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Communications

Unpredicted Cyclization of an Enyne Having a Keto-Carbonyl Group on an Alkyne Using a Ruthenium Catalyst under Ethylene Gas

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Summary: Ruthenium-catalyzed cyclization of an enyne having a keto-carbonyl group on an alkyne under ethylene gas gave a cyclized compound with a cyclopropane ring on the substituent. Coordination of the carbonyl oxygen to a ruthenium metal of an intermediary ruthenacyclopentene is important and causes the formation of ruthenium carbene followed by construction of a cyclopropane ring by ethylene.

Ruthenacyclopentene **I**, generated from an enyne and ruthenium complex via oxidative cyclization, is a useful intermediate in synthetic organic chemistry.[1] β-Hydrogen elimination from **I**[2] or insertion of carbon monoxide into **I**[3] gave various cyclized compounds. On the other hand, [5+2] or [4+2] cycloaddition via ruthenacyclopentene is an interesting reaction.[4] We have already reported ruthenium-catalyzed ethylenative cyclization of an enyne under ethylene gas.[5] In this reaction, insertion of ethylene into ruthenacyclopentene **I** occurs to afford ruthenacycloheptene **II**, which is followed by β-hydrogen elimination giving cyclized compound **2** with a diene moiety.

During the course of an investigation of substituent effects on ethylenative cyclization, we found an unpredicted cyclization of enyne **1**. When a toluene solution of enyne **1a**, having a methyl ketone on the alkyne, and 5 mol % of Cp*RuCl(cod)[6] was stirred under ethylene gas (1 atm) at room temperature for 3 h, a cyclized compound, whose mass spectrum indicates the insertion of ethylene into the molecule, was obtained in almost quantitative yield along with a trace amount of desired product **2a** ($R = COCH_3$, $R' = H$). The ^{1}H NMR spectrum of the product shows peaks of the cyclopropane ring at a higher field. From other spectral data, the structure of this compound was determined to be **3a**.

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(1) Recent review for cyclization of enyne: (a) Trost, B. M.; Toste, F. D.; Pinkerton, A. B.*Chem. Rev*. **2001**, *101*, 2067. (b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev*. **2002**, *102*, 813. (c) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215. (d) Diver, S. T.; Giessert, A. J. *Chem. Rev*. **2004**, *104*, 1317.

(2) (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 9728. (b) Trost, B. M.; Toste, F. D.; *J. Am. Chem. Soc.* **2000**, *122*, 714. (c) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc*. **2002**, *124*, 5025. (d) Trost, B. M.; Chisholm, J. D.; Wrobleski, S. T.; Jung, M. *J. Am. Chem. Soc*. **2002**, *124*, 12420. (e) Trost, B. M.; Surivet, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15592. (f) Trost, B. M.; Dong, L.; Schroeder, G. M. *J. Am. Chem. Soc*. **2005**, *127*, 10259.

(3) (a) Kondo, T.; Suzuki, N.; Okada, T.; Mitsudo, T. *J. Am. Chem. Soc*. **1997**, *119*, 6187. (b) Morimoto, T.; Chatani, N.; Fukumoto, Y.; Murai, S. *J. Org. Chem*. **1997**, *62*, 3762.

(4) [5+2] cycloaddition of an alkyne and vinylcyclopropane: (a) Trost, B. M.; Toste, F. D.; Shen, H. *J. Am. Chem. Soc.* **2000**, *122*, 2379. (b) Trost, B. M.; Schen, H. C. *Org. Lett*. **2000**, *2*, 2523. (c) Trost, B. M.; Schen, H. C.; Schulz, T.; Koradin, C.; Schirok, H. *Org. Lett*. **2003**, *5*, 4149. (d) Trost, B. M.; Toste, F. D.; Shen, H. *J. Am. Chem. Soc.* **2000**, *122*, 6138. [4+2] cycloaddition of yne-enones: (e) Trost, B. M.; Brown, R. E.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 5877. Ruthenium-catalyzed skeletal reorganization: (f) Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc*. **1994**, *116*, 6049. (g) Chatani, N.; Kataoka, K.; Murai, S. *J. Am. Chem. Soc*. **1998**, *120*, 9104.

(5) Mori, M.; Saito, N.; Tanaka, D.; Takimoto, M.; Sato, Y. *J. Am. Chem. Soc*. **2003**, *125*, 5606.

(6) Oshima, N.; Suzuki, H.; Moro-oka, Y. *Chem. Lett.* **1984**, 1161.

