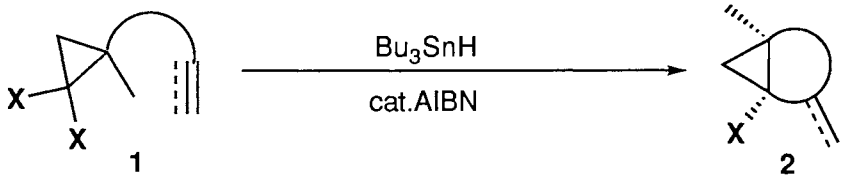
CHEMISTRY LETTERS, pp. 1757-1760, 1994. 

# A Novel and Regioselective Radical Cyclization of *gem*-Dihalocyclopropyl Substituted Alkenes and Alkynes Using Tributyltin Hydride and Catalytic AIBN

Yoo TANABE,* Yoshinori NISHII, and Ken-ichi WAKIMURA
School of Science, Kwansei Gakuin University, 1-1-155 Uegahara, Nishinomiya, Hyogo 662

Various *gem*-dihalocyclopropyl substituted alkenes and alkynes were transformed into the corresponding bicyclo[3.1.0]- or [4.1.0] compounds with high regioselectivity through a reductive radical cyclization using tributyltin hydride in the presence of catalytic azobisisobutyronitrile (AIBN).

Radical cyclization is now established as a methodology to enhance the synthetic potentiality of organic syntheses.[1] Among the various types of reactions so far exploited, 5-*exo-trig* type cyclopentane annulation by radical reduction of ω-haloolefins is recognized as the most representative one. Meanwhile, *gem*-dihalocyclopropanes readily prepared by the dihalocarbene addition to olefins are known to be reduced to the halocyclopropanes by tributyltin hydride ($Bu_3SnH$) and catalytic azobisisobutyronitrile (AIBN) *via* a radical path.[2] We now report that various *gem*-dihalocyclopropyl substituted alkenes and alkynes **1** undergo reductive radical cyclization to give the corresponding bicyclo[3.1.0]- or [4.1.0] compounds **2** with high site-selectivity using $Bu_3SnH$ and catalytic AIBN, along with our interest in new reactions utilizing *gem*-dihalocyclopropanes.[3]




First, 1-allyl-1-(2,2-dihalo-1-methylcyclopropyl)-3-buten-1-ols **3a** and **3b**[4] were treated with 1.1 equiv. of $Bu_3SnH$ and 0.10 equiv. of AIBN and found to give the bicyclo[3.1.0]-1-halohexane products **4a** and **4b,** respectively, in good yield (Table 1, Entries 1 and 2). A typical procedure is exemplified by the reaction of **3a** (Table 1, Entry 1): To a toluene solution (4.0 ml) of diallyl substrate **3a** (400 mg, 1.7 mmol), AIBN (30 mg, 0.17 mmol) and $Bu_3SnH$ (552 mg, 1.83 mmol) was added successively at 70 °C and the reaction mixture was kept at 110 °C for 12 h. 10% KF water (10 ml) were added to the mixture and stirred for several minutes. After Celite filtration, the mixture was extracted with ether and washed with water and brine, dried and concentrated. The obtained crude oil was purified by silica-gel column chromatography (hexane/ethyl acetate = 10:1-5:1) to give diastereomer **4a-1** (faster eluent; 100 mg, 29%) and diastereomer **4a-2** (later eluent; 163 mg, 49%).[5]

Based on these facts, other 1-(2,2-dihalocyclopropyl)-3-buten-1-ols **3c-3e** were next examined and these results are summarized in Table 1. Of note is that all cyclizations proceeded with high regioselectivity in a 5-*exo*-trig manner and competitive 6-*endo*-trig products were not detected at all, although the radical cyclization of the 5-hexenyl radical bearing heteroatom on the radical carbon generally enhances 6-*endo* reaction, and that bearing a Me group on the 5-position give about the 1:2 mixture of 5-*exo* and 6-*endo* products.[6] In addition, new *exo*-methyl groups were formed *trans* to the adjacent Cl group with high stereoselectivity (>95%) in the case of **4a** and **4b** and with moderate one (82%) in the case of **4c-1**, which was determined by $^1$H NMR and their NOESY measurements between a proton on the cyclopropane and the methyl protons of **4a- 4c-1**.[5] Moderate stereospecificity was observed between certain diastereomers of the substrates (**3c** and **3d**: R$^1$=Me) and the just reduced by-products (monohalocyclopropanes) were predominantly obtained from **3c-2** and from **3d-2** which is presumably due to the fact that the radical intermediate does not orient itself toward olefin parts.[7]

