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Synthesis of Eight-Membered Ring Compounds Using Enyne Metathesis

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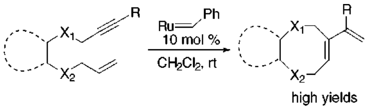
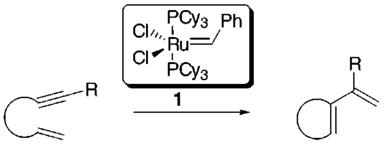
ABSTRACT



A novel procedure for synthesizing eight-membered ring compounds was developed using ruthenium-catalyzed enyne metathesis. When a CH_2Cl_2 solution of enyne connected with catechol, *o*-amino phenol, or *o*-phenylenediamine was stirred in the presence of benzylidene ruthenium carbene complex (10 mol %) at room temperature overnight, an eight-membered ring compound was obtained in high yield. In a similar manner, monocyclic 1,4-diaza- or 1-oxa-4-azacyclooctene derivative was obtained in high yield.

Olefin metathesis is very interesting and useful in synthetic organic chemistry because the two carbon−carbon double bonds are cleaved and new carbon−carbon bonds are formed between the two double bonds.[1] Olefin metathesis is usually used as an intramolecular reaction, since in an intermolecular olefin metathesis the substrate is in a state of equilibrium with the products in the presence of ruthenium catalyst, many olefins are formed. Intramolecular enyne metathesis is also very interesting and useful.[1b,2] Formally, the reaction proceeds through the formation of a new carbon−carbon bond between the triple bond and the double bond to give cyclized product **3**, and the alkylidene part of the alkene of **2** migrates onto the alkyne carbon to form a diene moiety[1b,2] (Scheme 1).

Scheme 1. Ethyne Metathesis



1

2

3

We previously reported the synthesis of five- to seven-membered cyclized products[2g] using intramolecular enyne metathesis, and the novel synthesis of 1,3-diene using intermoleular enyne metathesis.[2m,3]

Here, we report the synthesis of eight-membered ring compounds using ruthenium-catalyzed enyne metathesis. In general, synthesis of eight-membered ring compounds[4] is difficult. We planned the synthesis of eight-membered ring compounds from enyne connected to an aromatic ring. When a CH_2Cl_2 solution of catechol derivative **4a** and ruthenium carbene complex **1** (10 mol %)[5] was stirred at room temperature for 7 days, the desired product **5a** was obtained in 49% yield along with **4a** in 31% yield (Table 1, run 1).

The reaction was further extended to the synthesis of various eight-membered ring compounds **5** connected with the aromatic ring (Table 1). The tosyl group on the nitrogen accelerated the reaction rate for the formation of eight-membered ring compounds **5c−e** (runs 3−5).[6] The enyne

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(1) (a) Fu, G.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426. (b) Furstner, *A. Topics in Organometallic Chemistry*; Vol 1, Springer-Verlag: Berlin Heidelberg, 1998; Vol. 1.

(2) (a) Katz, T. J.; Sivavec, T. M. *J. Am. Chem. Soc.* **1985**, *109*, 737. (b) Kim, S.-H.; Bowden, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801. (c) Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049 (d) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636. (e) Mori, M.; Watanuki, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1083. (f) Watanuki, S.; Ochifuji, N.; Mori, M. *Organometallics* **1994**, *13*, 4129. (g) Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020. (h) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356. (i) Kim, S.-H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073. (j) Barrett, A. G. M.; Baugh, S. P. D.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Procopiou, P. A. *J. Chem. Soc., Chem. Commun.* **1997**, 1375. (k) Kinoshita, A.; Mori, M. *Heterocycles* **1997**, *46*, 287. (l) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082. (m) Kinoshita, A.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388.

