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Radical-Induced Epoxide Fragmentation Chemistry. n-Bu_3Sn• Radical Catalyzed Isomerization of Epoxyketones to Carbocycles

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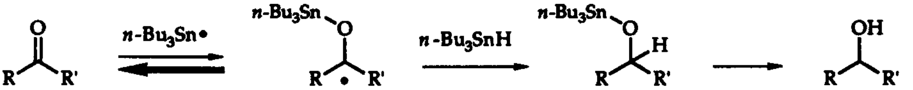
Summary: Cyclic α,β–epoxyketones are converted to bi- or tricyclic β-hydroxyketones in the presence of n-Bu_3Sn• radical. Addition of n-Bu_3Sn• to the carbonyl group gives a ketyl radical that triggers the epoxide fragmentation which is then followed by a 1,5-hydrogen abstraction and cyclization. Reversibility in the last two steps of the sequence is demonstrated.

The radical-induced fragmentation of epoxides offers a convenient method for generating highly reactive oxygen-centered radicals.[1, 2] For the past few years we have been exploring the synthetic potential of this and related fragmentations. We have shown that the epoxide fragmentation can be incorporated in a tandem sequence that involves a 1,5-hydrogen abstraction followed by a radical cyclization, and leads to various bicyclic compounds.[3] The tandem sequence can also be initiated by other methods which allow functionality at the original radical site to be retained in the product.[4-6] Because such functionalized compounds are more useful synthetically, we have examined many other processes for generating the initial radical. We report here our results on the use of n-Bu_3Sn• to trigger the tandem sequence on readily available α,β–epoxyketones.

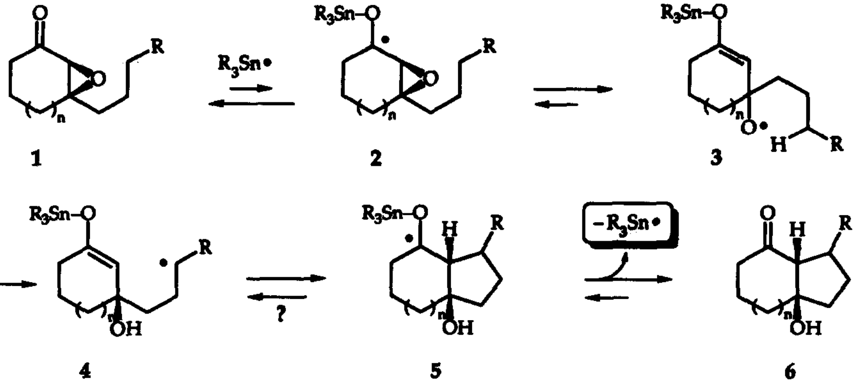
The present method was devised relying on the known reduction of ketones with Bu_3SnH.[7] This reaction is believed to involve the reversible addition of tin radical (R_3Sn•) to the carbonyl oxygen, Equation 1, a process that is slow for alkyl-substituted ketones.[8] The resulting ketyl-like radical intermediate then abstracts a hydrogen to give a tin ether, which upon hydrolysis gives the alcohol.



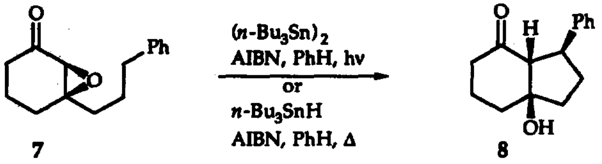
(Eq. 1)

We recognized that addition of the tin radical to α,β–epoxyketones would generate an oxiranylcarbinyl radical (**2**) which, like all such species reported to date, would rearrange rapidly to allyloxy radical **3** (see Scheme). A 1,5-hydrogen abstraction would form the labile β-hydroxy enol stannyl ether moiety (**4**). Provided that this functionality survived, the system would be set for a cyclization onto the enol stannyl ether, a closure that appeared to be unprecedented, to yield another stannyl ketyl radical (**5**). Ejection of the tin radical from **5** should occur with great facility to give bicyclic compound **6**, which is isomeric with the starting material.[9]

Scheme: Plausible Mechanism for $R_3Sn\cdot$ Mediated Isomerization of Epoxyketones