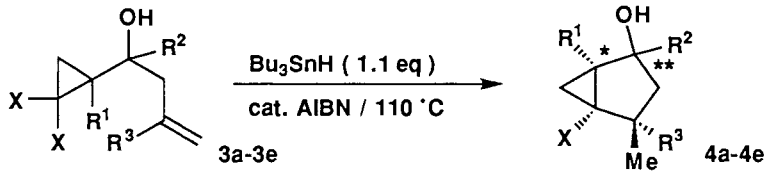
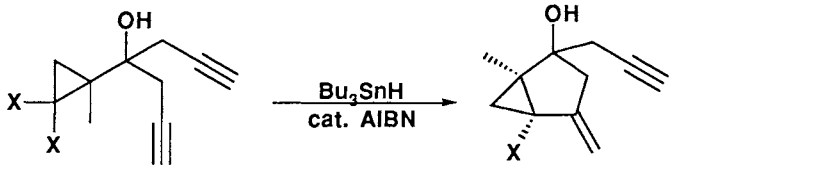



Table 1. Radical Cyclization of 1-(2,2-dihalocyclopropyl)-3-buten-1-ols **3a-3e**

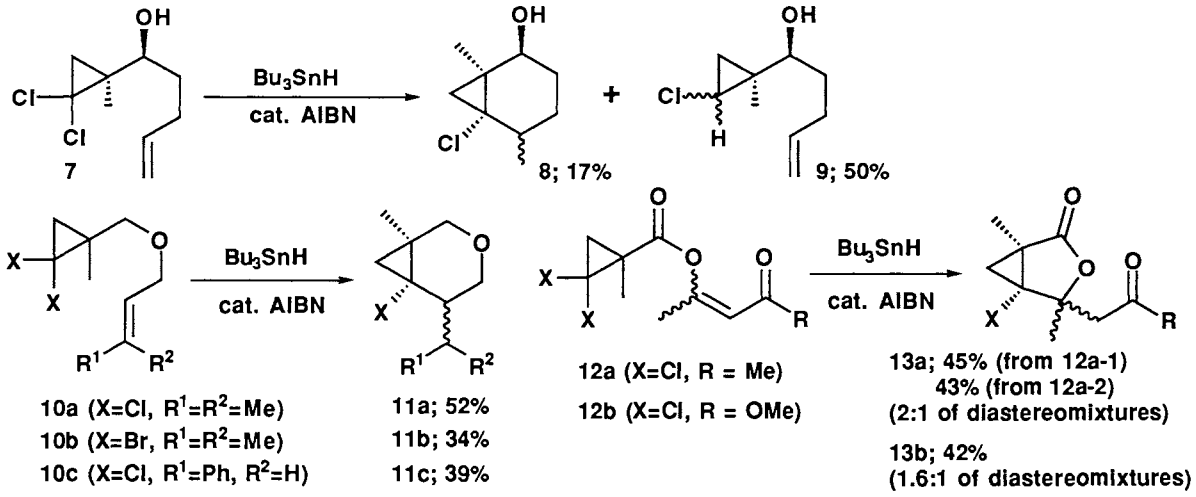
| Entry | Substrate[a] | X | R$^1$ | R$^2$ | R$^3$ | Product[b] | Yield/% |
|---|---|---|---|---|---|---|---|
| 1 | **3a** | Cl | Me | Allyl | H | **4a** | 78 |
| 2 | **3b** | Br | Me | Allyl | H | **4b** | 53 |
| 3 | **3c-1** | Cl | Me | H | H | **4c-1** | 68 |
| 4 | **3c-2** | Cl | Me | H | H | **4c-2** | ~25[c] |
| 5 | **3d-1** | Cl | Me | H | Me | **4d-1** | 80 |
| 6 | **3d-2** | Cl | Me | H | Me | **4d-2** | 15 |
| 7 | **3e-1** | Cl | H | H | Me | **4e-1** | 38 |
| 8 | **3e-2** | Cl | H | H | Me | **4e-2** | 38 |

a) Use of each diastereomer in the case of **3c-3e**. b) The relative configuration between R$^1$ and OH of **4a** (**4a-1**:**4a-2**=1.6:1) or **4b** (**4b-1**:**4b-2**=1.8:1) was not determined.[5] Those of **4c-1**, **4d-1**, and **4e-1** were *cis* and **4c-2**, **4d-2**, and **4e-2** were *trans*, respectively.[8]
c) Estimation of the crude mixtures by $^1$H NMR measurement.

