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Free-Radical Chemistry of Lactones: Fragmentation of *β*-Lactones. The Beneficial Effect of Catalytic Benzeneselenol on Chain Propagation

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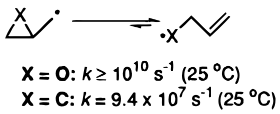
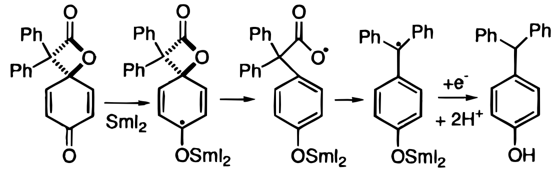
It is widely appreciated that oxiranylcarbinyl radicals undergo reversible[1,2] ring opening some 2 or more orders of magnitude more rapidly than the corresponding cyclopropylcarbinyl radicals.[3−7] In these reactions, the C−O bond is typically cleaved in preference to the C−C bond (Scheme 1). Likewise, it is well-known that cyclobutylcarbinyl radicals undergo ring opening several orders of magnitude more slowly than cyclopropylcarbinyl radicals: as such they are rarely used in synthetic schemes.[8−10] Thus stimulated, we hypothesized that the strategic inclusion of an oxygen in a cyclobutylcarbinyl radical, as in a 2-oxetanylcarbinyl or 2-oxetanon-4-ylcarbinyl radical, would lead to a substantial acceleration in the rate of ring opening. We further reasoned that ring opening would occur by preferential cleavage of a C−O rather than a C−C bond. This line of reasoning finds support in an isolated example of fragmentation of a 2-oxetanylcarbinyl radical, with cleavage of the C−O bond, described by the Kim group.[11] Such ring openings of *β*-lactones would stand in contrast to the ring contractions and/or expansions of similarly constituted higher homologs[12] and, more generally, with the chemistry of *β*-(acyloxy)alkyl radicals, which is characterized by a series of 1,2- and 2,3-shifts proceeding via polarized three-electron-three-center and five-electron-five-center cyclic transition states.[13] The fragmentation of *β*-(acyloxy)alkyl radicals to alkenes and carboxyl radicals is an extremely rare event and occurs only when an exceptional thermodynamic driving force is provided.[14]

In a preliminary experiment, the known, spirocyclic *β*-lactone **1** was exposed to SmI_2[15] (2 equiv) in THF at −78 °C resulting, after workup, in the isolation of **5** in 76% yield. We rationalize this result in terms of rapid fragmentation of the initial Sm(III) ketyl **2** to give carboxyl radical **3**, which then decarboxylates to provide **4**. A second electron transfer then gives the corresponding triarylmethyl anion, which on workup, provides **5** (Scheme 2). However, we also recognize the possibility that the second electron transfer could occur at the level of **2** and that we might be observing an anionic fragmentation and decarboxylation sequence.

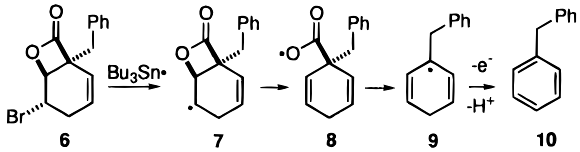
Scheme 1



Scheme 2

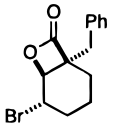


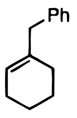
Scheme 3



To provide unambiguous evidence for the radical fragmentation, we turned to the reaction of **6** with tributyltin hydride, initiated by AIBN.[16] When the reaction was conducted at either reflux, or at room temperature under irradiation from a sunlamp, diphenylmethane was isolated typically in 60−65% yield. This suggests that the initial radical (**7**) does indeed undergo rapid fragmentation, followed by decarboxylation (Scheme 3). The product (**10**) must arise from oxidation either of **9** or of a cyclohexadiene formed following chain transfer with Bu_3SnH.