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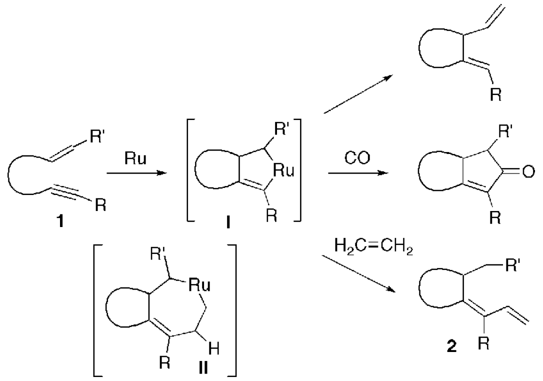
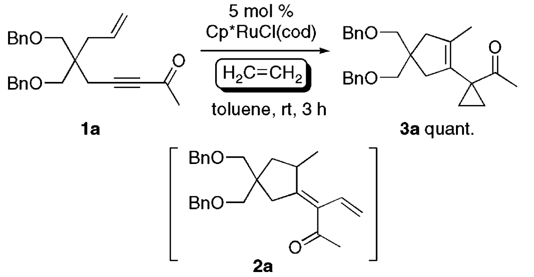
Scheme 1. Ruthenium-Catalyzed Enyne Cyclization



Scheme 2. Reaction of Enyne Having a Methyl Ketone on the Alkyne



Although the reason for formation of this compound is not clear at this stage, various enynes having a keto-carbonyl group on the alkyne were examined under similar reaction conditions, and in each case, cyclized compound **3**, having a cyclopropane ring on a substituent, was obtained in high yield (Table 1). Enynes **1b**−**f**, having methyl, *n*-propyl, isopropyl, cyclohexyl, and phenylpropyl ketones, gave the corresponding cyclized compounds **3b**−**f** in high yields (entries 1−5). No product was formed in the case of enyne **1h**, having a *tert*-butyl ketone on the alkyne, and the starting material remained unchanged. Enyne **1g**, having a benzyloxypropyl ketone on the alkyne, gave cyclized compound **3g** in high yield (entry 6).

However, surprisingly, enynes **1i** and **1j**, having a heteroatom in the carbon chain, gave cyclized compounds **2i** and **2j**, having a conjugated diene moiety, in moderate yields. Furthermore, the carbonyl group of aldehyde did not show the same role as that of the ketone, and compound **2k**, having a diene moiety, was produced from enyne **1k** in 71% yield.

Scheme 3. Ethylenative Cyclization of Enyne

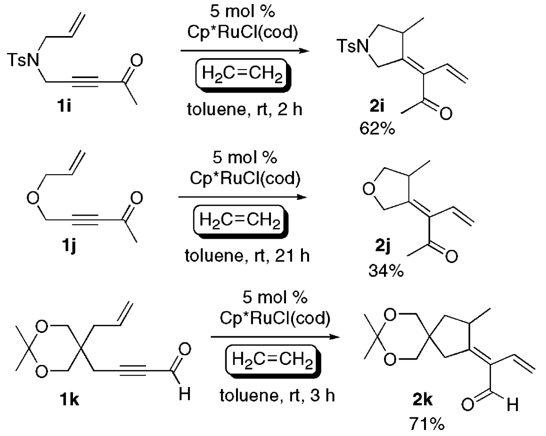
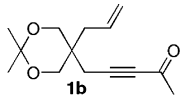
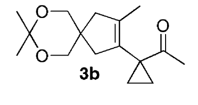
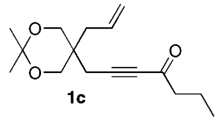
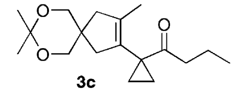
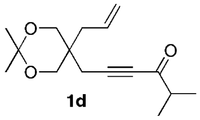
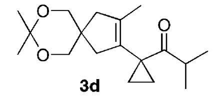
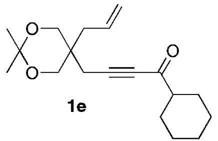
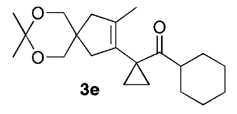
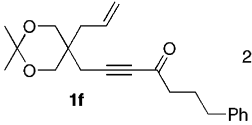
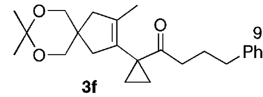
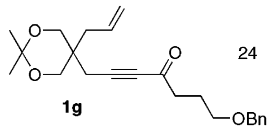
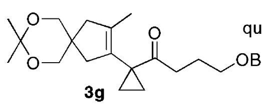
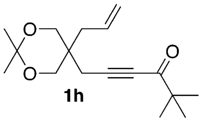


