

Ruthenium-Catalyzed Ring-Opening and
Ring-Closing Enyne Metathesis

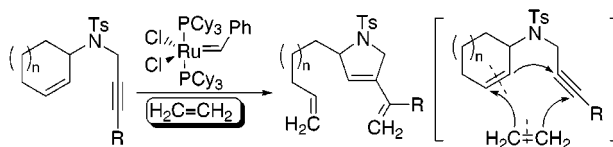
Tsuyoshi Kitamura and Miwako Mori*

Graduate School of Pharmaceutical Sciences, Hokkaido University,
Sapporo 060-0812, Japan

mori@pharm.hokudai.ac.jp

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ABSTRACT

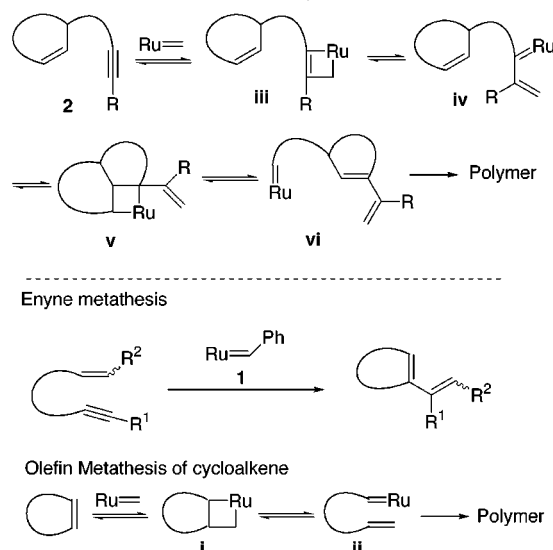


When a CH_2Cl_2 solution of an enyne containing the cycloalkene moiety was stirred in the presence of ruthenium–carbene complex (10 mol %) at room temperature under ethylene gas (1 atm), ring-opening and ring-closing metathesis occurred to afford cyclized triene. The reaction was carried out under argon gas, and no cyclized product was obtained. Enynes with a terminal alkyne gave good results.

Enyne metathesis is very interesting and useful in synthetic organic chemistry, because carbon–carbon bond formation occurs between alkene and alkyne carbons to afford a cyclized product and the alkylidene part of alkene migrates to the alkyne carbon.¹ Thus, the initial double bond is cleaved and the triple bond is converted into a single bond. We recently developed this reaction using Grubbs' ruthenium–

carbene complex **1**.^{2,3} Usually, olefin metathesis of cycloalkene affords a polymer via the formation of ruthenacyclobutane **i** and then formation of ruthenium–carbene complex **ii** (Scheme 1).⁴ The metathesis of an enyne containing a cycloalkene moiety would also afford a polymer.

Scheme 1. Metathesis of Enynes Containing a Cycloalkene Moiety



(1) (a) For a review on enyne metathesis, see: Mori, M. *Top. Organomet. Chem.* **1998**, *1*, 133. For recent reviews on olefin metathesis, see: (b) Grubbs, R. H.; Miller, S. J. *Acc. Chem. Res.* **1995**, *28*, 446. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (d) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833. (e) Fürstner, A. *Topics in Organometallic Chemistry*, Vol 1; Springer-Verlag: Berlin, Heidelberg, 1998. (f) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (g) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (h) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75. (i) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013.

(2) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039.

(3) (a) Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020. (b) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356. (c) Kinoshita, A.; Mori, M. *Heterocycles* **1997**, *46*, 287. (d) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082. (e) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Am. Chem. Soc.* **1997**, *119*, 12388. (f) Mori, M.; Kitamura, T.; Sakakibara, N.; Sato, Y. *Org. Lett.* **2000**, *2*, 543.

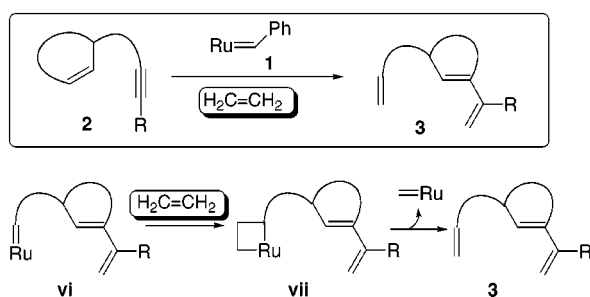
(4) In the presence of olefin, ROM-CM proceeds. For ROM-CM, see: (a) Randall, M. L.; Tallarico, J. A.; Snapper, M. L. *J. Am. Chem. Soc.* **1995**, *117*, 7, 9610. (b) Schneider, M. F.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 411. (c) Michaut, M.; Parrain, J.-L.; Santlli, M. *Chem. Commun.* **1996**, 2567. (d) Schneider, M. F.; Lucas, N.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 257. (e) La, D. S.; Ford, J. G.; Sattely, S. E.; Bonitatebus, P. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 11603.