Hydrogenation of **6** over Pt/C provided the saturated analogue **11** in 65% isolated yield. On irradiation with a sunlamp at 60 °C, a mixture of **11**, Bu_3SnH, and AIBN provided a 22% yield of an 88:12 mixture of the alkenes **12** and **13** and a 31% yield of their assorted dimers.


11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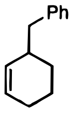
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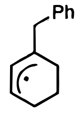
14

Clearly, the initial radical undergoes rapid cleavage of the *β*-lactone C−O bond followed by decarboxylation. This provides an allyl radical (**14**) that gives rise to **12** and **13**, by chain transfer with Bu_3SnH, and to the various dimers. As in the reaction of **6**, as much as 40 mol % of AIBN was required to drive the reaction to completion. We reasoned that, under the dilute conditions employed, allyl radical **14** does not react efficiently with the stannane, resulting in a breakdown of chain propagation. We hypothesized that a catalytic quantity of PhSeSePh, reduced in situ to PhSeH (and $Bu_3SnSePh$)[17−19] with its

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(16) Blank experiments demonstrated that the various *β*-lactones were thermally stable under the conditions employed for the radical fragmentations.

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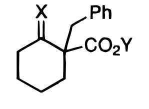
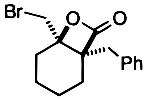
superior hydrogen-atom-donating capacity,[20] would overcome this problem. In the event, both at reflux and at 40 °C, the inclusion of 10 mol % of PhSeSePh in the reaction mixture enabled the amount of AIBN to be reduced to 10 mol % when smooth conversion of substrate to alkene **12** (84% isolated yield) was still observed. It is noteworthy that no dimers were formed in this PhSeH-catalyzed reaction, indicating that the selenol is efficient in the quenching of allyl radical **14**. Moreover, quenching of **14** was highly regioselective, providing only **12** (**12**:**13** ≥ 95:5).

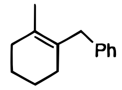
A final example was provided by the halo lactone **18**. This was synthesized in a straightforward manner by Wittig olefination of **15** to give **16**, followed by saponification to **17** and bromolactonization in the kinetic mode.[21]



15: X = O, Y = Et
16: X = CH$_2$, Y = Et
17: X = CH$_2$, Y = H



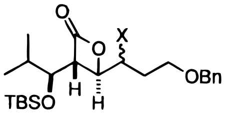
18



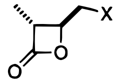
19

Treatment of **18** with Bu$_3$SnH and AIBN alone was again inefficient, owing to poor chain propagation by the intermediate allyl radical. However, exposure of **18** to Bu$_3$SnH and 5 mol % of PhSeSePh, with initiation by only 5 mol % of di-*tert*-butyl peroxalate at room temperature, resulted in the isolation of alkene **19** in 78% yield. This again demonstrates the facile cleavage of the β-lactone ring and the ability of PhSeH to transfer a hydrogen atom to relatively unreactive radicals.

It is noteworthy in the reaction of both **11** and **18** with Bu$_3$SnH and catalytic PhSeH, and in the reaction of **6** with Bu$_3$SnH alone, that the products of simple reduction (i.e., replacement of Br by H) were not observed (<5%). This suggests that the key radical fragmentation reaction is a relatively rapid process and that synthetic chemists preparing β-lactones by a halolactonization/radical dehalogenation sequence may encounter problems. A search of the literature revealed two such sequences. Mead reported dehalogenation of **20** to occur with Bu$_3$SnH, giving **21** in 72% yield for a reaction conducted at −78 °C,[22] and Shibata claimed an 89% yield of **23** on treatment of **22** with Bu$_3$SnH (0.5 M) at reflux in benzene.[23] The implication is that the fragmentation may be prevented by working at a sufficiently low temperature (Mead) or with a high concentration of Bu$_3$SnH (Shibata). A full kinetic characterization of the reactions of oxetanonylcarbinyl radicals, which we hope will help to illuminate the situation, will be undertaken and reported on in due course.



20: X = Br
21: X = H



22: X = Br
23: X = H

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Supporting Information Available: Characterization data (4 pages).

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