Radical Cyclization of 1,6-Enynes Using Allylstannanes[1]

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Radical cyclization of dienes and enynes using radical transfer agents (X−Y) provides a powerful method for constructing carbocycles and heterocycles simultaneously with introduction of one or two functionalities.[2−9] This process includes three propagation steps: intermolecular addition of X• to one unsaturated bond, intramolecular radical addition to another unsaturated bond, and intermolecular homolytic substitution with the X−Y reagent accompanied with regeneration of X• (Scheme 1). A variety of radical transfer agents can be utilized to achieve the radical chain process. In particular, the use of X−H reagents (Y = hydrogen) has been extensively studied because of the ease of hydrogen abstraction (the last propagation step) and their good availability.[2−6] When Y is not hydrogen, the X−Y reagents become more valuable from the standpoint of functionalization because they can introduce two functionalities into the cyclized products. In most cases, such reagents have a halogen or an organochalcogen group as Y.[7,8] There are few examples of the cyclization using an X−C type of reagent bearing an alkyl group as Y.[9]

Scheme 1

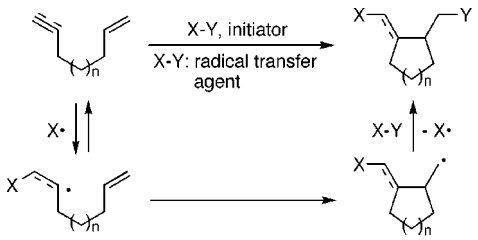
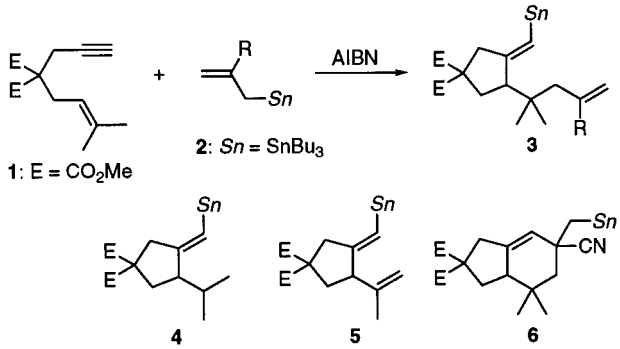


Table 1. Radical Cyclization of Enyne 1[a]



entry	allylstannane R		refluxing time (h)	product (yield (%), ratio)[b]
1	H	**2a**	10	**3a** + **4** + **5** (11, 85:10:5)[c]
2[d]	H	**2a**	10	**3a** + **4** + **5** (39, 80:11:9)
3	Me	**2b**	10	**3b** + **4** + **5** (8, 85:9:6)
4[d]	Me	**2b**	10	**3b** + **4** + **5** (38, 70:17:13)
5[d]	$SiMe_3$	**2c**	10	**3c** (63)
6	Ph	**2d**	5	**3d** (57)
7[e]	Ph	**2d**	5	**3d** (78)
8	CO_2Me	**2e**	3	**3e** (87) (74)[f](62)[g]
9	CN	**2f**	5	**3f** (59), **6** (19)[h]

[a] Unless otherwise noted, all reactions were performed with a 1,6-enyne (0.50 mmol), **2** (2.00 mmol, 4.0 equiv), and AIBN (0.025 mmol, 5 mol %) in benzene (2.5 mL) at reflux (82−85 °C of bath temp) (method A). [b] The molar ratio of products was determined by ^{1}H NMR analysis. [c] 65% of **1** was recovered. [d] AIBN (30 mol %). [e] AIBN (10 mol %). [f] **2e** (2.0 equiv), 5 h. [g] **2e** (1.2 equiv), 7 h. [h] Diastereomeric mixture (dr = 86:14). The relative configuration was not determined.

Previously we have reported homolytic allylstannylation of alkenes and alkynes with allylstannanes.[10] In this carbometalation reaction, allylstannanes work as an X−C type of radical transfer agent to allylate carbon radicals and provide a stannyl radical. On the other hand, it is well-known that hydrostannanes are fairly effective in radical cyclization of dienes and enynes.[3] These facts prompted us to investigate the radical cyclization using allylstannanes.