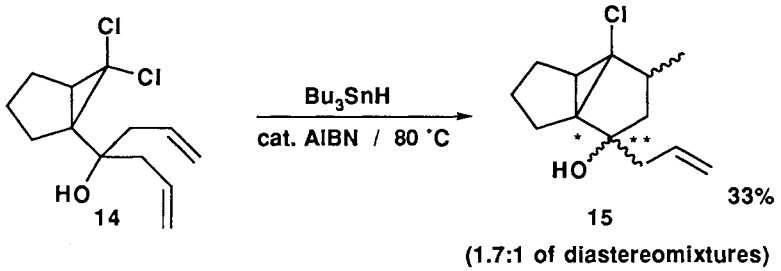
Secondly, 1-propargyl-1-(2,2-dihalo-1-methylcyclopropyl)-3-butyn-1-ols **5a** (X=Br) and **5b** (X=Cl) were tried and dibromide **5a** was found to undergo a similar 5-*exo*-dig type regioselective cyclization to give the bicyclic product **6a**,[9] while uncertain hydrostannylated products were mainly obtained with only 19% of the desired product **6b** in the case of dichloride **5b**.



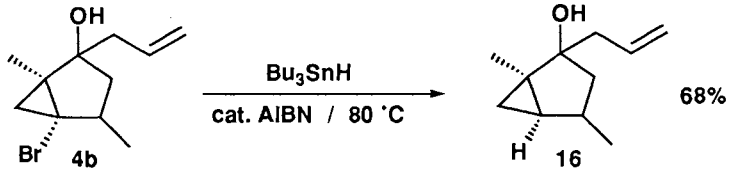
Third, 6-*exo*-trig cyclization was observed for a diastereomer of the 1-(2,2-dichloro-1-methylcyclopropyl)-4-penten-1-ol (**7**) giving **8**[10] though in poor yield (17%) while the main product was the monochloride **9** (50%). On the other hand, oxy-substrates **10a-c**, displacing methylene moiety of **7** with oxygen, gave the desired 6-*exo*-trig bicyclo compounds **11a**,[11] **11b**, and **11c** as the diastereomixtures in moderate yields. In addition, enol ether **12a-1** (*Z*-enol), **12a-2** (*E*-enol), and **12b** (*Z*-enol) could also be subjected to the reaction to give the corresponding 5-*exo*-trig bicyclo compounds **13a**[12] and **13b**, respectively.




Finally, the tricyclic compound **15**[13] was also successfully obtained from the bicyclic substrate **14**.




In conclusion, novel 5-*exo*-trig or dig and 6-*exo*-trig type radical cyclizations of versatile *gem*-dihalocyclopropyl substituted olefins were performed. These results basically agree with the Baldwin's rule.[14] For a further extension, dehalogenation of the resultant bridgehead bromide of **4b** by Bu3SnH/cat.AIBN was found to proceed to give a bicyclo[3.1.0] compound **16**. Accordingly, the sequential radical generation would promise further C-C bond formation such as a tandem (bifurcating) radical cyclization,[15] which is now under investigation in our laboratory.




We thank Dr. Kazunori Yanagi (Sumitomo Chemical Co., Ltd.) for the X-ray crystallographic measurement. This work was partially supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture.

