New Elements in the Reactivity of α-Cyclopropyl Vinyl Radicals

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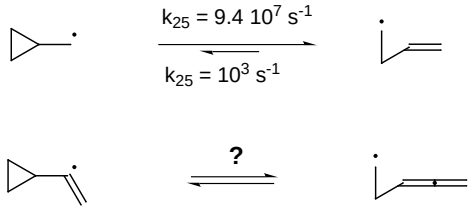
Abstract: The reactivity of the α-cyclopropyl vinyl radical has been examined through the use of propargylic bromomethyldimethylsilyl ethers bearing a cyclopropyl group on the acetylenic moiety. With unsubstituted precursors, allenes can be obtained. With appropriate trapping possibilities (5-*exo* cyclization or hydrogen transfer), the cyclopropyl moiety on the vinyl radical is retained.

Key words: vinyl radicals, cyclizations, ring opening, hydrogen transfer, cyclopropanes

Thanks to its well-established kinetic and thermodynamic parameters, the ring opening of the cyclopropylcarbinyl radical is one of the most popular radical clocks.[1,2] As it provides ultrafast mechanistic probes of radical intermediacy and lifetime, its uses span biological systems[3] to surface science.[4] A related but much less assessed system is the vinyl analog (Scheme 1), for which, to the best of our knowledge, no physical data have been reported.

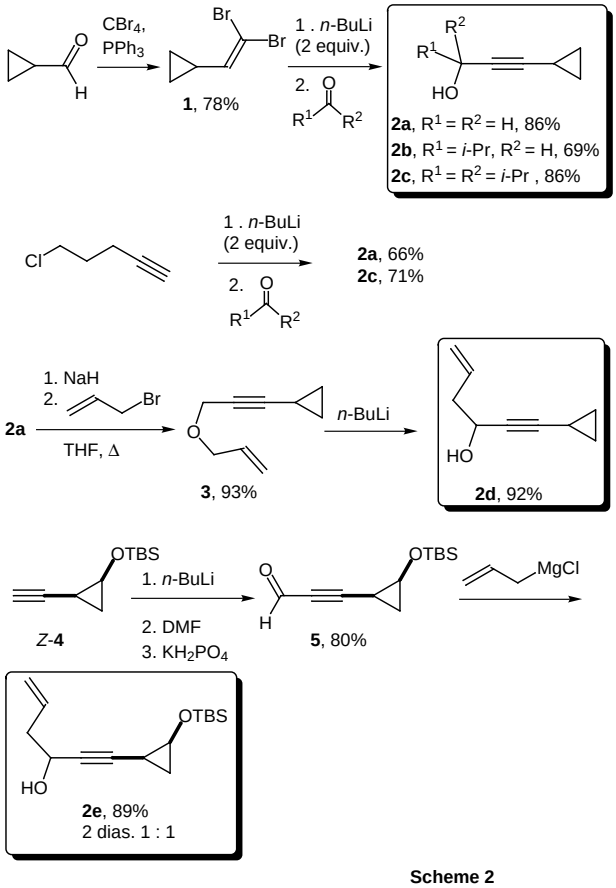


Scheme 1

Inspection of the literature provided only sporadic reports. One of the first investigators in that area was Crandall[5] who showed that at high concentration almost no allene was observed from the reduction of an α-cyclopropyl vinyliodide. Only under dilute reaction conditions a substantial amount of allene was formed. Another important contribution was given by Back,[6] who studied the selenosulfonation of cyclopropylacetylene, and found a mixture where the allene is the minor component. Interestingly, when run with vinylcyclopropane, the same reaction afforded only ring-opened adducts.

All these findings suggested that the ring opening of the vinyl radical is probably slower. We wanted to examine this, and for that purpose utilized our tool, the radical cyclization of propargylic bromomethyl-dimethylsilyl ethers.[7]

This required us to prepare a certain number of cyclopropyl propargylic alcohols of type **2** whose synthesis is scarcely described in the literature (Scheme 2). As cyclopropylacetylene is an expensive and not so readily available starting material, we preferred using the two following routes. Starting from commercially available cyclopropanecarboxaldehyde, a Corey–Fuchs sequence,[8] via dibromoolefin **1**, provided good yields of alcohols **2a**–**c**. Alternatively, an even more straightforward route involved the dimetallation of the commercially available chloropentyne,[9] followed by trapping with a carbonyl derivative, and provided comparable yields of **2a** and **2c**. Secondary alcohol **2d** was obtained through a sequence we already reported and which involves the formation of the allyl ether **3** followed by a Wittig [2,3]-rearrangement.[10] For the OTBS-substituted cyclopropyl alcohol **2e**, we prepared the cyclopropyl acetylenic derivative **4** in its *Z* form according to the method of de Meijere.[11]



