JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Bromine Radical-Mediated Sequential Radical Rearrangement and Addition Reaction of Alkylidenecyclopropanes

Takashi Kippo, Kanako Hamaoka, and Ilhyong Ryu*

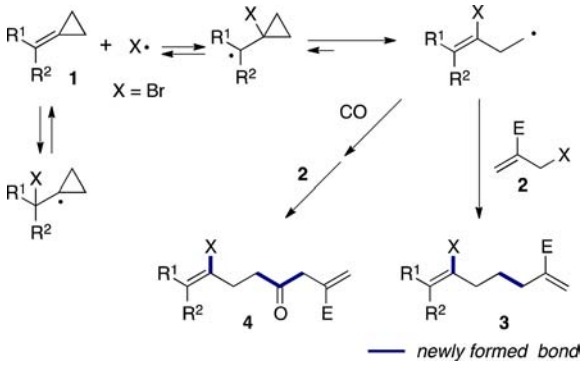
Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan

Supporting Information

ABSTRACT: Bromine radical-mediated cyclopropylcarbinyl-homoallyl rearrangement of alkylidenecyclopropanes was effectively accomplished by C−C bond formation with allylic bromides, which led to the syntheses of 2-bromo-1,6-dienes. A three-component coupling reaction comprising alkylidenecyclopropanes, allylic bromides, and carbon monoxide also proceeded well to give 2-bromo-1,7-dien-5-ones in good yield.

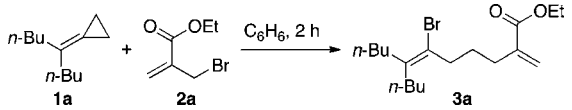
Alkylidenecyclopropanes are useful building blocks in organic synthesis[1] and are found in bioactive compounds.[2] Based on their high reactivity derived from ring strain, the ring-opening reactions of alkylidenecyclopropanes by transition metal catalysts have been pursued vigorously. However, in contrast the utilization of alkylidenecyclopropanes in radical C−C bond forming reactions has received much less attention.[1i,3−5] Inspired by the work of Tanko and co-workers,[6] we have previously developed the radical bromoallylation of alkynes[7] and allenes[8] affording 1-bromo-substituted 1,4- and 2-bromo-substituted 1,5-dienes respectively, in which the bromine radical serves as a chain propagator[6] and the source of the vinyl bromide moiety in the products. In the hope of extending radical-mediated diene synthesis further, we believed that 2-bromo-substituted 1,6-dienes would be obtained by the reaction of alkylidenecyclopropanes and allylic bromides in the presence of a radical initiator, via regioselective bromine radical addition so as to form cyclopropylcarbinyl radicals with their resulting ring opening leading to homoallyl radicals (Scheme 1).[3h] Herein we report an efficient synthesis of 2-bromo-substituted 1,6-dienes **3** via radical bromoallylation of alkylidenecyclopropanes **1** with allylic bromides **2**. We also report that alkylidenecyclopropanes **1** undergo sequential addition to carbon monoxide and allylic bromides **2** to give 2-bromo-1,7-dien-5-ones **4** in good yield, representing the first bromine radical-mediated carbonylation reaction.[9,10]

Scheme 1. Bromoallylation and Carbonylative Bromoallylation of Alkylidenecyclopropanes 1



Initially, (1-butylpentylidene)cyclopropane (**1a**) and ethyl 2-(bromomethyl)acrylate (**2a**) were chosen to test the feasibility of our hypothesis. When a benzene (1.0 mL) solution of **1a** (1.0 mmol), **2a** (1.8 mmol), and V-70 (2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile)), 0.1 mmol) was stirred for 2 h at 40 °C under an argon atmosphere, ethyl 6-bromo-7-butyl-2-methylene-6-undecenoate (**3a**) was obtained in 30% yield (Table 1, entry 1). Since the ring-opening products from the reaction of **1a** with hydrogen bromide were observed as byproducts, we added anhydrous trisodium phosphate as an HBr scavenger, which improved the yield of 1,6-diene **3a** up to 74% (entry 2). Maintaining the reaction temperature at 40 °C or lower is very important to obtain a good yield of **3a**, since, at temperatures such as 60 and 80 °C, the isomerization of **1a** becomes serious (entries 3 and 4). The use of increased amounts of base improved the yields of **3a** (entries 5 and 6) but no better than that obtained by the reaction at 40 °C.

