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Tandem Radical [2 + 1] Cycloaddition. Remarkable Silyl Substituent Effect on the Chemoselectivity of the Radical Cyclization Reactions†

Wu-Wang Weng and Tien-Yau Luh*

Department of Chemistry, National Taiwan University, Taipei, Taiwan 106, Republic of China

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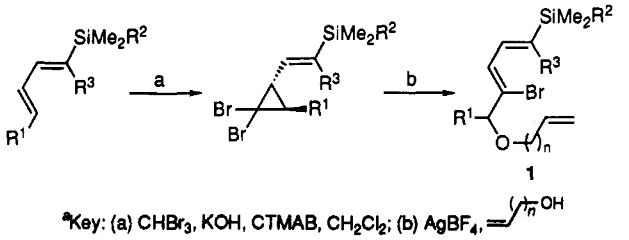
Summary: Tandem radical cyclization of bromides **1** with Bu_3SnH is extremely sensitive to the nature of the substituent on the diene moiety. Bicyclo[3.1.0] skeleton **3** is obtained in the presence of the silyl substituent. The *tert*-butyl substituent gives exclusively six-membered ring products **15**. Tributyltin radical addition to the double bond becomes predominant when the substituent is phenyl.

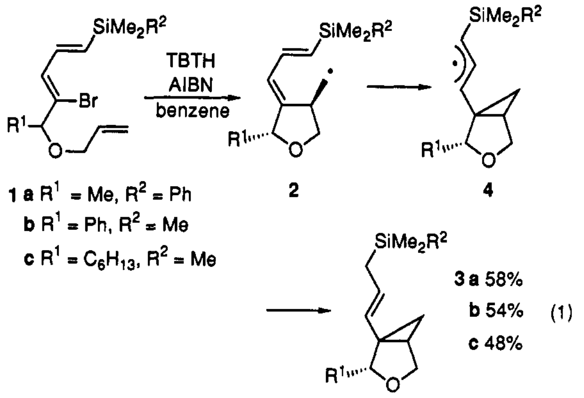
Although cyclization of a homoallylic radical to form a three-membered ring intermediate is feasible, only a few specially designed cases are known.[1-5] The rate for the interconversion between a homoallylic radical and a cyclopropylcarbinyl radical is well documented, and the rapid ring-opening process is responsible for the paucity of the methodology for the isolation of the corresponding cyclopropane derivatives.[5] The key to solving this problem relies on designing a substrate such that the cyclopropylcarbinyl radical has the right stability and right reactivity. As such, the rate of the ring-opening process of this carbinyl radical may be slower than that of the trapping processes of this radical. In this regard, the nature of the substituent at the radical center may demonstrate a pivotal function in determining the chemoselectivity of this interconversion.[6] It is noted that an α-silyl substituent can facilitate the formation of the corresponding radicals[7] and the rate of hydrogen abstraction reaction by the thus formed radical is faster than that of the carbon analog.[8] Described herein are the results of our initial investigation that demonstrates the remarkable silyl substituent effect on the chemoselectivity of the tandem radical cyclization of bromides **1**.

Bromides **1** were chosen as a probe because the radical debromination of **1** followed by cyclization would generate the homoallylic radical **2** possessing different sites for radical reaction prototypes. Scheme I summarizes a convenient procedure for the preparation of **1**.[9] Under nitrogen atmosphere the slow addition of a benzene solution of tributyltin hydride (TBTH) and 10 mol % of AIBN over 1 h into a refluxing benzene solution of **1a–c**. After refluxing for an additional 16 h the corresponding bicyclic products **3a-c** were obtained (eq 1).[10] As each of these compounds is a single diastereomer,[11] this transformation demonstrates an intriguing tandem radical [2 + 1] cycloaddition process. *The presence of the silyl group in* **1** *is indispensable for this conversion.* Evidently, the hydrogen abstraction reaction was significantly faster than the rearrangement process for the radical **4**.[12] It is particular noteworthy that the hydrogen abstraction process was regioselective in giving allylsilanes **3a–c** stereoselectively. Neither the simple reduction product **5** nor the rearranged product **6** was observed. The ozonolysis of **3a** to **7** unequivocally proved the position of the double bond in **3**.