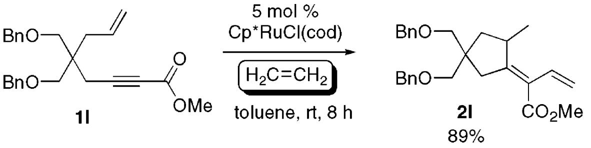
Table 1. Reaction of Enyne Having Various Keto-Carbonyl Groups[a]

entry	substrate	time (h)	product	yield (%)
1	 **1b**	2	 **3b**	86
2	 **1c**	10	 **3c**	98
3	 **1d**	17	 **3d**	quant.
4	 **1e**	7	 **3e**	99
5	 **1f**	24	 **3f**	98
6	 **1g**	24	 **3g**	quant.

[a] All reactions were carried out using 5 mol % of Cp*RuCl(cod) in toluene at room temperature under ethylene gas (1 atm).

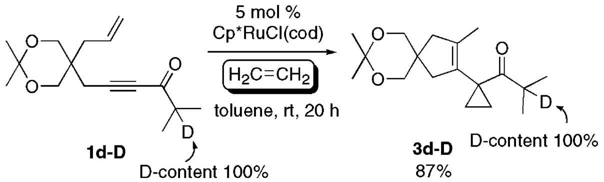

1h

It is interesting that although enyne **1l**, having an ester group on the alkyne, gave **2l**, having a diene moiety, in 89% yield (eq 1),[5] enynes having an alkyl-ketone afforded cyclized compounds **3**, having a cyclopropane ring on the substituent, in high yields.



To determine whether the enolizable proton is important or not in this reaction since **1h** or **1k** did not give **3h** or **3k**, compound **1d-D** (D-content, 100%) was synthesized and the reaction of **1d-D** with Cp*RuCl(cod) was carried out under ethylene gas at room temperature. As a result, **3d-D** was obtained in 87% yield and deuterium remained at the initial position of the isopropyl group.

Scheme 4. Reaction of D-Labeled Enyne with Ethylene



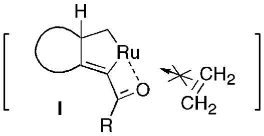
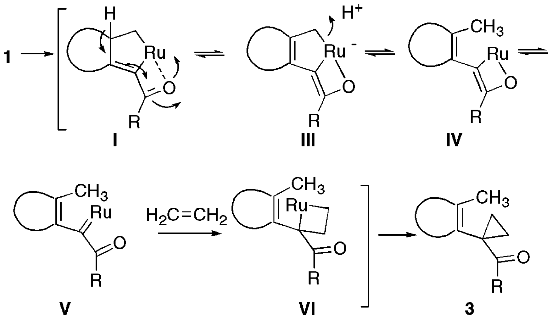


Figure 1.

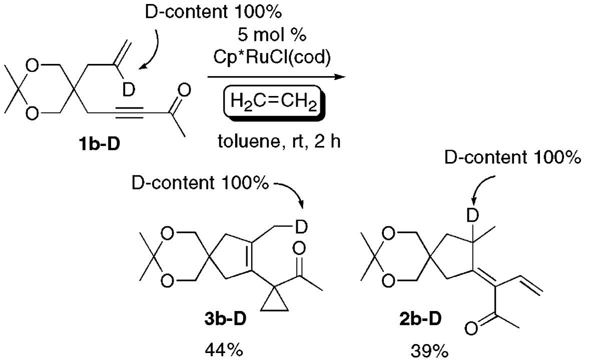
The fact that the cyclopropane ring was formed on the alkyne carbon of the starting enyne suggested that the ruthenium carbene should be generated at this position.[7] On the basis of these results, the possible reaction course for formation of compound **3** was considered as shown in Scheme 5. The reaction proceeds via oxidative cyclization of the enyne by Cp*RuCl(cod) to form ruthenacyclopentene **I**. Since carbonyl oxygen should coordinate to the ruthenium metal, complex **III** is formed. Then it is converted into oxaruthenacyclobutene **IV**, which is in a state of equilibrium with ruthenium carbene complex **V**. Then ethylene reacts with **V** to form ruthenacyclobutane **VI**, and reductive elimination from **VI** gives compound **3**, having a cyclopropane ring.

