Tetrahedron Letters, Vol. 33, No. 48, pp. 7391-7392, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Stereoselective Radical Cyclization of Epoxy Silyl Enol Ethers

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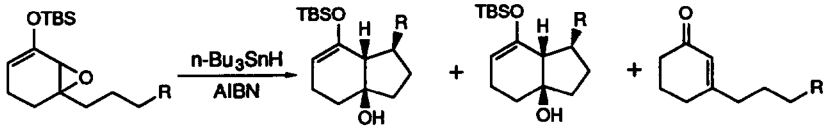
Abstract : *n-Bu$_3$Sn radical catalyzed stereoselective radical cyclization of epoxy silyl enol ethers is described.*

We recently reported radical cyclizations of vinyl epoxides[1] and epoxy ketones[2] via radical translocations by a 1,5-n-Bu$_3$Sn group or a 1,5-hydrogen atom transfer.[3] In our approach, originally present functional groups such as exo methylene and keto groups are retained in the product, which would be synthetically very useful for further functional group manipulation. Very recently, Rawal and Krishnamurthy have reported phenylthio radical catalyzed cyclization of acetoxyalkenyl epoxides.[4] Their recently published work has prompted us to communicate our preliminary results as shown in equation 1.[5]



(1)

1 2 3 4

a : R= Ph	68 % (2/3=100:0)	11 %
b : R= OCH$_2$Ph	80 % (2/3=88:12)	7 %
c : R= CH=CH$_2$	61 % (2/3=95:5)	8 %
d : R= CH$_3$	67 %	13 %

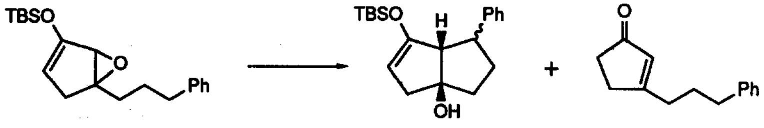
Our approach relied on n-Bu$_3$Sn radical addition to the olefin, the epoxide fragmentation to the alkoxy radical, 1,5-H transfer to generate the carbon centered radical, cyclization, and elimination of n-Bu$_3$Sn radical to produce the cis-fused bicyclic compound.[6] Reaction of **1a** with 0.3 equiv of n-Bu$_3$SnH (TBTH) and 0.05 equiv of AIBN in refluxing benzene for 3 h afforded the cis-fused bicyclic compound **2a** in 68% yield along with 11% of **4a**. The stereochemistry of phenyl group was determined by NOE experiments. Of special synthetic importance is that the radical reaction of **1a** proceeded with a complete stereocontrol of three chiral centers. The diastereoselectivity was somewhat lower for **1b**, showing a 88:12 mixture of **2b** and **3b**. The similar result was obtained with **1c**. In the case of **1d**, the diastereoselectivity could not be determined by NMR experiments.

In order to improve the diastereoselectivity, the radical reaction of **1b** was carried out in benzene under several reaction conditions and the results are summarized in Table 1. Lowering the reaction temperature helped the diastereoselectivity but the reaction was incomplete. The use of sterically bulky triphenyltin hydride and UV initiated radical reaction also improved the diastereoselectivity but the

Table 1. Stereocontrol in Radical Cyclization of **1b**

Condition	**2b** : **3b**	yield, % **2b**+**3b**	 **4b**
0.3 eq TBTH, AIBN, 80°C, 3h	88 : 12	80	7
0.3 eq TBTH, AIBN, 50°C, 3h	95 : 5	12	1
0.8 eq TBTH, UV, r.t., 12h	95 : 5	23	14
0.5 eq Ph_3SnH, AIBN, 80°C, 7h	95 : 5	30	37
0.3 eq PhSSPh, AIBN, hv, 100 °C, 3h	65 : 35	60	0

formation of a byproduct **4b** was accelerated. It is noteworthy that phenylthio radical initiated radical cyclization of **1b** obviated the problem of the formation of **4b** but the diastereoselectivity was relatively low. In the case of **5**, n-Bu_3Sn radical catalyzed radical cyclization gave only 14 % of **6** along with 25 % of **7**. The reaction was considerably improved by using 0.3 equiv of diphenyl disulfide and AIBN as shown in equation 2.



(2)

5 **6** **7**

0.3 equiv n-Bu_3SnH-AIBN : 14 % (exo/endo=93:7) 25 %
0.3 equiv PhSSPh-AIBN : 55 % (exo/endo=69:31) 0

In conclusion, we have shown that radical reaction of epoxy silyl enol ethers provide a useful method for the synthesis of highly stereocontrolled cis-fused bicyclic compounds. Further studies on related systems and rationalization of stereochemical outcome in the radical cyclization will be reported in due course.[7]

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7. We thank OCRC for financial support of this work.

(Received in Japan 13 August 1992)