Scheme I[a]



[a] Key: (a) $CHBr_3$, KOH, CTMAB, CH_2Cl_2; (b) $AgBF_4$,



1 a R^1 = Me, R^2 = Ph
b R^1 = Ph, R^2 = Me
c R^1 = C$_6$H$_{13}$, R^2 = Me

3 a 58%
b 54% (1)
c 48%

Structural rigidity seemed to be important for the formation of the bicyclo[3.1.0] skeleton. On the other hand, reaction of **8** with TBTH under the same conditions afforded **9**, presumably via a less strained intermediate **10** (eq 2). This later reaction furnishes a convenient procedure for the preparation of the basic skeleton of iridoids.[13]

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† Dedicated to the memory of the late Professor Paul G. Gassman.

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(1) Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321.

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(3) (a) Cekivic, Z.; Saicic, R. *Tetrahedron Lett.* **1990**, *31*, 6085. (b) Srikrishna, A.; Sharma, G. V. R.; Hemamalini, P. *J. Chem. Soc., Chem. Commun.* **1990**, 1681. (c) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Chem. Soc., Chem. Commun.* **1990**, 923.

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(6) For example, an ester group can facilitate the formation of the cyclopropane derivatives from the electrochemical reductive cyclization of enolphosphates containing an olefinic linkage, without ring opening (ref 4).

(7) Wilt, J. W.; Belmonte, F. G.; Zieske, P. A. *J. Am. Chem. Soc.* **1983**, *105*, 5665.

(8) (a) Wilt, J. W. *Tetrahedron* **1985**, *41*, 3979. (b) Wilt, J. W.; Lusztyk, J.; Peeran, M.; Ingold, K. U. *J. Am. Chem. Soc.* **1988**, *110*, 281.

(9) The details on the preparation of **1** will be described elsewhere.

(10) In a typical procedure, a solution of **1** (1.00 mmol) in degassed benzene (40 mL) was heated under reflux to which was slowly added TBTH (2.00 mmol), AIBN (10 mol %), and benzene (60 mL) over a period of 1 h. The reaction mixture was further refluxed for an additional 16 h. The solution was evaporated in vacuo to give a yellow oil which was chromatographed on silica gel (2% EtOAc in hexane) to give the products. The isomeric compounds were purified by preparative HPLC.

(11) The stereochemical assignments were based on the NOE experiments.

(12) Alternatively, the difference in thermodynamic stability of radical **4**, which is both allylic and silicon stabilized, and the corresponding ring-opened homoallylic congener may account for the chemoselectivity of such tandem radical cyclization.

(13) For example, Liao, C.-C.; Wei, C.-P. *Tetrahedron Lett.* **1989**, *30*, 2255.

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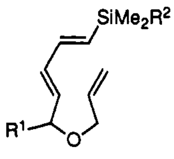

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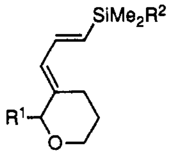

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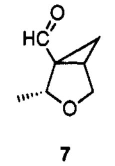

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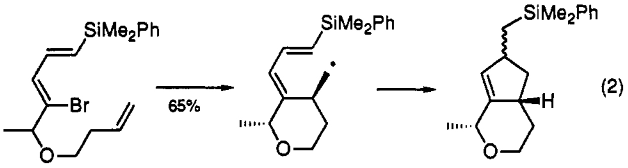
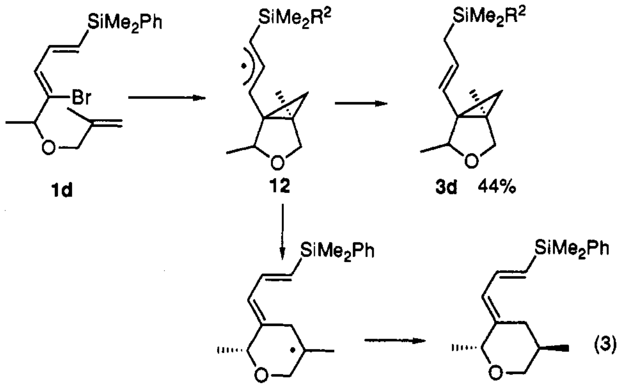


