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The Application of Radicals in Organic Synthesis (V)

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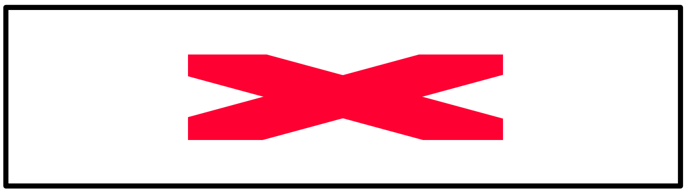
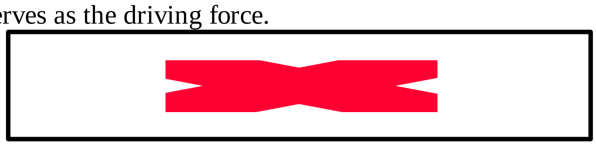
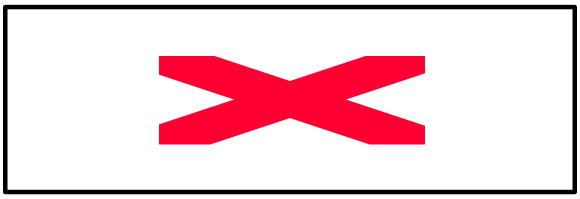
ABSTRACT



Reactions of ~-stannyl bromides and xanthates with tributyltin hydride generate ~-stannyl radicals. Intramolecular cyclizations of these radicals with a formyl group afford ¥-stannyl alkoxy radicals that undergo a 1,3-stannyl shift from carbon to oxygen. The carbon radicals obtained can be trapped inter- or intramolecularly. Approximately, the rates of 5-*exo* cyclizations of ~-stannyl radicals with a formyl group and terminal olefin are similar.

Intramolecular radical addition to a carbonyl to give cyclic alcohol is a potentially useful reaction.[1] However, this type of cyclizations is reversible, and the reverse reaction is generally faster than the cyclization.[2] In the cases of acylgermanes,[3] acylsilanes,[1] thioesters and selenoesters,[4] intramolecular radical additions to the carbonyl moiety in these compounds are followed by irreversible processes. Therefore, these cyclizations can be stopped at the cyclization side.[5] Herein, we wish to report the intramolecular cyclization of a formyl group with an α-stannyl radical[6] (eq 1) In this cyclization, a novel homolytic 1,3-stannyl shift from carbon to oxygen[7,8,9,10] serves as the driving force.





[1] Chang, S.-Y.; Jiaang, W.-T.; Cherng, C.-D.; Tang, K.-H.; Huang, C.-H.; Tsai, Y.-M. *J. Org. Chem.* **1997**, *62*, 9089–9098 and references cited therein.

[2] (a) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 230–234. (b) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 2674–2681. (c) Beckwith, A. L. J.; Raner, K. D. *J. Org. Chem.* **1992**, *57*, 4954–4962.

[3] (a) Curran, D. P.; Liu, H. *J. Org. Chem.* **1991**, *56*, 3463–3465. (b) Curran, D. P.; Palovich, M. *Synlett* **1992**, 631–632. (c) Curran, D. P.; Diederichsen, U.; Palovich, M. *J. Am. Chem. Soc.* **1997**, *119*, 4797–4804. (d) Diederichsen, U.; Curran, D. P. *J. Organomet. Chem.* **1997**, *531*, 9–12.

[4] Kim, S.; Jon, S. Y. *J. Chem. Soc., Chem. Commun.* **1996**, 1335–1336.

[5] For other strategies to drive the equilibrium, see: (a) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 6375–6381. (b) Kim, S.; Oh, D. H. *Synlett* **1998**, 525–527. (c) Batey, R. A.; MacKay, D. B. *Tetrahedron Lett.* **1998**, *39*, 7267–7270.

[6] Tsai, Y.-M.; Chang, S.-Y. *J. Chem. Soc., Chem. Commun.* **1995**, 981–982.

[7] For homolytic 1,5-stannyl shift from carbon to oxygen, see: (a) Kim, S.; Lee, S.; Koh, J. S. *J. Am. Chem. Soc.* **1991**, *113*, 5106–5107. (b) Kim, S.; Lim, K. M. *Tetrahedron Lett.* **1993**, *34*, 4851–4854.