Table 1. Optimization of Reaction Conditions Using (1-Butylpentylidene)cyclopropane (1a) and Ethyl 2-(Bromomethyl)acrylate (2a)[a]



entry	initiator (mol %)	Na_3PO_4 (equiv)	temp (°C)	yield[b] (%)
1	V-70, 10	–	40	30
2	V-70, 10	0.2	40	74[c]
3	V-65, 10	0.2	60	38
4	AIBN, 10	0.2	80	30
5	V-65, 30	3.0	60	63
6	AIBN, 30	3.0	80	54

[a]Conditions: **1a** (1.0 mmol), **2a** (1.8 equiv), V-70 (2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile)) or V-65 (2,2′-azobis(2,4-dimethylvaleronitrile)) or AIBN (2,2′-azobisisobutyronitrile), Na_3PO_4, degassed C_6H_6 (1.0 mL) under an argon atmosphere. [b]NMR yield using anisole as an internal standard. [c]Isolated yield by column chromatography on SiO_2 and preparative HPLC.

Received: December 4, 2012
Published: December 26, 2012

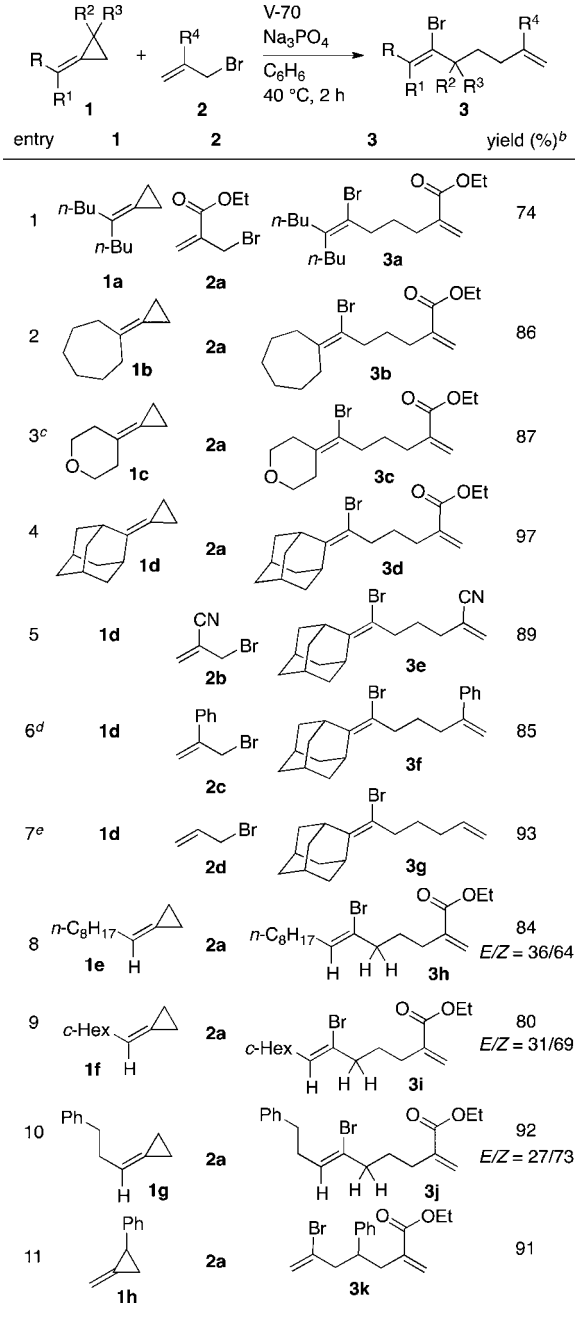
   dx.doi.org/10.1021/ja311821h | J. Am. Chem. Soc. 2013, 135, 632−635