In this reaction, the alkyne part of enyne **2** reacts with ruthenium–carbene complex **1** to give metalacyclobutene **iii**. Ring opening of **iii** gives ruthenium–carbene complex **iv**, which reacts with the cycloalkene part intramolecularly to give ruthenacyclobutane **v**, which is converted into ruthenium–carbene complex **vi**. Thus, a polymer should result from an intermolecular metathesis reaction with **2**.⁵

If this reaction were carried out under ethylene gas, ruthenium–carbene complex **vi** reacts with ethylene to give ruthenacyclobutane **vii** and, as a result, cyclized triene **3** would be formed.

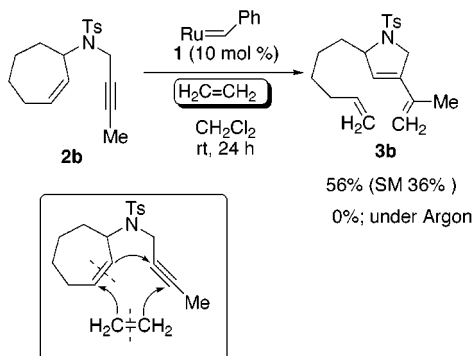
Here, we report the ring-opening and ring-closing metatheses (ROM-RCM) of enyne **2** under ethylene gas (Scheme 2).⁶

Scheme 2. Our Plan for ROM-RCM of Enyne



When a CH_2Cl_2 solution of **2b** and 10 mol % of **1** was stirred at room temperature for 24 h under ethylene gas (1 atm), we found that ROM-RCM occurred to afford the five-membered ring compound **3b** in 56% yield along with the starting material **2b** in 36% yield (Scheme 3). When this

Scheme 3. ROM-RCM of Enyne Containing a Cycloheptene Moiety



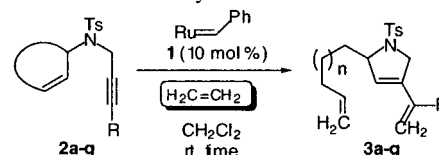
reaction was carried out under argon gas instead of ethylene gas, polymerization occurred and no cyclized product was

(5) If ROM-RCM proceeded first by reaction of the cycloalkene part of enyne **2** and the ruthenium–carbene complex, a similar reaction pathway is considered, and the ruthenium–carbene complex would be formed at the methylene part of the diene moiety of **vi**, which reacts with **2** to afford polymer.

obtained. Formally, in this reaction, the double bonds of ethylene and cycloalkene in **2b** are cleaved, and one alkene carbon in **2b** reacts with an alkyne carbon to afford a five-membered ring, while the other alkene carbon and alkyne carbon react with the methylene parts of ethylene, respectively.

The enynes **2a** and **2c** with six- and eight-membered rings were treated in a similar manner, and the desired ROM-RCM products **3a** and **3c** were obtained in 15% and 22% yields, respectively (Table 1, runs 1 and 3).

Table 1. ROM-RCM of Enyne



run	R	ring size	<i>n</i>		time (h)	yield ^a (%)	2 (%)
1	Me	6	1	2a	24	15	75
2	Me	7	2	2b	24	56	36
3	Me	8	3	2c	24	22	73
4	H	6	1	2d	4	78	0
5	H	7	2	2e	1	70	15
6	H	8	3	2f	1	75	20

^a Yields were calculated from ¹H NMR.

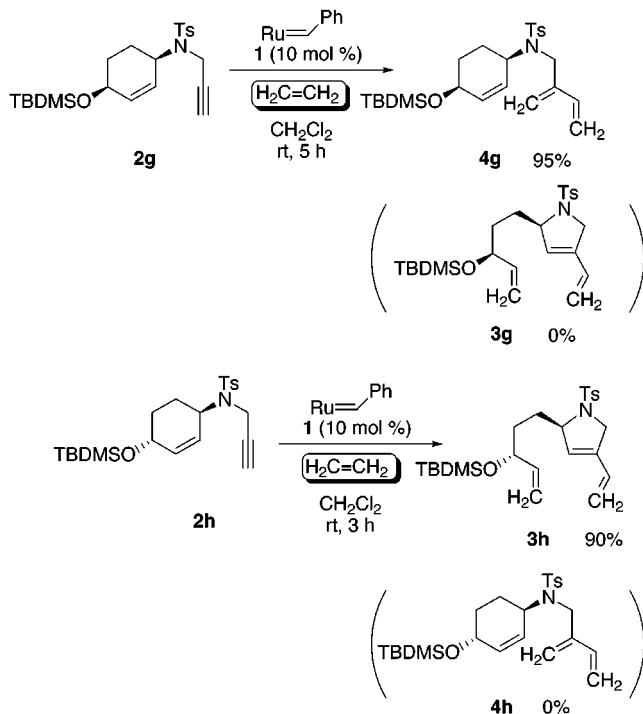
We have already reported that the metathesis reaction rate of an enyne containing a terminal alkyne was slow because the terminal alkene part of the cyclized product reacts with the ruthenium–carbene complex.^{3a} However, a remarkable effect for metathesis of an enyne containing a terminal alkyne was shown under ethylene gas, and the desired cyclized product was obtained in high yield.^{3d} Since this ROM-RCM of enyne was carried out under ethylene gas, an enyne containing a terminal alkyne should be applied to the ROM-RCM of an enyne.