The initial studies were conducted using photochemical conditions for the generation of stannyl radicals. Irradiation of a benzene solution of ketoepoxide 7 [0.02M], AIBN (10 mol%), and $Me_3SnSnMe_3$ (1.0 eq) using a Hanovia mercury vapor lamp for 6h yielded the desired cyclization product in 56% yield as a single diastereomer (by NMR). The β orientation assigned to the phenyl group is consistent with NOE experiments and with analogous products that we had obtained using enolacetate substrates.[4,10] It is worth noting that during the reaction a small amount of a second product was observed by TLC, but it was found to disappear on further irradiation. The second product was later identified to be the α diastereomer of 8 (*vide infra*). A similar result was obtained when the tin radical source was $(n\text{-}Bu_3Sn)_2$, although the reaction proceeded more slowly. The expected mechanism for this transformation indicates that the stannyl radical is regenerated at the end of the sequence and should be required in only catalytic amounts. We found, however, that with catalytic amounts of the distannane the reaction required much longer to go to completion and gave the product in lower yield.



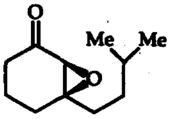
(Eq. 2)

We have examined many different conditions to carry out this tandem sequence.[11] The most convenient procedure involves the use of thermally generated stannyl radicals.[12] For example, hydroxyketone 8 was formed in 65% yield by refluxing a solution of epoxyketone 7 in benzene [0.03M] with Bu_3SnH and AIBN (0.5 equivalents each). The highest yields were obtained when solutions of $n\text{-}Bu_3SnH$ and AIBN (1 equiv each) were added by syringe pump over 1-2 hours to a refluxing solution of the epoxyketone in benzene [0.03M]. The tin hydride and AIBN were used in a 1:1 ratio to minimize the amount of excess hydride source present. Under these optimized conditions epoxyketone 7 was converted to hydroxyketone 8 in 72% yield, with the β diastereomer predominating by 22:1 ratio.

Interestingly, the diastereoselectivity of this cyclization varied from 10:1 to >50:1 as the reaction conditions were changed. Furthermore, as was observed using the photochemical conditions, we noted that the proportion of the minor diastereomer decreased as the reaction progressed, suggesting reversibility in the last two steps of the proposed mechanism. In order to test for this possibility, a pure sample (>97% by GC) of the minor diastereomer (8, with α phenyl) was subjected to the thermal reaction conditions. After three hours, the minor diastereomer had converted to a 1:1 mixture of the α and β diastereomers. This result confirms that *the last two steps in the tandem sequence are reversible for certain substrates.*[13]

We have explored the scope of the tin radical triggered isomerization of epoxyketones. The best yields were obtained in systems where the 1,5-hydrogen transfer (3 → 4) leads to a stabilized radical. Epoxyketone 9, which would give a tertiary radical intermediate, gave the expected product (10) in good yield (70%) along with small amounts of its dehydration product, enone 11 (5-10%), and recovered starting material. On the other hand, substrate 12, which lacks a methyl group, reacted more slowly under the same reaction conditions and gave in low yield the desired bicyclic product 13 (20-30%, β:α = 1.2:1). A significant side-product was again the enone resulting from dehydration of the β-hydroxyketone. The dehydration appears to take place both during the reaction and during the workup procedure.

Among the many substrates that we have examined for the stannyl radical mediated isomerization by far the most effective are the β-tolyl substituted epoxyketones. The simple tolyl substituted substrate 14 reacted rapidly and cleanly to afford the expected benzofused product 15 in 89% yield. The methoxy substituted derivative 16 also reacted smoothly and afforded tricyclic ketone 17 in quantitative yield (>97%) with high diastereoselectivity (β:α = 13:1). Reversibility also appears to play a role in the cyclization of this substrate. When ketone 17 containing 1:1 mixture of α:β methoxy diastereomers was heated in the presence of n-Bu_3SnH and AIBN (1 equiv each), the diastereomer ratio changed to 1:4 after 1.5 h and to 1:14 after 10h. Substituted epoxycyclopentanones (18 and 20) were found to be poor substrates for the tandem sequence (10-30%).[14]