With the optimized reaction conditions for **1** (Table 1, entry 2) in hand, we examined the generality of the present allylative ring-opening reaction for a wide range of alkylidenecyclopropanes **1** and allylic bromides **2** (Table 2). Cyclopropylidenecycloheptane (**1b**) produced the desired 2-bromo-substituted 1,6-diene **3b** in 86% yield (entry 2). Similarly, 4-cyclopropylidenetetrahydropyran (**1c**) reacted with **2a** to give **3c** in 87% yield (entry 3). The reaction of sterically hindered adamantylidenecyclopropane **1d** also proceeded well to give **3d** in 97% yield (entry 4). Some other allylic bromides such as α-bromomethylacrylonitrile (**2b**), α-bromomethylstyrene (**2c**), allyl bromide (**2d**) were also tested, all of which worked well. For example, the bromoallylation reaction of **1d** with **2b** gave the expected diene **3e** in 89% yield (entry 5). Since 2-phenyl-substituted allyl bromide **2c** exhibited modest reactivity, we used 3 equiv of **2c** to increase the yield of the addition product **3f** (entry 6). In the case of allyl bromide (**2d**), the use of a large excess of **2d** compensated for the lack of reactivity toward nucleophilic alkyl radicals (entry 7).[11] Monosubstituted alkylidenecyclopropanes **1e**, **1f**, and **1g** gave the corresponding products, **3h**, **3i**, and **3j**, in high yields, all of which were obtained as *E*/*Z* mixtures favoring the *Z* isomer (entries 8–10). Phenyl-functionalized methylenecyclopropane **1h** gave 2-bromo-4-phenyl-1,6-dienes **3k** as a sole product (entry 11), which originated from the more stable benzylic radical.

Since the ring-opening reaction generates homoallylic radicals, we believed that these radicals could trap CO. Indeed, the three-component coupling reaction comprising alkylidenecyclopropanes **1**, CO, and **2a** worked well to give good yields of 2-bromine-substituted 1,7-dien-5-ones **4** (Table 3). For instance, treatment of a benzene solution of (1-butylpentylidene)cyclopropane (**1a**), ethyl 2-(bromomethyl)-acrylate (**2a**), anhydrous trisodium phosphate, and V-65 with 80 atm of CO at 60 °C for 6 h resulted in the synthesis of ethyl 7-bromo-8-butyl-2-methylene-4-oxo-7-dodecenoate (**4a**) in 72% yield after purification by column chromatography on SiO_2.

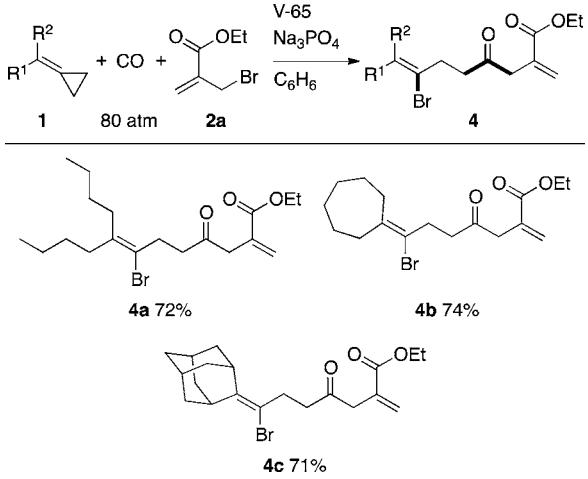
A proposed reaction mechanism for the present bromoallylation and the carbonylative bromoallylation of alkylidenecyclopropanes is shown in Scheme 2. Initially, a bromine radical is generated from allylic bromide **2** through a radical initiation process. Then the bromine radical adds to the central carbon of alkylidenecyclopropane **1** to give cyclopropylmethyl radical **A**, which undergoes rearrangement leading to homoallyl radical **B**.[12] The homoallyl radical **B** adds to CO to form acyl radical **D**. **D** then adds to **2** to produce intermediate **E**, which undergoes β-fission to give 2-bromo-substituted 1,7-dien-5-one **4** and a bromine radical. In the absence of CO, the path to give intermediate **C** operates to sustain the radical chain.

Table 2. Generality of the Reaction of Alkylidenecyclopropanes and Allylic Bromides To Give 2-Bromo-1,6-dienes[a]



[a]Conditions: **1** (1.0 mmol), **2** (1.8 mmol), V-70 (0.1 mmol), Na_3PO_4 (0.2 mmol), C_6H_6 (1.0 mL), 40 °C, 2 h under an argon atmosphere. See Supporting Information for details. [b]Isolated yield. [c]50 °C, 6 h. [d]**2c** (3.0 equiv), 6 h. [e]**2d** (58 equiv), 6 h, neat.