References


1) a) B. Giese, "Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds," Pergamon, Oxford (1986), Chap. 4; b) D. P. Curran, *Synthesis*, **1988**, 417 and 489.
2) D. Seyferth, H. Yamazaki, and D. L. Alleston, *J. Org. Chem.*, **28**, 703 (1963); H. G. Kuivila, *Synthesis*, **1970**, 499.
3) S. Seko, Y. Tanabe, and G. Suzukamo, *Tetrahedron Lett.*, **31**, 6883 (1990).
4) Substrates **3a** and **3b** were prepared by allyl magnesium bromide (2.4 equiv.) with methyl 2,2-dichloro-1-methylcyclopropane carboxylate (commercially available) in 58% and 31% yield, respectively. Secondary alcohols **3c-3e** were prepared similarly from the corresponding allyl bromides and aldehydes. $^1$H NMR (90MHz, $CDCl_3$) of **3a:** δ 1.15 (1H, d, $J_{gem}$ = 8 Hz), 1.40 (3H, s), 2.05 (1H, d, $J_{gem}$ = 8 Hz), 2.18 (1H, brs, -OH), 2.40-2.70 (4H, m), 4.95-5.25 (4H, m), 5.70-6.20 (2H, m).
5) $^1$H NMR and $^{13}$C NMR (400 MHz, $CDCl_3$) of **4a-1**: δ 0.62 (1H, d, $J_{gem}$ = 7.5 Hz), 0.88-0.92 (2H, m), 1.06 (3H, d, $J$ = 6.6 Hz), 1.26 (3H, s), 1.65 (1H, m ), 1.73 (1H, brs, -OH), 2.18 (1H, dd, $J_{gem}$ = 7.8 Hz, $J$ = 6.1 Hz), 2.36 (1H, dd, $J_{gem}$ = 7.8 Hz, $J$ = 6.1 Hz), 2.59–2.68 (1H, m), 5.12–5.14 (2H, m), 5.80-5.87 (1H, m), and δ 12.47, 14.72, 21.15, 36.36, 39.25, 41.72, 42.79, 57.65, 81.01, 118.67, 133.41. And those of **4a-2**: δ 0.57 (1H, d, $J$ = 6.3 Hz), 0.79 (1H, m), 1.08 (3H, d, $J$ = 6.6 Hz), 1.22 (1H, d, $J$ = 6.3 Hz), 1.27 (3H, s), 1.60 (1H, brs, -OH), 1.92 (1H, m), 2.25-2.33 (2H, m), 2.43-2.48 (1H, m), 5.14-5.18 (2H, m), 5.83-5.89 (1H, m), and δ 13.68, 14.78, 19.75, 36.26, 40.10, 41.54, 42.26, 56.74, 80.24, 118.91, 133.42. In the case of **4b**, almost the similar results of the diastereomer ratios (**4b-1**:**4b-2**=1.8:1) and $^1$H NMR spectral pattern were obtained. $^1$H NMR (400 MHz, $CDCl_3$) of **4c-1**: δ 0.55 (1H, d, $J_{gem}$ = 6.3 Hz), 0.65-0.75 (1H, m), 1.06 (3Hx9/11, d, $J$ = 6.4 Hz), 1.08 (3Hx2/11, d, $J$ = 6.5 Hz), 1.18 (1H, d, $J$ = 6.3 Hz), 1.34 (3Hx9/11, s), 1.37 (3Hx2/11, s), 1.60 (1H, brs, -OH), 2.04-2.12 (1H, m), 2.30-2.40 (1Hx9/11, m), 2.40-2.45 (1Hx2/11, m), 4.20 (1Hx9/11, t, $J$ = 8.3 Hz), 4.36 (1Hx2/11, t, $J$ = 8.5 Hz).
6) Ref. 1-a) p. 144; Ref. 1-b) p. 420; A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron*, **41**, 3925 (1985).
7) The non-specificity in the case of **4e-1** and **4e-2** would be explained due to more plausible free rotation of the center C-C bond compared with the other products **4a-4d** bearing methyl group ($R^1$).
