to produce **4**, followed by water quench, alcohol **5** is expected to be the final product.

This reaction uses an unprecedented allylic *O*-stannyl ketyl to promote a [3,3]-sigmatropic shift in which a carbon−oxygen ether bond is lost and a new ketone carbonyl bond is gained. Tributyltin hydride is a reagent normally used in organic synthesis to replace a halogen with a hydrogen atom, and interestingly, it is not considered to be useful in promoting sigmatropic rearrangements.[4] It is noteworthy that **2** → **4** proceeds in a manner somewhat the opposite of the oxyanion-accelerated Cope rearrangement, where a metal alkoxide leads to a metal enolate.[1a,e] In the transformation in Scheme 1, the tin(IV) enolate in **2** leads to the tin(IV) alkoxide **4**. The driving force in the reaction, which shifts the equilibrium toward the product, is likely the formation of the strong ketone carbonyl bond.[1]

Scheme 1



This study will show several examples of this sigmatropic rearrangement which was conducted entirely at 80 °C under normal free radical conditions with tributyltin hydride. Mechanistic support for the presence of a radical-anion species during the rearrangement was obtained (vide infra). Moreover, new carbon−carbon bonds were obtained from intermediate radical-anion intermediate **3** via a reaction with electron-deficient allylstannanes. The tin−alkoxide moiety in **4** can be trapped with an electrophile prior to workup.

In the first example studied, treatment of **6** with tin hydride (1 equiv) and 2,2′-azobisisobutyronitrile (AIBN) (0.2 equiv), followed by reflux over 3 h, afforded the rearranged α-hydroxy ketone **7** in 74% yield.[8] Other substrates were studied as well and are shown in Table 1. Examination of the ^{1}H and ^{13}C NMR data of products **11** and **13** indicates that only one diastereomer is present in each case. Enone **8** reacted to form **9** in 51% yield in entry 2; however, a new method using a catalytic amount of tin hydride increased the yield to 61% in entry 3.[9] Although nearly all of the enone precursors underwent the [3,3]-sigmatropic rearrangement, acetylenic ketone **14** did not produce the desired product. Only the enone was reduced and ketone **15** was isolated, probably due to difficulty in the alkyne attaining the desired six-membered transition state normally required for the Claisen.[10]

Radical-anion intermediate **3**, resulting from the sigmatropic shift, possesses two reactive sites which can further extend the utility of the rearrangement reaction. In addition to the nucleophilic tin−alkoxide, a resonance-stabilized carbon-centered radical adjacent to the carbonyl should permit free radical reactions. Both of these centers can be utilized to add further functionalization in the same reaction vessel. If an ethyl ester substituted allyltin reagent is reacted with **6** instead of tributyltin hydride, the diallylcyclohexanone **16** is produced as a single diastereomer in 61% yield as shown in Scheme 2.[13] Quenching the intermediate tin alkoxide with acetyl chloride prepares acetate ester **17** in 46% overall yield.

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[1] (a) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205. (b) Chubert, P. S.; Srebnik, M. *Aldrichemica Acta* **1993**, *26*, 17. (c) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Chapter 7.2, p 827. (d) Bronson, J. J.; Danheiser, R. L. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Chapter 8.3, p 999. (e) Wilson, S. R. In *Organic Reactions*; Paquette, L. A., Ed.; J. Wiley and Sons: New York, 1993; Vol. 43, Chapter 2.

[2] For reviews of radical-anions, see: (a) Russell, G. A. In *Radical Ions*; Kaiser, E. T., Kevan, L., Eds.; Wiley-Interscience: New York, 1968. (b) Hirota, N. In *Radical Ions*; Kaiser, E. T., Kevan, L., Eds.; Wiley-Interscience: New York, 1968. (c) Forrester, A. R.; Hay, J. M.; Thompson, R. H. *Organic Chemistry of Stable Free Radicals*; Academic Press: New York, 1968.

[3] Recently $\mathrm{SmI_2}$ has been used to promote a [2,3]-sigmatropic rearrangement by an entirely different approach, see: Kunishima, M.; Hioki, K.; Kono, K.; Kato, A.; Tani, S. *J. Org. Chem.* **1997**, *62*, 7542.