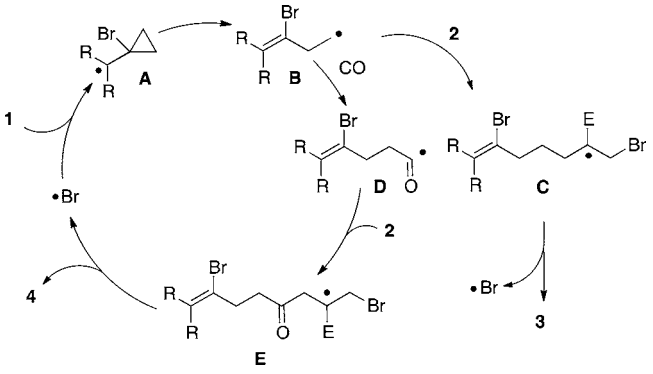
Table 3. Radical Carbonylation Reaction of 1 with 2a[a]



[a]Conditions: **1** (0.5 mmol), **2a** (1.0 mmol), V-65 (0.25 mmol), Na_3PO_4 (0.1 mmol), CO (80 atm), C_6H_6 (20 mL), 60 °C, 6 h under an argon atmosphere.

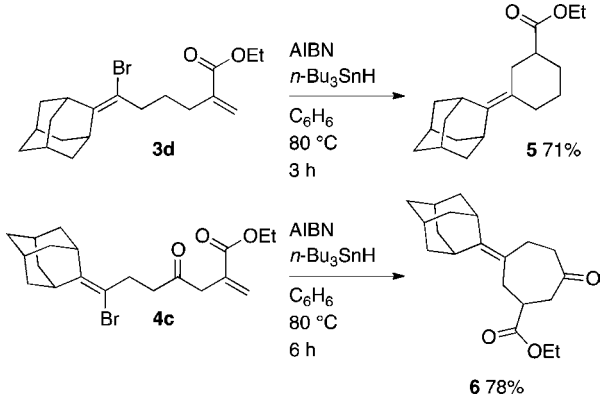
dx.doi.org/10.1021/ja311821h | J. Am. Chem. Soc. 2013, 135, 632–635

Scheme 2. Radical Chain Reaction Mechanisms



Since the products have vinyl bromide moieties, they are amenable to many further transformations. For example, the tributyltin hydride mediated 6-endo cyclization of **3d** and 7-endo cyclization of **4c** proceeded smoothly to form disubstituted cyclohexane **5** and cycloheptanone **6** as the sole products, respectively (Scheme 3).

Scheme 3. Radical Cyclization of 3[a] and 4[b]



[a]Conditions: **3d** (0.5 mmol), *n*-Bu_3SnH (0.75 mmol), AIBN (0.1 mmol), C_6H_6 (10 mL), 80 °C, 3 h under an argon atmosphere. [b] Conditions: **4c** (0.5 mmol), *n*-Bu_3SnH (0.75 mmol), AIBN (0.1 mmol), C_6H_6 (10 mL), 80 °C, 6 h under an argon atmosphere.

In conclusion, we have developed a novel protocol for the synthesis of 2-bromo-1,6-dienes from alkylidenecyclopropanes and allylic bromides via radical ring-opening and S_H2' reactions. We also demonstrated that radical carbonylation could be incorporated in the reaction sequence, leading to 2-bromo-1,7-dien-5-ones. Further applications of the products as well as other multicomponent reactions are currently in progress in this laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

ryu@c.s.osakafu-u.ac.jp

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work has been supported by a Grant-in-Aid for Scientific Research on Innovative Areas (No. 2105) from the MEXT. T.K. acknowledges the Research Fellowship of the Japan Society for the Promotion of Science for Young Scientists.

■ REFERENCES

(1) For leading reviews, see: (a) Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (c) Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589. (d) Nakamura, E.; Yamago, S. *Acc. Chem. Res.* **2002**, *35*, 867. (e) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111. (f) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213. (g) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (h) Masarwa, A.; Marek, I. *Chem.—Eur. J.* **2010**, *16*, 9712. (i) Pellissier, H. *Tetrahedron* **2010**, *66*, 8341. (j) Audran, G.; Pellissier, H. *Adv. Synth. Catal.* **2010**, *352*, 575.

(2) (a) Baldwin, J. E.; Parker, D. W. *J. Org. Chem.* **1987**, *52*, 1475. (b) Lai, M.-T.; Oh, E.; Shih, Y.; Liu, H.-W. *J. Org. Chem.* **1992**, *57*, 2471 and cited references therein. (c) Nemoto, T.; Yoshino, G.; Ojika, M.; Sakagami, Y. *Tetrahedron* **1997**, *53*, 16699.