When a CH_2Cl_2 solution of enyne **2d** containing a cyclohexene part and the terminal alkyne was treated with 10 mol % of **1**, surprisingly, triene **3d** was obtained in 78% yield (run 4). The reason for the remarkably higher yield of **3d** as compared with that of **3a** is thought to be the release of the steric factor for the formation of **v** in the reaction of **2a**. The ROM-RCM of enynes **2e** and **2f** containing a cycloheptene or a cyclooctene ring was carried out in a similar manner, and the desired trienes **3e** and **3f** were obtained in good yields, respectively (runs 5 and 6).

(6) For a recent application of ROM-RCM, see: (a) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634. (b) Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901. (c) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305. (d) Burke, S. D.; Quinn, K. J.; Chen, V. J. *J. Org. Chem.* **1998**, *63*, 8626. (e) Adams, J. A.; Ford, J. G.; Stamatou, P. J.; Hoveyda, A. H. *J. Org. Chem.* **1999**, *64*, 9690. (f) Voigtmann, U.; Blechert, S. *Synthesis* **2000**, 893. (g) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801. (h) Ovaa, H.; Stragies, R.; van der Malel, G. A.; van Boom, J. H.; Blechert, S. *Chem. Commun.* **2000**, 1501. (i) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785. (j) Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584. (k) Voigtmann, U.; Blechert, S. *Org. Lett.* **2000**, *2*, 3971 and references therein.

When enyne **2g** with *cis*-substituents on the cyclohexene ring was treated in a similar manner, triene was obtained in 95% yield. Although the spectral data of triene (^1H NMR, ^{13}C NMR, and MASS) supported the structure of **3g**, the result of the spectrum of HMQC did not agree with this structure. Since this reaction was carried out under ethylene gas, it should be considered that the formation of 1,3-diene **4g** would occur by intermolecular enyne metathesis between the alkyne part of **2g** and ethylene,^{3e} and all the spectral data supported this structure (Scheme 4). It is likely that steric

Scheme 4. Application of ROM-RCM of Enyne



hindrance between the ruthenium-carbene part and the *tert*-butyldimethylsilyloxy group in **ix** prevents intramolecular enyne metathesis (Figure 1), and intermolecular enyne metathesis of **2g** with ethylene proceeded to give **4g**. On the other hand, when enyne **2h** with *trans*-substituents on the cyclohexene moiety was treated in a similar manner, only

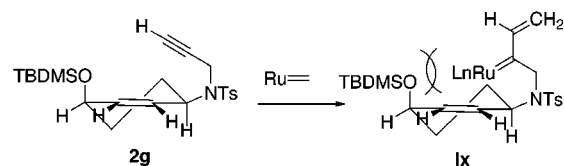
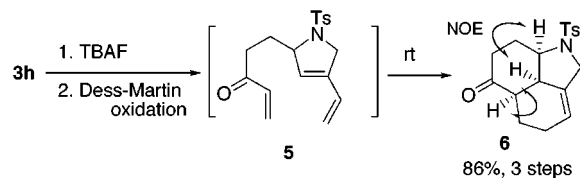


Figure 1.

the desired product **3h** was obtained in 90% yield, and 1,3-diene **4h** was not produced.

Desilylation of **3h** followed by Dess–Martin oxidation⁷ at room temperature afforded a mixture of ketone **5** and tricyclic compound **6** in 86% yield (Scheme 5). When a

Scheme 5. Synthesis of Tricyclic Compound by Diels–Alder Reaction



mixture of these compounds was allowed to stand at room temperature for several days, it was converted into tricyclic compound **6**, which was formed by intramolecular Diels–Alder reaction of **5**. The stereochemistry of **6** was determined by an NOE experiment. The results indicated that, formally, tricyclic compound **6** was obtained from enyne **2h** and ethylene gas.

Further studies on ROM-RCM of enyne under ethylene gas are in progress.

Supporting Information Available: Spectral data of enynes **2a–h**, trienes **3a–f**, **3h**, **4g**, and **6**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(7) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.