[4] For reviews of $^{n}\mathrm{Bu_3SnH}$ in organic synthesis, see: (a) Giese, B. *Radicals in Organic Synthesis*: *Formation of Carbon−Carbon Bonds*; Pergamon Press: New York, 1986. (b) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (c) Curran, D. P. *Synthesis* **1988**, *417*, 489. (d) Hart, D. J. *Science* **1984**, *223*, 883. (e) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: New York, 1992.

[5] Pereyre, M.; Quitard, J. P.; Rahm A. *Tin in Organic Synthesis*; Buttersworths: Boston, 1987.

[6] (a) Enholm, E. J.; Whitley, P. E.; Xie, Y. *J. Org. Chem.* **1996**, *61*, 5384. (b) Enholm, E. J.; Kinter, K. S. *J. Org. Chem.* **1995**, *60*, 4850. (c) Enholm, E. J.; Whitley, P. E. *Tetrahedron Lett.* **1995**, *36*, 9157.

[7] Koreeda, M.; Luengo, J. I. *J. Am. Chem. Soc.* **1985**, *107*, 5572.

[8] Ikeda, M.; Takahashi, M.; Ohno, K.; Tamura, Y.; Kido, M. *Chem. Pharm. Bull.* **1982**, *30*, 2269.

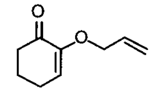
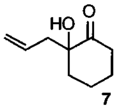
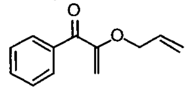
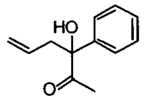
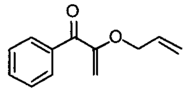
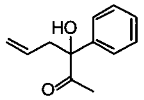
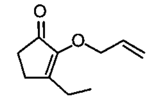
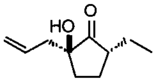
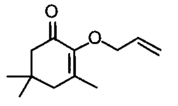
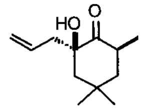
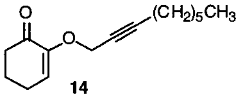
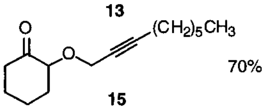
[9] Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 4−5.

[10] We could find very few examples of successful Claisen rearrangements with terminal acetylenes: (a) Black, D. K.; Landor, S. R. *J. Chem. Soc.* **1965**, 6784. (b) Fischer, J.; Kilpart, C.; Klein, U.; Steglich, W. *Tetrahedron* **1986**, *42*, 2063.

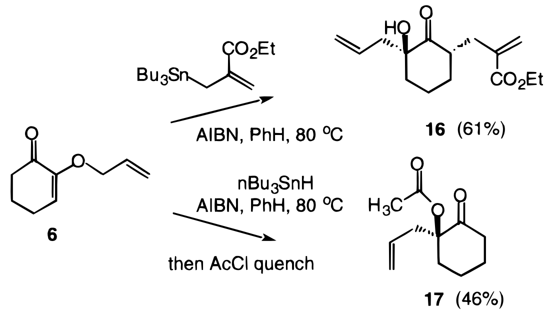
[11] At this point, the reaction of **6** → **7** is 69% complete (average of 3 runs).

S0002-7863(97)04272-8 CCC: $15.00

Table 1

Entry	Enone Precursor	Product	Yield
1.	 **6**	 **7**	74%
2.	 **8**	 **9**	51%
3.	 **8**	 **9**	61%[9]
4.	 **10**	 **11**	62%[13]
5.	 **12**	 **13**	62%[13]
6.	 **14**	 **15**	70%