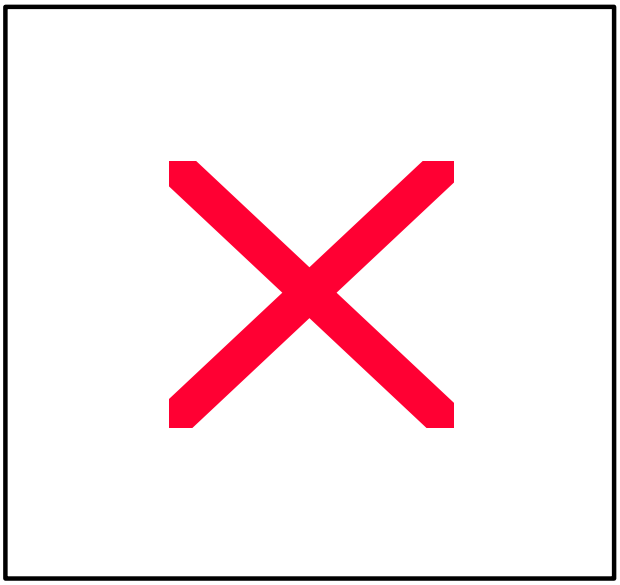
[8] For homolytic 1,6-stannyl shift from carbon to oxygen, see: (a) Kim, S.; Lim, K. M. *J. Chem. Soc., Chem. Commun.* **1993**, 1152–1153. (b) Kim, S.; Do, J. Y.; Lim, K. M. *Chem. Lett.* **1996**, 669–670.

[9] For homolytic 1,4-stannyl shift from oxygen to oxygen, see: Alberti, A.; Hudson, A. *Chem. Phy. Lett.* **1977**, *48*, 331–333.

[10] For homolytic 1,5-stannyl shift from oxygen to oxygen, see: Davies, A. G.; Tse, M.-W. *J. Organomet. Chem.* **1978**, *155*, 25–30.

As shown in eq 2, the aldehydes **1**[11] were coupled with tributyltin lithium,[12] and the resulting α-stannyl alcohols were converted to α-stannyl bromides using carbon tetrabromide and triphenylphosphine.[13] The dithiane moiety was then deprotected[14] to give the aldehydes **2** in mild yields over three steps. Treatment of the aldehyde **2a** with tributyltin hydride[15] (Scheme 1) followed by quenching the reaction with benzoyl chloride gave cyclopentyl benzoate (**3**) in 57% yield. The uncyclized reduction product aldehyde **4** was also isolated in 12% yield along with trace amount of the benzoate **5**. The benzoate **5** was presumably derived from over-reduction of the aldehyde **4** by the excess tributyltin hydride followed by benzoate formation.

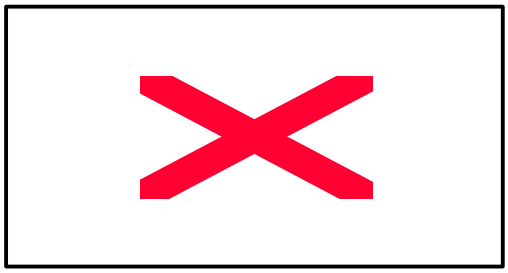
Mechanistically, this cyclization reaction occurs through the formation of the α-stannyl radical **6** first. This radical then cyclizes with the formyl group to generate the γ-stannyl alkoxy radical **7**. Because the radical cyclizations of carbonyl compounds are generally reversible,[2] it is likely that the oxygen radical and stannyl group may have a chance to adopt a *syn*-relationship as shown in **7**. The alkoxy radical **7** presumably undergoes a 1,3-stannyl shift from carbon to oxygen to generate the carbon radical **8**. It is known that the O-Sn bond is stronger than the C-Sn bond by about 25 kcal/mol.[16] This big difference provides a strong thermodynamic driving force to trap the alkoxy radical **7**. Abstraction of hydrogen from tributyltin hydride by the radical **8** gives the stannyl ether **9**. The oxygen atom in stannyl ethers is known to be quite



nucleophilic.[17] Therefore, for the convenience of isolation and identification, the stannyl ether **9** was converted directly to the corresponding benzoate **3**.