Treatment of a 0.2 M solution of 1,6-enyne **1** in benzene with allyltributylstannane **2a** (4 equiv) in the presence of AIBN (5 mol %) at reflux (method A) gave a mixture of cyclized products **3a**, **4**, and **5** in rather low yield (11%, entry 1 in Table 1). An increased amount of AIBN (30 mol %) improved the yield to some extent (39%, entry 2). Methallylstannane **2b** showed a similar reactivity to

(1) Free Radical Chemistry No. 35. For No. 34, see: Miura, K.; Saito, H.; Itoh, D.; Hosomi, A. *Tetrahedron Lett.* **1999**, *40*, 8841.

(2) For C−H, see: Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon Press: Oxford, 1986; pp 172−173.

(3) For Sn−H, see: (a) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547. (b) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 2829. (c) Hanessian, S.; Léger, R. *J. Am. Chem. Soc.* **1992**, *114*, 3115 and references therein. (d) Alcaide, B.; Rodríguez-Campos, I. M.; Rodríguez-López, J.; Rodríguez-Vicente, A. *J. Org. Chem.* **1999**, *64*, 5377.

(4) For Si−H, see: (a) Kraus, G. A.; Liras, S. *Tetrahedron Lett.* **1990**, *31*, 5265. (b) Kulicke, K. J.; Giese, B. *Synlett* **1990**, 91. (c) Miura, K.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1992**, 2477.

(5) For P−H, see: (a) Brumwell, J. E.; Simpkins, N. S.; Terrett, N. K. *Tetrahedron Lett.* **1993**, *34*, 1215. (b) Brumwell, J. E.; Simpkins, N. S.; Terrett, N. K. *Tetrahedron* **1994**, *50*, 13533.

(6) For S−H, see: (a) Padwa, A.; Nimmesgern, H.; Wong, G. S. K. *J. Org. Chem.* **1985**, *50*, 5620. (b) Ichinose, Y.; Wakamatsu, K.; Nozaki, K.; Birbaum, J.-L.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1987**, 1647. (c) Broka, C. A.; Reichert, D. E. C. *Tetrahedron Lett.* **1987**, *28*, 1503.

(7) For C-heteroatom, see: (C-halogen atom) ref 2 pp 173−174. (a) Bellus, D. *Pure Appl. Chem.* **1985**, *57*, 1827. (b) Yang, Z.-Y.; Burton, D. J. *J. Org. Chem.* **1991**, *56*, 5125. (C−Hg) (c) Russell, G. A.; Li, C.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 9831.

(8) For S-heteroatom and Se−Se, see: (SO_2−halogen atom) (a) Smith, T. A. K.; Whitham, G. H. *J. Chem. Soc., Chem. Commun.* **1985**, 897. (b) De Riggi, I.; Surzur, J.-M.; Bertrand, M. P.; Archavlis, A.; Faure, R. *Tetrahedron* **1990**, *46*, 5285. (c) Serra, A. C.; da Silva Corréa, C. M. M.; do Vale, M. L. C. *Tetrahedron* **1991**, *47*, 9463. (d) Chuang, C.-P. *Tetrahedron* **1991**, *47*, 5425 and references therein. (SO_2−Se) (e) Brumwell, J. E.; Simpkins, N. S.; Terrett, N. K. *Tetrahedron Lett.* **1993**, *34*, 1219. (Se−Se) (f) Ogawa, A.; Takami, N.; Sekiguchi, M.; Yokoyama, H.; Kuniyasu, H.; Ryu, I.; Sonoda, N. *Chem. Lett.* **1991**, 2241.

(9) For S−C, see: Chuang, C.-P. *Synlett* **1990**, 527.