(3) For radical addition and ring opening of methylenecyclopropanes, see: (a) Kozhushkov, S. I.; Brandl, M.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, 1535. (b) Xu, B.; Chen, Y.; Shi, M. *Tetrahedron Lett.* **2002**, *43*, 2781. (c) Tsuchii, K.; Imura, M.; Kamada, N.; Hirao, T.; Ogawa, A. *J. Org. Chem.* **2004**, *69*, 6658. (d) Huang, J.-W.; Shi, M. *J. Org. Chem.* **2005**, *70*, 3859. (e) Yu, L.; Huang, X.; Xie, M. *Synlett* **2006**, 423. (f) Yu, L.; Huang, X. *Synlett* **2007**, 1371. (g) Fu, W.-J.; Huang, X. *J. Organomet. Chem.* **2007**, *692*, 740. (h) Yu, L.; Chen, B.; Huang, X.; Wu, L. L. *Chin. Chem. Lett.* **2007**, *18*, 121. (i) Hayashi, N.; Hirokawa, Y.; Shibata, I.; Yasuda, M.; Baba, A. *J. Am. Chem. Soc.* **2008**, *130*, 2912. (j) Miao, M.; Huang, X. *J. Org. Chem.* **2009**, *74*, 5636.

(4) For radical cyclization onto methylenecyclopropanes, see: (a) Destabel, C.; Kilburn, J. D. *J. Chem. Soc., Chem. Commun.* **1992**, 596. (b) Boffey, R. J.; Whittingham, W. G.; Kilburn, J. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 487. (c) Underwood, J. J.; Hollingworth, G. J.; Horton, P. N.; Hursthouse, M. B.; Kilburn, J. D. *Tetrahedron Lett.* **2004**, *45*, 2223. (d) Ardura, D.; Sordo, T. L. *J. Org. Chem.* **2006**, *71*, 4803.

(5) For thiyl radical mediated radical ring opening and annulations of methylenecyclopropanes, see: (a) Singleton, D. A.; Church, K. M. *J. Org. Chem.* **1990**, *55*, 4780. (b) Singleton, D. A.; Huval, C. C.; Church, K. M.; Priestley, E. S. *Tetrahedron Lett.* **1991**, *32*, 5765. (c) Huval, C. C.; Church, K. M.; Singleton, D. A. *Synlett* **1994**, 273. (d) Huval, C. C.; Singleton, D. A. *J. Org. Chem.* **1994**, *59*, 2020.

(6) (a) Tanko, J. M.; Sadeghipour, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 159. (b) Struss, J. A.; Sadeghipour, M.; Tanko, J. M. *Tetrahedron Lett.* **2009**, *50*, 2119.

(7) Kippo, T.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2010**, *12*, 4006.

(8) Kippo, T.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2011**, *13*, 3864.

(9) For reviews on radical carbonylation reactions using carbon monoxide, see: (a) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed.* **1996**, *35*, 1050. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (c) Ryu, I. *Chem. Soc. Rev.* **2001**, *30*, 16. Also see a review on acyl radicals: (d) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.

(10) For recent work, see: (a) Ryu, I.; Fukuyama, T.; Tojino, M.; Uenoyama, Y.; Yonamine, Y.; Terasoma, N.; Matsubara, H. *Org. Biomol. Chem.* **2011**, *9*, 3780. (b) Ryu, I.; Tani, A.; Fukuyama, T.; Ravelli, D.; Fagnoni, M.; Albini, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1869. (c) Fusano, A.; Sumino, S.; Nishitani, S.; Inoue, T.; Morimoto, K.; Fukuyama, T.; Ryu., I. *Chem.—Eur. J.* **2012**, *18*, 9415.

(11) (a) Walbiner, M.; Wu, J. Q.; Fischer, H. *Helv. Chim. Acta* **1995**, *78*, 910. (b) Zytowski, T.; Fischer, H. *J. Am. Chem. Soc.* **1997**, *119*, 12869. (c) Fischer, H.; Radom, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 1340. (d) Fischer, H.; Radom, L. *Macromol. Symp.* **2002**, *182*, 1.

(12) (a) Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7024. (b) Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.*

1989, *111*, 275. (c) Hollis, R.; Hughes, L.; Bowry, V. W.; Ingold, K. U. *J. Org. Chem.* **1992**, *57*, 4284. (d) Horner, J. H.; Tanaka, N.; Newcomb, M. *J. Am. Chem. Soc.* **1998**, *120*, 10379.