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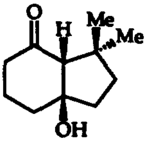

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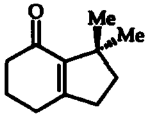

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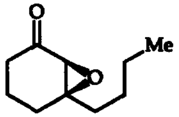

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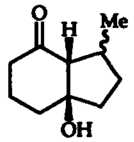

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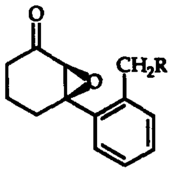
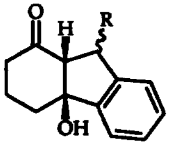
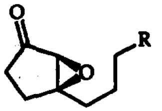


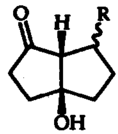
14: R=H
16: R=OMe



15: R=H
17: R=OMe



18: R=Ph
20: R=Me



19: R=Ph
21: R=Me

In conclusion, we have found that the reaction of $R_3Sn\bullet$ with α,β–epoxyketones triggers a cascade of radical mediated reactions which result in the formation of bi- and tricyclic β-hydroxyketones. We have shown that the last two steps in the transformation, a radical cyclization onto a stannyl enol ether and subsequent elimination of the tin radical, can be reversible.

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References and Notes

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2. See, *inter alia:* (a) Sabatino, E. C.; Gritter, R. J. *J. Org. Chem.* **1963,** *28,* 3437. (b) Stogryn, E. L.; Gianni, M. H. *Tetrahedron Lett.* **1970,** 3025; (c) Murphy, J. A.; Patterson, C. W.; Wooster, N. F. *J. Chem. Soc., Chem. Commun.* **1988,** 294. (d) Johns, A.; Murphy, J. A. *Tetrahedron Lett.* **1988,** *29,* 837;
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7. (a) For an overview of tin chemistry, see: Pereyre, M.; Quintard, J.; Rahm, A. *Tin in Organic Synthesis;* Butterworths: Boston, 1987. (b) Pereyre, M.; Quintard, J. *Bull. Chim. Soc. Fr.* **1972,** 1950. (c) Pereyre, M.; Godet, J. *Bull. Chim. Soc. Fr.* **1976,** 1005
8. The reaction of ketoepoxides with *n*-Bu$_3$SnH and AIBN at 80°C is known to give the corresponding enone as the major product. See, (a) Degueil-Castaing, M.; Rahm, A.; Dahan, N. *J. Org. Chem.* **1986,** *51,* 1672. (b) Hasegawa, E.; Ishiyama, K.; Kato, T.; Horaguchi, T.; Shimizu, T.; Tanaka, S.; Yamashita, Y. *J. Org. Chem.* **1992,** *57,* 5352, and references cited therein.
9. The first example of the epoxyketone isomerization was presented at the 199th American Chemical Society National Meeting, Boston, MA. (4/25/90, paper # 336). Other developments in this chemistry, including all the results described herein, were presented at the American Chemical Society 24th Central Regional Meeting (5/27/92, paper # 426). Upon completion of our studies, a report appeared on the use tin radicals to initiate the tandem sequence: Kim, S.; Koh, J. S. *J. Chem. Soc., Chem. Commun.* **1992,** 1377.
10. The major diastereomer was assigned the opposite stereochemistry by Kim et al. (see Ref. 9).
11. The use of some other ketyl forming conditions were not effective. Samarium iodide, for example, gave reduction of the epoxide to the enone, and (Me$_3$Si)$_3$SiH gave a messy, sluggish reaction.
12. Curiously, the tin pinacolate compound "TIN-PIN" was completely ineffective for this transformation, presumably because addition of the tin radical to benzophenone is much faster than to the ketoepoxide. See, (a) Hillgärtner, H.; Neumann, W. P.; Schroeder, B. *Justus Liebigs Ann. Chem.* **1975,** 586. (b) Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988,** *110,* 1631.
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14. The structure assigned to all new compounds is consistent with spectroscopic data (200, 250, or 300 MHz ^{1}H NMR, ^{13}C, IR, HRMS).

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