(10) (a) Miura, K.; Itoh, D.; Hondo, T.; Saito, H.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* **1996**, *37*, 8539. (b) Miura, K.; Matsuda, T.; Hondo, T.; Ito, H.; Hosomi, A. *Synlett* **1996**, 555.

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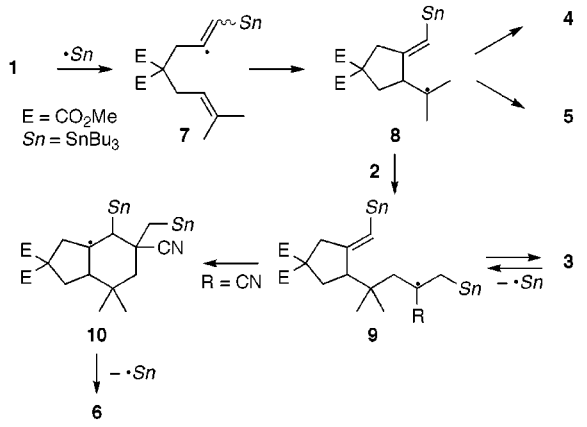
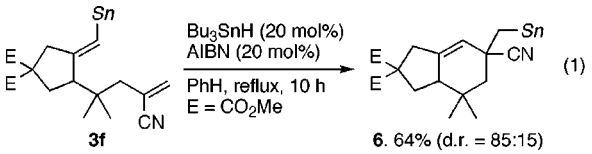
Scheme 2



1 (entries 3 and 4). In contrast, β-trimethylsilyl- and β-phenyl-allylstannanes **2c**,**d** smoothly reacted with **1** to afford **3** in moderate to good yields without the formation of **4** and **5** (entries 5−7). Introduction of a methoxycarbonyl group into the β-position further enhanced the reactivity of allylstannane toward the radical cyclization (entry 8). The high reactivity brought about efficient cyclization of **1** even with a decreased amount (2.0 or 1.2 equiv) of **2e**. Interestingly, the cyclization with β-cyano-substituted allylstannane **2f** formed a certain amount of bicyclized product **6** as a byproduct (entry 9).

A plausible mechanism for the present cyclization is shown in Scheme 2. The process from **1** to **3** includes three radical intermediates **7**, **8**, and **9**. The reason for the formation of **4** and **5** with **2a**,**b** is probably that the radical **8** suffers termination reactions such as disproportionation and hydrogen abstraction because of slow allylation of **8**. The increase in the ratio of **4** and **5** to **3** with an increased amount of AIBN (entries 2 and 4) would be the result that high concentration of radical species facilitates the termination reactions. In contrast to the case with **2a**,**b**, high reactivities of **2c**−**f** to carbon radicals, imparted by the radical-stabilizing group at the β-position, would effectively promote the allylation step to suppress the side reactions.

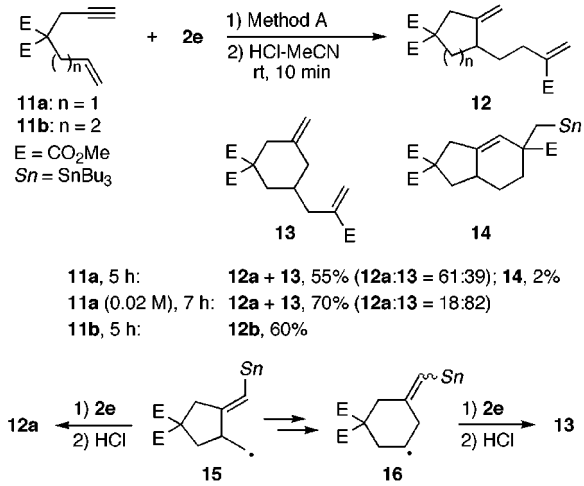
The bicyclization forming **6** can be rationalized by the path including intramolecular homolytic substitution of **9** via **10**. There is a possibility that **6** is formed by the stannyl radical-mediated isomerization of **3f**. To ascertain it, **3f** was treated with Bu_3SnH−AIBN in benzene at reflux (eq 1). As a result, this reaction gave **6** in a good



yield with a similar diastereoselectivity (dr = 85:15) as in the cyclization of **1** with **2f**. The results of Table 1 indicate that the presence of a cyano group as R induces the bicyclization. In the cyclization of **9** to **10**, a strong polar effect of the cyano group may assist the addition of the radical center to the electron-rich vinylstannane moiety.[11] Radical-mediated [2 + 2 + 2] cycloadditions among one triple bond and two double bonds have been