Scheme 2

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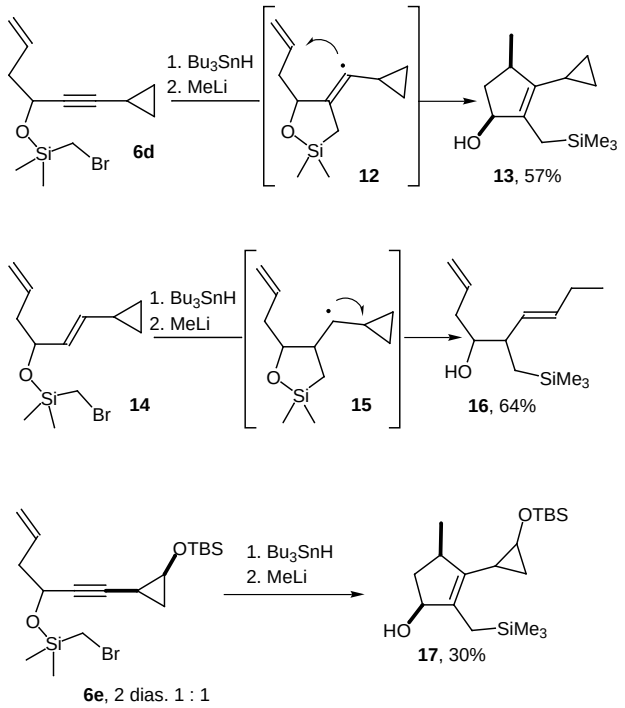
Formylation[12] and alkylation furnished a 1:1 mixture of alcohol **2e**. All these propargylic alcohols could be uneventfully silylated with bromomethyldimethylchlorosilane in presence of triethylamine and DMAP to give the corresponding silyl ethers **6a**–**e**.

Our preliminary attempts focused on the simplest precursor **6a**. Upon treatment with Bu_3SnH under slow addition conditions (2×10^{-4} molh^{-1}) in order to favor the initial 5-*exo-dig* cyclization, followed by Tamao oxidation, allene diol **9** was obtained in a low yield (24%) which did not reflect the cleanliness of the reaction (Scheme 3). A methyllithium treatment and further trapping by methyl chloroformate resulted in a much better yield of functionalized allene **10**.[13] Thus under these conditions, no intermolecular reduction of the vinyl radical **7** seems to intervene at the expense of the ring opening process which generates homoallenyl radical **8**.

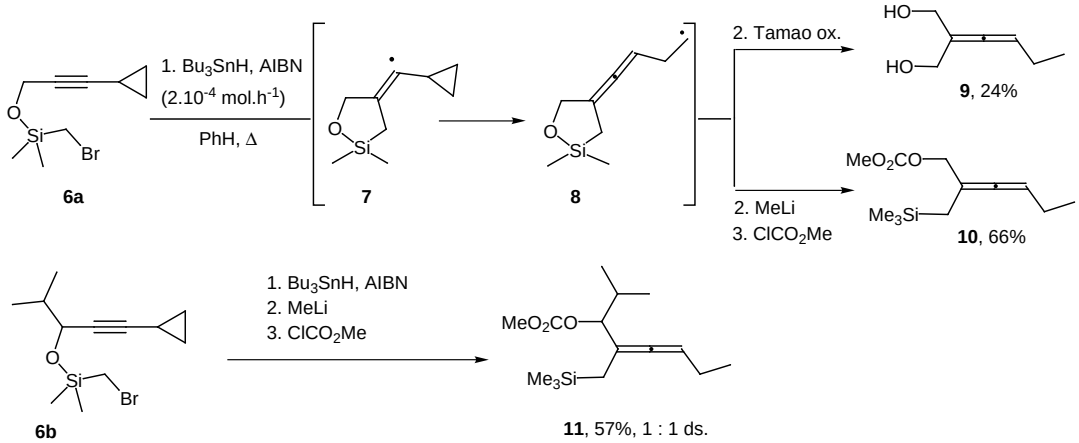
We performed the same transformation on precursor **6b** and showed that a stereogenic center at the propargylic position does not control the diastereoselectivity of the ring opening of the cyclopropyl ring, since a 1:1 diastereomeric mixture of allenes **11** was obtained. This reaction constitutes one of the rare example of radical allene synthesis,[14] and gives an access to functionalized allene derivatives.[15]