8 10 9

isomer ratio 1 : 1

(2)

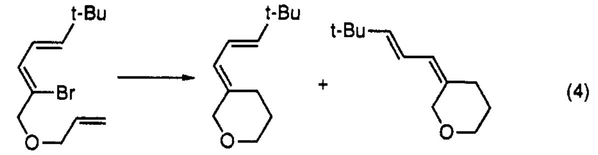
Modification of the substituent on the isolated double bond or on the diene moiety, however, has provoked a significant change in chemoselectivity. Thus, the reaction of **1d** under the same conditions afforded a mixture of **3d** and **11** (eq 3). Rearrangement of the cyclopropylallyl radical **12** which gave a tertiary radical **13** appeared to be competitive against the direct hydrogen abstraction by **12**.



1d **12** **3d** 44% **13** **11** 22%

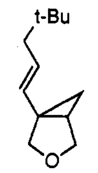
(3)

When the silyl group was replaced by the *tert*-butyl group as in **14**, the rearranged products **15a** and **b** were obtained in 90% yield (eq 4), no bicyclic **16** having been detected. This result suggested that the silyl substituent played a key role on the stability and reactivity of the corresponding cyclopropylallyl radical (e.g., **12**). It is noteworthy that the presence of an alkyl group on the silyl-substituted diene also affected the selectivity. Thus, the reaction of **17** with TBTH afforded stannane **18** in addition to the expected products **3e**, **19** and **20** (eq 5). The formation of **18** may have involved the addition of the tributyltin radical to the isolated double bond[14] to generate a new radical **21** which added to C-5 giving intermediate **22** followed by an extrusion of a bromine atom (eq 6).



14 **15a** 60% **15b** 30%

(4)



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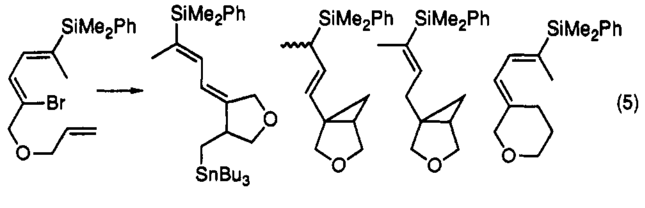
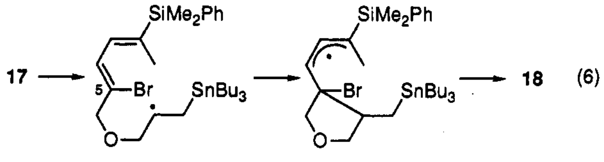


17 **18** 9 % **3e** 15% **19** 5% **20** 29 %

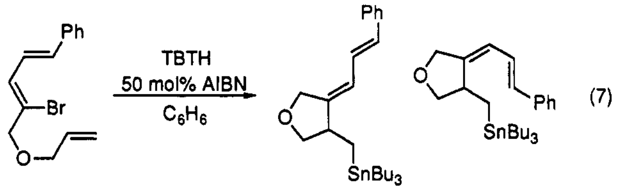
(5)



21 **22**

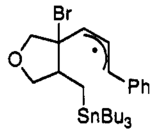
(6)

Strikingly, the reaction of the phenyl-substituted substrate **23** with TBTH followed a similar pathway as that described in eq 5 to yield **24** and **25** (eq 7). It was noted that at least 50 mol % of AIBN was required to drive this reaction to completion. This observation indicated that this reaction may not be a radical chain process. Presumably, the phenyl substituent significantly stabilized allyl radical **26** which led to the chemoselective formation of dienes **24** and **25**.



23 **24** 39% **25** 6%

(7)



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In summary, we have demonstrated three different features on the tandem radical cyclizations. The substituent on the diene moiety in these substrates can exert a subtle influence on the chemoselectivity of the radical cyclization reaction, and the silyl substituent seems to play a unique role in the generation of the bicyclic skeleton **3**. The nature of such interactions and the potential synthetic applications of these reactions are being investigated.

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Supplementary Material Available: Experimental details and characterization of the products from the reactions of **1a-d**, **3a**, **8**, **14**, **17**, and **22** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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