(11) (a) Tedder, J. M.; Walton, J. C. *Tetrahedron* **1980**, *36*, 701. (b) Giese, B.; Horler, H.; Leising, M. *Chem. Ber.* **1986**, *119*, 444.

Scheme 3



reported by a few research groups;[12] however, there is no example using an enyne and an alkene as substrates.

To disclose the applicability of the present cyclization, a variety of enynes were used as substrates. The reaction of 1,6-enyne **11a** with **2e** resulted in a complex mixture of adducts (Scheme 3). Therefore, the crude product was destannylated with aq HCl in MeCN to facilitate separation of the cyclized products and their identification by NMR analysis. Purification of the acid-treated product by column chromatography gave a mixture of **12a** and **13** along with a slight amount of **14** (dr = 66:34). The formation of **13** would be due to isomerization of radical intermediate **15** to **16**.[13] As expected, high dilution of **11a** induced the isomerization to give **13** as a major product. The cyclization of **1** gave no six-membered ring products unlike the result with **11a**. In the case with **1**, the isomerization of radical intermediate **8** to the corresponding cyclohexyl radical would be inhibited by both radical stabilization and steric bulkiness arising from two methyl groups at the radical center. A similar reaction of 1,7-enyne **11b** formed **12b** as the only cyclized product. Thus, the present method also serves to construct a six-membered ring.

Allyl propargyl ethers **17** and **19** underwent the radical cyclization with **2d**,**e** to give five- or six-membered cyclic ethers (Scheme 4). The substrate **19b** bearing a methyl group at the allylic position showed high stereoselectivity in contrast with **19a**. The single diastereomer obtained was determined to be a *trans*-isomer by NOE experiments (see Supporting Information). The high *trans*-selectivity is probably because intramolecular addition of the vinyl radical intermediate corresponding to **7** proceeds via a chair-equatorial conformation to minimize allylic 1,3-strain.[14] The reaction of **19c** afforded a diastereomeric mixture of **20c** with moderate stereoselectivity.[15] The reactivity of enyne **19d** bearing a phenyl

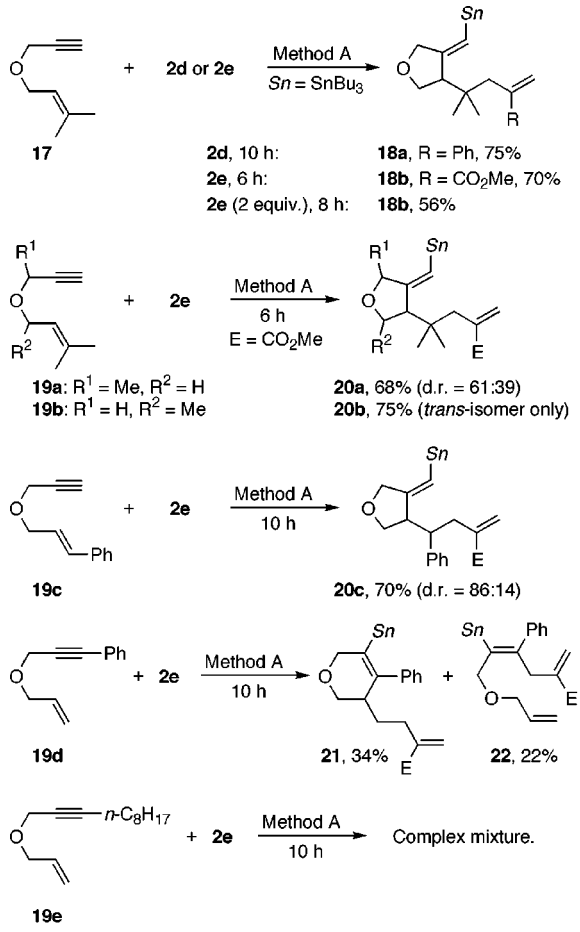
(12) (a) Lee, E.; Hur, C. U.; Rhee, Y. H.; Park, Y. C.; Kim, S. Y. *J. Chem. Soc., Chem. Commun.* **1993**, 1466. (b) Marco-Contelles, J. *J. Chem. Soc., Chem. Commun.* **1996**, 2629. (c) Spino, C.; Barriault, N. *J. Org. Chem.* **1999**, *64*, 5292.