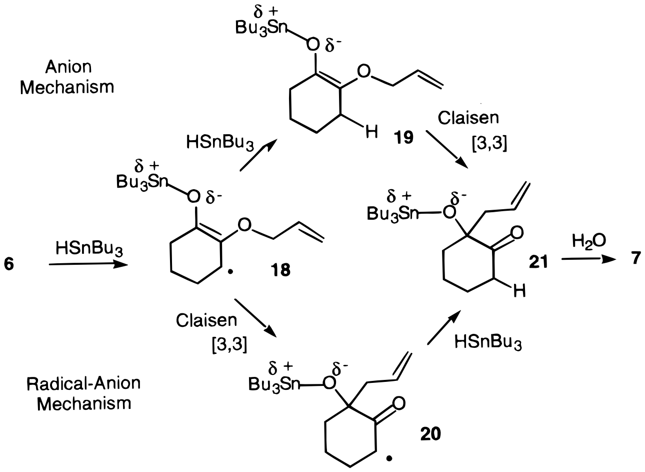
Scheme 2

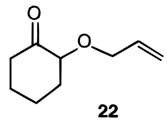


There are two mechanistic pathways proposed to account for the conversion of **6** → **7** shown in Scheme 3; these differ by the timing of events. An "anion mechanism," in which the anion alone is present during rearrangement proceeds via structures **6** → **18** → **19** → **21** → **7**. In this sequence, **18** first undergoes a bimolecular radical reaction with $^{n}Bu_3SnH$ to give tin(IV) enolate intermediate **19** prior to the Claisen reaction. A second "radical-anion mechanism" is shown in the sequence **6** → **18** → **20** → **21** → **7** where Claisen rearrangement of **18** to **20** occurs prior to hydrogen atom transfer from $^{n}Bu_3SnH$. This mechanism suggests the presence of a radical anion intermediate during the rearrangement. Radical-anion enhancement of the Claisen has not been studied; however, anionic-acceleration alone is well-established.[1]

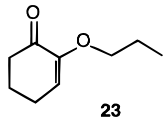
In an effort to distinguish which pathway is preferred, substrates **22**−**24** were synthesized. Water quenched aliquots were removed at 0.5 h time intervals during the reaction of **6** → **7** and compared by capillary GC with **22**. At no time during the formation of **7** was **22** (the water-quenched form of **19**) observed even in trace amounts. This indicates that tin enolate intermediate **19** is probably never present during the reaction, lending support to the alternative radical-anion mechanism.

Scheme 3

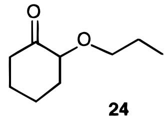




22



23



24

In a second competition study, enone **23** (1.0 equiv) and **6** (1.0 equiv) were reacted in the same flask with $^{n}Bu_3SnH$ (2.1 equiv) in benzene with AIBN (catalytic). Product formation was monitored by GC. Enone **23** cannot undergo the Claisen rearrangement; however, upon quenching its tin enolate with water, **24** was the only product observed.[11] The competition reaction was quenched after 1.0 h, and a 9.5:1 ratio (average of 3 runs) of **7**:**24** was observed, indicating that **7** is forming much faster than **24**. Because the rate of formation of **24** from **23** should be similar to the rate of formation of **19** from **6**, the anion mechanism is probably not the preferred mechanism.[12,14] The presence of a radical-anion during the Claisen rearrangement appears to be the more favored pathway from these investigations.

In summary, it has been demonstrated that Claisen rearrangements can be "triggered" by a tin-associated ketyl radical-anion. This unprecedented free-radical-mediated approach to sigmatropic shifts offers the advantage of mild neutral conditions. Two additional reactive sites in the intermediate also offer the useful advantage of further functionalization. Two mechanistic studies support an unusual radical-anion-accelerated Claisen rather than just enhancement from the anion alone.[15]

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Supporting Information Available: Experimental procedures, spectral data for all new compounds (16 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(12) It is assumed that both **7** and **24** have similar flame ionization properties (FID) in the GC competition study.

(13) The stereochemistry depicted for **11**, **13**, and **16** should be regarded as tentative at this time. An upcoming full paper will provide more information on these structures.

(14) The assumption that $k_{[3,3]} > k_{H}$ in the radical-anion mechanism is not unreasonable.[7]

(15) When **10** was reacted to form **11** (Table 1, entry 4), a D_2O quench revealed no carbon−deuterium bonds in the product by 300 MHz ^{1}H NMR.