Because we run these reactions under slow addition conditions in a dilute medium to favor the initial 5-*exo-dig* cyclization, it will always be difficult to assess the reactivity of these α-cyclopropyl vinyl radicals by intermolecular trapping. So, we concentrated on intramolecular competitive trapping reactions. For instance, we set an unsaturation for a further 5-*exo-trig* cyclization from the initial vinyl radical as in precursors **6d** and **6e**. A clean reaction was observed with **6d**, giving cyclopentenol **13**[16] as a single diastereomer.[10] This suggests that the 5-*exo* cyclization of **12** was faster than the ring-opening process (Scheme 4). This result is especially significant when compared to the outcome of the cyclization of the allyl precursor **14** that gave 1,6-diene **16** as sole adduct, which originates from the fast opening of the cyclopropyl ring on **15**.[17] Precursor **6e** possesses a OTBS group which could be useful for further organic synthesis and should accelerate the ring opening process.[18] Nevertheless, the radical cyclization of **6e** furnished a complex mixture from which no allene was detected. Only one diastereomer of **17,** displaying a *cis* relationship between the hydroxy group and the methyl group as determined by NOE, was isolated, albeit in low yield.



Scheme 4

Another type of possible trapping is hydrogen transfer and previous studies have established that the diisopropyl precursor **6c** is perfectly suited for that purpose.[19] Here also, two possibilities are open for the vinyl radical **18**. The ma-



Scheme 3

jor pathway is the opening of the cyclopropyl ring which delivers allene **21**. The minor one is a diastereoselective 1,5-H transfer, followed by a 5-*endo-trig* cyclization and diastereoselective reduction to give a single diastereomer of **22** (Scheme 5), whose stereochemistry was deduced by analogy with our previous reports.[19]

In conclusion, we have uncovered new and useful pieces of information on the reactivity of α-cyclopropyl vinyl radicals. With unsubstituted precursors, allenes can be obtained. With appropriate trapping possibilities (5-*exo* cyclization or hydrogen transfer), the cyclopropyl moiety on the vinyl radical is retained. This allows the construction of cyclic derivatives incorporating a versatile cyclopropyl ring. Our results seem to confirm that the ring opening of α-cyclopropyl vinyl radicals is a relatively slow process, especially when compared to the alkyl series. The loss of conjugation of the vinylcyclopropane moiety which results from a 90° flip in order to reach the C-C bond breaking conformation could constitute the retarding factor. To pursue this work, two directions are now followed. The first one will consist in the determination of kinetics, which could be useful for the development of a new radical clock. The second one will focus in the application of the α-cyclopropyl vinyl radical as a new partner for radical cascades leading to the synthesis of biologically relevant molecules.