(13) (a) Beckwith, A. L. J.; O'Shea, D. M. *Tetrahedron Lett.* **1986**, *27*, 4525. (b) Stork, G.; Mook, R., Jr. *Tetrahedron Lett.* **1986**, *27*, 4529.

(14) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996; pp 46−48.

(15) The relative configuration of the major diastereomer was not determined. However, the major isomer is expected to have (4*R**,1′*R**)-configuration on the basis of the model described by Hart et al. Hart, D. J.; Krishnamurthy, R. *J. Org. Chem.* **1992**, *57*, 4457.

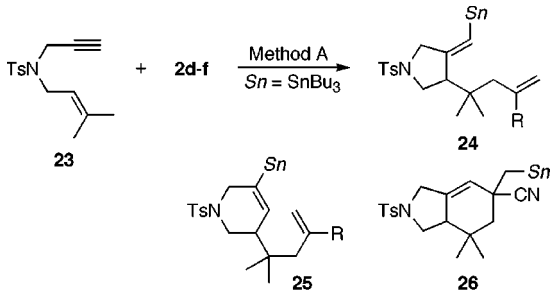
Scheme 4



group on the sp-carbon was quite different from that of **19c** in both reaction site and cyclization efficiency. In the case with **19d**, the stannyl group added to the β-position of the propargyl moiety to give cyclic ether **21** and allylstannylated product **22** in low yields. The change in reaction site is easily explained by a strong stabilizing effect of the phenyl group on the intermediary vinyl radical. The formation of **22** is probably because slow 6-exo cyclization of the radical intermediate allows the competition of allylation with **2e**. The use of **19e** bearing an octyl group on the sp-carbon gave a complex mixture of unidentified products with a considerable amount of unreacted **19e** (ca. 60%). Thus, the present method is not suitable for the cyclization of 1,6-enynes substituted at the alkyne terminus.

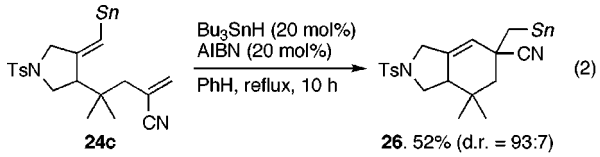
The present cyclization is available for the synthesis of cyclic amines as well (Table 2). Allyl propargylamine **23** smoothly reacted with **2d**,**e** to provide pyrrolidines **24** in good yields along with cyclic byproducts **25** (entries 1−3). The formation of **25** means that tributylstannyl radical adds to the internal sp-carbon in **23**; however, the origin of the unusual reaction site is unclear. In the cyclization with **2f**, bicyclized product **26** was also formed as a byproduct (entries 4 and 5). It is notable that an increased amount of AIBN raised the yield of **26**. The reason for this observation would be that the stannyl radical generated by the action of AIBN induces isomerization of **24c** to **26** via radical intermediates corresponding to **9** and **10** (Scheme 2). Indeed, **24c** was smoothly isomerized to **26** with Bu_3SnH and AIBN similarly to the case with **3f** (eq 2).