Scheme 5. Possible Reaction Course

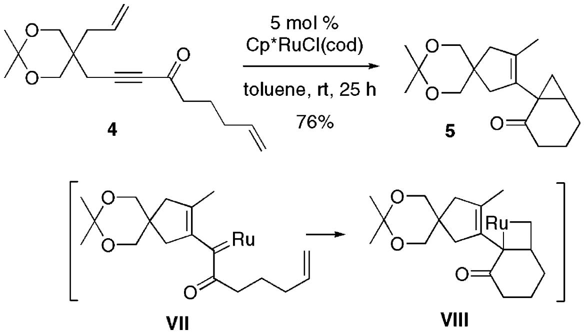


To confirm this reaction mechanism, compound **1b-D** was synthesized and the reaction of **1b-D** with Cp*RuCl(cod) was carried out in a similar manner to afford compound **3b-D**. Deuterium was incorporated into the methyl group of **3b-D**, and the D-content was the same as that of the starting enyne **1b-D**. The result does not contradict the reaction course shown in Scheme 5. Presumably, coordination of oxygen to the ruthenium metal is the driving force in this reaction, and ethylene could not be inserted into the ruthenium-sp2 carbon bond of ruthenacyclopentene **I** to form ruthenacycloheptene **II** (Figure 1). It is interesting that a considerable amount of **2b-D** was formed in this case.[8] The reason for formation of **2i**−**k** from **1i**−**k** is not clear.[9]

Scheme 6. Reaction of Enyne Having Deuterium on the Alkene



Scheme 7. Reaction of Enyne Having an Alkene Moiety on the Alkyne



To confirm the generation of ruthenium carbene on the initial alkyne carbon, enyne **4**, having an alkene moiety tethered to the alkyne, was synthesized.[10] When a toluene solution of enyne **4** and 5 mol % of Cp*RuCl(cod) was stirred at room temperature under argon gas for 25 h, compound **5** was obtained in 76% yield. This result indicates that the ruthenium carbene **VII** is formed on the alkyne carbon and the alkene part reacts with this carbene intramolecularly to form ruthenacyclobutane **VIII**, and reductive elimination gives compound **5**.

A substituent effect on ruthenium-catalyzed alkenylative cyclization was examined. When enyne **1**, having a keto-carbonyl group on the alkyne, was reacted with Cp*RuCl(cod) under ethylene gas, an unpredicted reaction occurred from ruthenacyclopentene **I** to give cyclized compound **3**, having a cyclopropane ring on the substituent. The reaction proceeds via the formation of ruthenium carbene on the alkyne carbon. The carbonyl oxygen of the alkyl-ketone on the alkyne plays an important role in the formation of ruthenium carbene. Further studies are in progress.

Supporting Information Available: Information on experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OM058053I

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(7) Some examples of the generation of a carbene on an alkyne by a ruthenium complex are known. (a) Yamamoto, Y.; Kitahara, H.; Ogawa, R.; Kawaguchi, H.; Tatsumi, K.; Itoh, K. *J. Am. Chem. Soc.* **2000**, *122*, 4310. (b) Yamamoto, Y.; Hata, K.; Arakawa, T.; Itoh, K. *Chem. Commun.* **2003**, 1290. (c) Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125*, 12143. (d) Yamamoto, Y.; Ishii, J. I.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2004**, *126*, 3712. (e) Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Takagishi, H.; Okuda, S.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 605. (f) Kirchner, K.; Calhorda, M. J.; Schmid, R.; Veiros, L. F. *J. Am. Chem. Soc.* **2003**, *125*, 11721. (g) Le Paih, J.; Derien, S.; Dixneuf, P. H. *Chem. Commun.* **1999**, 1437. (h) Le Paih, J.; Monnier, F.; Dérien, S.; Dixneuf, P. H.; Clot, E.; Eisenstein, O. *J. Am. Chem. Soc.* **2003**, *125*, 11964. (i) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2001**, *123*, 8862. (j) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4178. (k) Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003**, *5*, 1467. (l) Trost, B. M.; Rudd, M. T.; Costa, M. G.; Lee, P. I.; Pomerantz, A. E. *Org. Lett.* **2004**, *5*, 4235. (m) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2005**, *127*, 4763. (n) Trost, B. M.; Huang, X. *Org. Lett.* **2005**, *7*, 2097.

(8) Elimination of the proton from **I** may be the rate-determining step in this reaction.

(9) The reason for formation of **2k** from **1k** may be that the carbonyl oxygen is placed on the opposite site of the ruthenium metal due to the steric bulk of the carbonyl oxygen compared with that of the formyl proton.

(10) Murai confirmed the generation of a carbene on an alkyne by a similar procedure. See ref 4g.