Scheme 1

Scheme 2



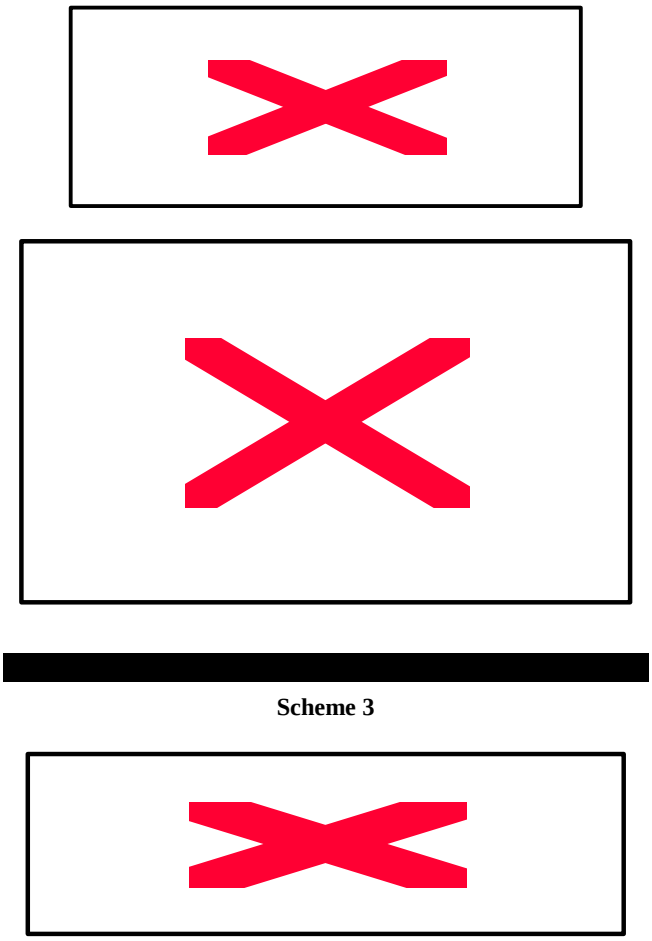
When the aldehyde **2a** (Scheme 2) was treated with allyltributyltin (4 equiv) in the presence of hexabutylditin (0.2 equiv) and initiated by the photolysis of long wavelength UV light[18] (12 h), we were able to isolate the alcohol **10**[19] in 35% yield. This reaction provided evidence that indeed the radical **8** was formed. In the case of 6-*exo* cyclization (eq 3), the aldehyde **2b** reacted with tributyltin hydride[15] and gave 27% of cyclohexanol (**11**), 29% of the uncyclized reduction product aldehyde **12**, and 9% of the over-reduction product alcohol **13**. The problem of this reaction was revealed by the reaction of the aldehyde **2b** with allyltributyltin (eq 4). Along with the alcohol **14**[20] (10%), we obtained 50% yield of the aldehyde **15** that contains an allyl group at the α-position

[11] Konosu, T.; Oida, S. *Chem. Pharm. Bull.* **1993**, *41*, 1012–1018.
[12] Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481–1487.
[13] Torisawa, Y.; Shibasaki, M.; Ikegami, S. *Tetrahedron Lett.* **1981**, *22*, 2397–2400.
[14] (a) Ho, T.-L.; Ho, H. C.; Wong, C. M. *J. Chem. Soc., Chem. Commun.* **1972**, 791–791. (b) Ho, H. C.; Ho, T.-L.; Wong, C. M. *Can. J. Chem.* **1972**, *50*, 2718–2721.
[15] The cyclization reaction was performed by slow addition (4 h) *via* syringe pump of a benzene solution of tributyltin hydride (1.3 equiv, 0.13 M in benzene) and AIBN (0.05 equiv) to a solution of the bromide (0.1 M) in refluxing benzene.
[16] Jackson, R. A. *J. Organomet. Chem.* **1979**, *166*, 17–19.
[17] Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1997; Chap 11, p 261.
[19] Curran, D. P.; Liu, H. *J. Chem. Soc. Perkin Trans. 1* **1994**, 1377–1393.
[20] Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444–2451.

of the carbonyl group. This result indicates that a 1,5-hydrogen transfer[21] occurs after the generation of the α-stannyl radical from the aldehyde **2b**. This process leads to the formation of an α-carbonyl radical . The α-carbonyl radical is then trapped by allyltributyltin to give the aldehyde **15**.