Table 2. Radical Cyclization of Enyne 23[a]



entry	reagent	time (h)	product (yield (%), ratio)[b]
1[c]	**2d**	8	**24a** (71), **25a** (7)
2	**2e**	2	**24b** (77), **25b** (9)
3[d]	**2e**	4	**24b** (65), **25b** (6)
4	**2f**	7	**24c** (51), **25c** + **26**[e] (17, 41:59)
5[c]	**2f**	7	**24c** (35), **25c** + **26**[e] (28, 18:82)

[a,b] See footnotes a and b in Table 1. [c] AIBN (10 mol %). [d] **2e** (2.0 equiv). [e] Diastereomeric mixture (dr = 93:7). The relative configuration was not determined.



In conclusion, we have demonstrated that allylstannanes such as **2c**−**f** serve as radical transfer agents to realize the radical cyclization of 1,6-enynes. The present cyclization can introduce two new functionalities into the product; therefore, it provides a convenient route to highly functionalized carbocycles and heterocycles.

Experimental Section

General Method. Unless otherwise noted, all reactions and distillation of solvents were carried out under N_2. Solvents were dried by distillation from sodium metal/ benzophenone ketyl (THF) and CaH_2 (benzene, DMF). Bu_3SnCl was simply distilled in vacuo. All other commercial reagents were used as received. Boiling points determined with Kugelrohr distillation apparatus are indicated by air-bath temperature (bath temp). ^1H and ^{13}C NMR were recorded in $CDCl_3$ at 270 and 67.7 MHz, respectively. The chemical shifts (δ) are reported with reference at 0.00 ppm (Me_4Si) or 7.26 ppm ($CHCl_3$) for the proton and at 77.00 ppm (centered on the signal of $CDCl_3$) for the carbon.

Synthesis of Enynes. Enyne **1** was prepared from dimethyl malonate according to the literature.[16] Enyne **11a** was synthesized by the reaction of dimethyl allylmalonate with 3-bromo-1-propyne (NaH, THF). A similar procedure was employed for the synthesis of enyne **11b** from dimethyl (3-butenyl)malonate. Allyl propargyl ethers **17** and **19a**,**d**,**e** were prepared by the condensation of 2-propyn-1-ol with 1-bromo-3-methyl-2-butene, 3-butyn-2-ol with 1-bromo-3-methyl-2-butene, 3-phenyl-2-propyn-1-ol with 3-bromo-1-propene, and 2-undecyn-1-ol with 3-bromo-1-propene (NaH, THF), respectively.[17] For the synthesis of allyl propargyl ethers **19b**,**c**, 4-methyl-3-penten-2-ol and (*E*)-3-phenyl-2-propen-1-ol were condensed with 3-bromo-1-propyne (NaH, THF). Allyl propargylamine **23** was synthesized by the reaction of *N*-(3-methyl-2-butenyl)*p*-toluenesulfonamide with 3-bromo-1-propene (NaH, DMF) according to the literature.[18]

(16) Mook, Jr., R.; Sher, P. M. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. VIII, p 381.
(17) Bartlett, A. J.; Laird, T.; Ollis, W. D. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1315.
(18) Kataoka, T.; Yoshimatsu, M.; Noda, Y.; Sato, T.; Shimizu, H.; Hori, M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 121.

The starting sulfonamide was prepared from *p*-toluenesulfonamide and 1-bromo-3-methyl-2-butene (K_2CO_3, acetone).[6a]

Synthesis of Allylstannanes. Allylstannanes **2a**−**d** were prepared by reductive coupling between the corresponding allyl bromides and Bu_3SnCl using Mg and a catalytic amount of $PbBr_2$.[19] 2-Trimethylsilyl-3-bromo-1-propene and 2-phenyl-3-bromo-1-propene were prepared by the reported procedures.[20,21] Allylstannanes **2e**,**f** were synthesized from the corresponding allyl sulfonates by homolytic substitution with Bu_3SnH.[22] The reductive coupling between methyl 2-(bromomethyl)acrylate and Bu_3SnCl was also usable for the synthesis of **2e**.