Acknowledgement

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(13) Spectroscopic data for **10**. IR(neat): 2960, 1960, 1750, 1450, 1370, 1270 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.21 (m, 1 H, vinyl), 4.48 (t, *J* = 2.0 Hz, 2 H, CH_2O), 3.75 (s, 3 H, CO_2CH_3), 1.97 (quint, *J* = 7.4 Hz, 2 H, CH_2CH_3), 1.32 (m_{AB}, 2 H, CH_2Si), 0.97 (t, *J* = 7.4 Hz, 3 H, CH_3), 0.02 (s, 9 H, Si(CH_3)$_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.8 (C, C=*C*=CH), 155.8 (C, *C*=O), 97.4 (C, *C*=C=CH), 94.8 (CH, C=C=*C*H), 70.1 (CH_2, *C*H_2O), 54.8 (CH_3, CO_2*C*H_3), 22.5 (CH_2, *C*H_2CH_3), 18.2 (CH_2, *C*H_2Si), 13.6 (CH_3), –1.3 (3 CH_3, Si(*C*H_3)$_3$). Anal. Calcd. for $C_{12}H_{22}O_3Si$: C, 59.46; H, 9.15. Found: C, 59.34; H, 9.35.
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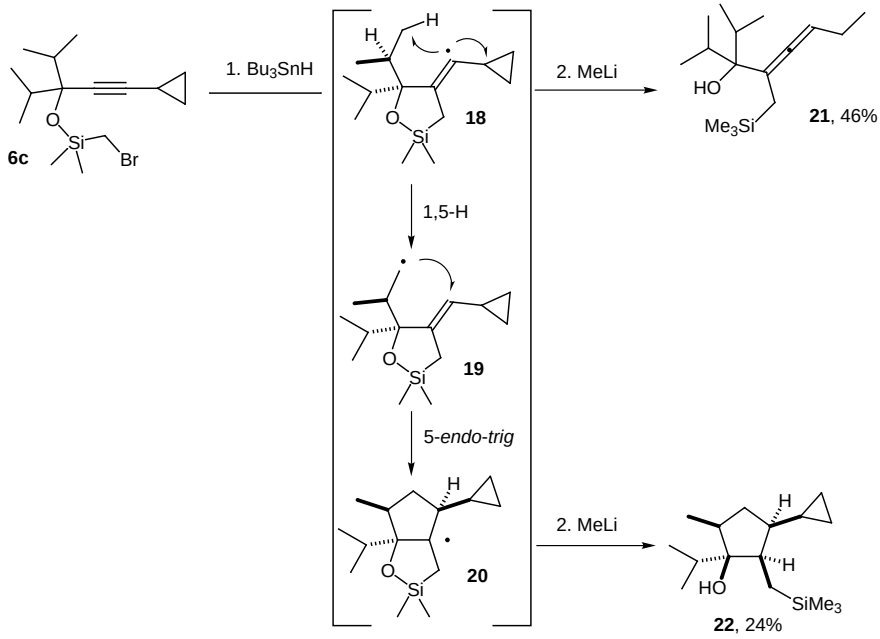

Scheme 5

(15) For instance, see: (a) Lee, P. H.; Bang, K.; Lee, K.; Lee, C.-H.; Chang, S. *Tetrahedron Lett.* **2000**, *41*, 7521. (b) Spino, C.; Fréchette, S. *Tetrahedron Lett.* **2000**, *41*, 8033. (c) Stichler-Bonaparte, J.; Kruth, H.; Lunkwitz, R.; Tschierske, C. *Liebigs Ann.* **1996**, 1375.

(16) (a) The *cis* relative stereochemistry was assigned by analogy with our previous work, see ref.[10] and: Devin, P.; Fensterbank, L.; Malacria, M. *J. Org. Chem*. **1998**, *63*, 6764. (b) Spectral data for **13**. IR(neat): 3350, 3080, 2950, 1640, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.40 (m, 1 H, C*H*-OH), 2.31 (m, 2 H, CH_2 cyclopentenol + C*H*CH_3), 1.76 (d, *J* = 13.8 Hz, 1 H, CH_2Si), 1.64 (d, *J* = 13.8 Hz, 1 H, CH_2Si), 1.34 (m, 1 H, C*H* cyclopropane), 1.26 (m, 1 H, CH_2 cyclopentenol), 1.11 (d, *J* = 6.6 Hz, 3 H, CH_3), 0.70 (m, 2 H, cyclopropane), 0.55 (m, 1 H, cyclopropane), 0.41 (m, 1 H, cyclopropane), 0.04 [9 H, Si(CH_3)$_3$]; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2 (C, C=C), 137.1 (C, C=C), 79.9 (CH, *C*H-OH), 41.9 (CH_2, cyclopentenol), 38.6 (CH, cyclopentenol), 23.0 (CH_3), 16.4 (CH_2, *C*H_2Si), 9.7 (CH, cyclopropane), 5.8 (CH_2, cyclopropane), 5.2 (CH_2, cyclopropane), –0.4 [3 CH_3, Si(*C*H_3)$_3$]. Anal. Calcd. for $C_{13}H_{24}OSi$: C, 69.58; H, 10.78. Found: C, 69.55; H, 10.89.

(17) (a) We thank one of the referees for bringing to our attention that the rate constant of a *5-exo* vinyl radical cyclization has been estimated to be: 3.2×10^8 s^{-1} at 60 °C: Beckwith, A. L. J.; O'Shea, D. M. *Tetrahedron Lett.* **1986**, *27*, 4525. (b) Compared to a value of 2.3×10^5 s^{-1} (20 °C) for the alkyl analog: Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739. (c) Although the Beckwith system cannot directly be compared to the system studied herein (different substitution pattern), this data could suggest an intrinsic faster cyclization of the vinyl radical, thus contributing significantly to the observed effect.

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