8) Since several NMR measurement attempts were unfruitful, relative configuration of the diastereomer **3d-1** (lager Rf value on TLC) was determined by X-ray analysis of the *p*-bromobenzoate of product **4d-1**: Selected data; $C_{16}H_{20}O_2ClBr$, M=356.69, monoclinic, space group C2/c, a=27.308(3)Å, b=5.984(2)Å, c=21.851(2)Å, b=113.249(6)°, V=3280.7(10)Å$^3$, Z=8, $D_{calcd}$=1.456 g/cm$^3$, R=0.051, $R_W$=0.086 for 2125 observations ($I$>3.00σ($I$)). The other diastereomers of **3c** and **3e** were tentatively determined based on the similarity of their $^1$H NMR and Rf values on TLC compared with **3d-1**.
9) About 1:1 diastereomeric mixtures of **6a** were obtained. $^1$H NMR (400 MHz, $CDCl_3$) of **6a-1** (lager Rf value on TLC) : δ 1.19 (1H, d, $J_{gem}$ = 8.0 Hz), 1.39 (3H, s), 1.43 (1H, d, $J_{gem}$ = 8.0 Hz), 2.02 (1H, t, $J$ = 1.5 Hz), 2.07 (1H, brs, -OH), 2.43-2.48 (2H, m), 2.45 (1H, dd, $J$ = 16.0 Hz, $J$ = 3.0 Hz), 2.63 (1H, dd, $J$ = 16.0 Hz, $J$ = 3.0 Hz), 5.01 (1H, s), 5.28 (1H, s). **6a-2**: δ 1.18 (1H, d, $J_{gem}$=4.0 Hz), 1.38 (3H, s), 1.74 (1H, d, $J_{gem}$ = 4.0 Hz), 2.09 (1H, t, $J$ = 1.5 Hz), 2.12 (1H, dd, $J$ = 7.0 Hz, $J$ = 1.5 Hz), 2.17 (1H, brs, -OH), 2.32 (1H, dd, $J$ = 7.0 Hz, $J$ = 1.5 Hz), 2.67 (2H, m), 4.91 (1H, d, $J_{gem}$ = 3.0 Hz), 5.28 (1H, d, $J_{gem}$ = 3.0 Hz).
10) **8** was obtained as 2:1 of diastereomixtures: $^1$H NMR (400 MHz, $CDCl_3$) δ 0.54 (1Hx1/3, d, $Jgem$ = 6.3 Hz), 0.79 (1Hx2/3, d, $Jgem$ = 6.0 Hz), 1.11 (1Hx1/3, d, $Jgem$ = 6.3 Hz), 1.14 (3Hx1/3, d, $J$ = 6.5 Hz), 1.20 (3Hx2/3, d, $J$ = 6.6Hz), 1.23 (1Hx2/3, d, $Jgem$ = 6.0 Hz), 1.42 (3H, s), 1.30-1.90 (4H and -OH, m), 2.18 (1Hx1/3, m), 2.25 (1Hx2/3, m), 3.97 (1Hx2/3, t, $J$ = 8.0 Hz), 4.02 (1Hx1/3, t, $J$ = 8.5 Hz).
11) $^1$H NMR (90 MHz, $CDCl_3$) of **11a** :δ 0.80 (1H, d, $J_{gem}$ = 7.5 Hz), 0.95 (6H, d, $J$ = 8.0 Hz), 1.15 (1H, d, $J_{gem}$ = 7.5Hz), 1.25 (3H, s), 1.60-1.90 (1H, m), 2.00-2.60 (1H, m), 3.10-4.75 (4H, m).
12) $^1$H NMR (400 MHz, $CDCl_3$) δ 0.88-0.94 (1H, m), 1.20-1.39 (1H, m), 1.43 (3Hx2/3, s), 1.48(3Hx1/3, s), 1.56 (3Hx2/3, s), 1.59 (3Hx1/3, s), 2.18 (3Hx2/3, s), 2.24 (3Hx1/3, s), 2.80 (1Hx1/3, d, $J$ = 4.0 Hz), 2.87 (1Hx1/3, d, $J$ = 4.0 Hz), 2.91 (1Hx2/3, d, $J$ = 16.0 Hz), 3.10 (1Hx2/3, d, $J$ = 16.0 Hz). IR (film) 1880, 1735 cm$^{-1}$.
13) $^1$H NMR (400 MHz, $CDCl_3$) of **15-1** (lager Rf value on TLC) : δ 0.97-1.12 (1H, m), 1.02 (3H, d, $J$ = 9.0 Hz), 1.32 (1H, m), 1.67-2.25 (9H, m), 2.41-2.46 (1H, m), 2.72-2.76 (1H, m), 5.09-5.14 (2H, m), 5.77-5.84 (1H, m). **15-2**: δ 0.86 (1H, m), 1.02 (3H, d, $J$ =8.0 Hz), 1.10-2.10 (10H, m), 2.31-2.45 (2H, m), 5.14-5.19 (2H, m), 5.82-5.90 (1H, m).
14) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 734.
15) M. Nagai, J. Lazor, and C. S. Wilcox, *J. Org. Chem.*, **55**, 3440 (1990).


(Received May 9, 1994)