Cyclization of Enynes (Typical Procedure). Allylstannane **2e** (790 mg, 2.0 mmol) was added to a solution of enyne **1** (119 mg, 0.500 mmol) and AIBN (4.2 mg, 0.025 mmol) in benzene (2.5 mL). The mixture was heated to reflux (82−85 °C of bath temp) and then stirred for 3 h. The reaction mixture was evaporated and purified by silica gel column chromatography (hexane−AcOEt 10:1) to give dimethyl 4-(3-methoxycarbonyl-1,1-dimethyl-3-butenyl)-3-((*E*)-tributylstannylmethylene)cyclopentane-1,1-dicarboxylate (**3e**, 273 mg) in 87% yield. **3e**: bp 220 °C (0.33 Torr, bath temp); IR (neat) 1733 (C=O), 1268, 1249, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79−0.93 (m, 21H), 1.23−1.61 (m, 12H), 1.94 (dd, J = 13.5, 8.2 Hz, 1H), 2.31 (d, J = 12.9 Hz, 1H), 2.38 (d, J = 12.9 Hz, 1H), 2.49−2.57 (m, 1H), 2.60−2.71 (m, 2H), 2.92 (dm, J = 14.5 Hz, 1H), 3.70 (s, 3H), 3.74 (s, 3H), 3.75 (s, 3H), 5.47 (d, J = 1.7 Hz, 1H), 5.68 (br s, J ($^{117}Sn-^1H$) = J ($^{119}Sn-^1H$) = ca. 64 Hz, 1H), 6.20 (d, J = 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.99 ($CH_2 \times 3$), 13.70 ($CH_3 \times 3$), 23.28 (CH_3), 24.21 (CH_3), 27.29 ($CH_2 \times 3$), 29.20 ($CH_2 \times 3$), 35.62 (CH_2), 37.49 (C), 40.00 (CH_2), 45.67 (CH_2), 51.84 (CH_3), 52.59 (CH_3), 52.72 (CH_3), 54.05 (CH), 58.84 (C), 124.89 (CH, J ($^{117}Sn-^{13}C$) = 366 Hz, J ($^{119}Sn-^{13}C$) = 384 Hz), 127.63 (CH_2), 138.29 (C), 157.63 (C), 168.70 (C), 171.73 (C), 172.12 (C). Found: C, 57.69; H, 8.48%. Calcd for $C_{30}H_{52}O_6Sn$: C, 57.43; H, 8.35%. Irradiation of the olefinic proton (δ 5.68) α to stannyl group in **3e** showed a 5.3% enhancement of the allylic methine proton (δ 2.49−2.57). Similar results were obtained in NOE experiments of **3b-d**,**f**. The geometry of the vinylstannane moiety in all cyclized products was deduced from these results, stereochemical outcomes in the radical cyclization with Bu_3SnH,[3b] and the reaction mechanism shown in Scheme 2.

Destannylation of Products. To ascertain the structures of products **21**, **22**, and **25c**, they were destannylated with concentrated HCl−CH_3CN at room temperature. NMR data for the destannylated products support that **21** and **25c** are 3,4-unsaturated heterocycles bearing a tributylstannyl group on the 3-position. The protonolysis proceeds with retention of the configuration;[23] therefore, the geometry of **22** was determined by NOE experiment with its destannylated form.

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Supporting Information Available: Experimental procedure for the synthesis of allylstannanes and spectral data for the substrates and the products including destannylated ones. This material is available free of charge via the Internet at http://pubs.acs.org.

JO005567C

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(22) (a) Baldwin, J. E.; Adlington, R. M.; Birch, D. J.; Crawford, J. A.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1986**, 1339. (b) Baldwin, J. E.; Adlington, R. M.; Lowe, C.; O'Neil, I. A.; Sanders, G. L.; Schofield, C. J.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1988**, 1030.

(23) Alvanipour, A.; Eaborn, C.; Walton, D. R. M. *J. Organomet. Chem.* **1980**, *201*, 233.