This stannyl shift that promotes the radical cyclization reaction can be employed in a tandem cyclization mode. Instead of using α-stannyl bromides, we synthesized the xanthates **16** and **17** for our studies.[6] The reaction of the xanthate **16** with tributyltin hydride[15] (eq 5) gave the monocyclic aldehyde **18** in 33% yield. This aldehyde was derived from the addition of an α-stannyl radical to the olefin first. An alcohol **19** (5%) was also obtained. This material was presumably derived from the reduction of the aldehyde **18** by the excess tributyltin hydride. The bicyclic alcohol **20** was isolated in 29% yield. Small amounts of the benzoate derived from the bicyclic alcohol **21** were

detected in 4% yield through benzoylation of the crude cyclization mixture. The benzoates derived from the alcohols **20** and **21** thus obtained are identical to that reported by Wilcox *et al*.[22] The stereochemistry of the alcohols **20** and **21** can therefore be determined. There appeared to be other stereoisomers of the alcohols **20** and **21**; however, the amount was very small and we were not able to identify these minor isomers. The bicyclic alcohols **20** and **21** are tandem cyclization products derived from the addition of the α-stannyl radical **22** (Scheme 3) to the formyl group first. The cyclization presumably prefers to adopt a chair transition state[23] with the large groups located at the equatorial position as shown in **22**. This leads to the formation of the alkoxy radical **23** with a predominant *trans*-1,3-relationship. The stannyl shift of the alkoxy radical **23** gives the radical **24**. This radical cyclizes with the olefin to give the bicyclic alcohol **20** as the major isomer with the known *endo*-selectivity.[24]



Scheme 3

The rates for the addition of an α-stannyl radical to an olefin and a formyl group appear to be similar because the total yield of the monocyclic products **18** and **19** is close to that of the bicyclic alcohols **20** and **21**. With this information available, it is possible to attenuate the tandem system to favor the bicyclic product. For example, it is known that the 5-*exo* cyclization of 5-hexynyl radical is slower than the corresponding 5-hexenyl radical cyclization by nearly ten folds.[25] Therefore, for the xanthate **17**, one would expect the carbonyl cyclization to be faster than the alkyne cyclization. As shown in eq 6, the cyclization of the xanthate **17** gave the four isomeric bicyclic alcohols **25** and **26** in a combined yield of 68%.[26] The monocyclic alcohol **27** was isolated in 10% yield. The ratio of carbonyl addition products versus alkyne addition products was about 7:1.

[21] Beckwith, A. L. J.; Ingold, K. U. *Rearrangements in ground and excited states*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol 1, pp161–310.

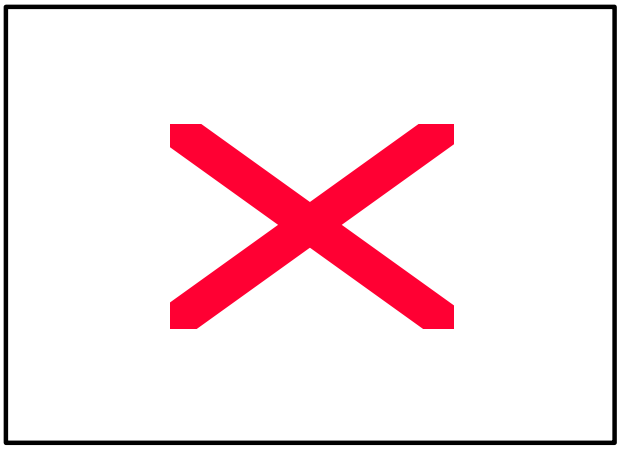
[22] Nagai, M.; Lazor, J.; Wilcox, C. S. *J. Org. Chem.* **1990**, *55*, 3440–3442.

[23] (a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373–376. (b) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925–3941. (c) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959–974.

[24] (a) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139-145. (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: New York, 1996; p 57.

[25] Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073–3100.

[26] The stereochemistry of these compounds were determined by NOE experiments.



In conclusion, a 1,3-stannyl shift promoted cyclization of an α-stannyl radical with a formyl group was developed. This process is successful for the 5-*exo* cyclization. In comparison, the corresponding 6-*exo* cyclization seriously competes with a 1,5-hydrogen transfer reaction. Approximately, the 5-*exo* cyclization of an α-stannyl radical with a formyl group or with a terminal olefin have similar rates. This information will be useful in the design of tandem cyclizations. However, the reversibility of the formyl group cyclization requires further investigation. In the tandem cyclizations, the α-stannyl xanthate moiety serves as a novel *gem*-diyl equivalent.[27]

[27] For the use of *gem*-dihalide as *gem*-diyl equivalent, see ref 22.