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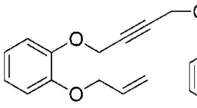
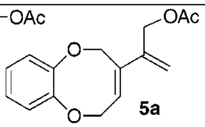
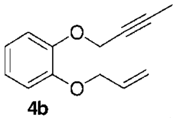
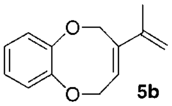
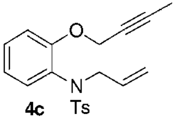
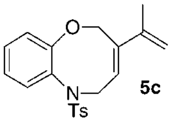
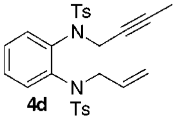
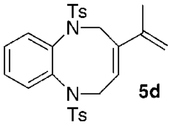
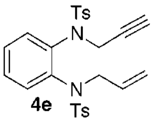
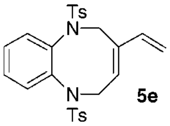
Table 1. Synthesis of Benzocyclooctene Derivatives **5** from Enynes **4**

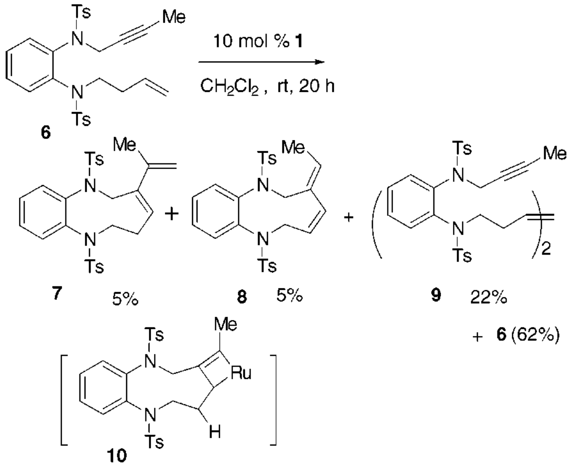
Run	Substrate	Product	Time	Yield (%)^{a,b}
1	 **4a**	 **5a**	7 d	49 (31)
2	 **4b**	 **5b**	50 h	61
3	 **4c**	 **5c**	24 h	84
4	 **4d**	 **5d**	7 h	97
5	 **4e**	 **5e**	21 h	84

a) All reactions were carried out using 10 mol % of **1** in CH_2Cl_2 at rt. b) The yield in parentheses is that of the recovered **4**.

having the terminal alkyne **4e** gave **5e** in 84% yield (run 5).[7]

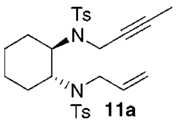
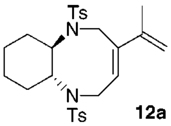
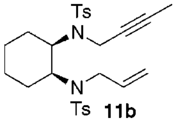
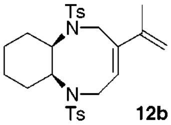
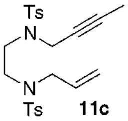
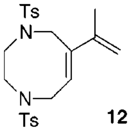
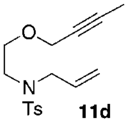
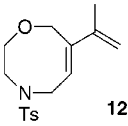
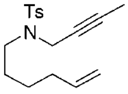
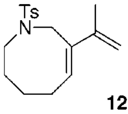
Subsequently, the synthesis of a nine-membered ring compound was attempted (Scheme 2). Compound **6** was treated in a similar manner overnight, but black ruthenium metals were gradually deposited, and the starting material **6** remained on TLC. After the usual workup, the desired nine-membered ring compound **7** was obtained in only 5% yield along with dimeric compound **9** (22% yield) and a small amount of **8** (5% yield), and the starting material was recovered in 62% yield. The compound **8** would be formed by β-hydride elimination from the intermediary ruthenacyclobutane **10**. Accordingly, ruthenium−methylidene carbene complex **1** is not regenerated.

Scheme 2. Formation of Nine-Membered Ring Compound



Furthermore, various eight-membered ring compounds **12** were synthesized from the corresponding starting materials **11**, respectively (Table 2). Formation of *cis*-fused bicyclooctene derivative **12b** is easier than that of *trans*-fused bicyclooctene derivative **12a** (runs 1 and 2). It is quite interesting that monocyclic eight-membered ring compound **12c** was obtained in high yield from **11c** (run 3), and compound **11d** gave the cyclized product **12d** along with its olefin isomer **13** in high yield. However, compound **11e** gave **12e** in only 11% yield under the same reaction conditions and the main product was dimeric product **14** (45% yield) (run 5). These results indicate that the formation

Table 2. Synthesis of Eight-Membered Ring Compounds **12** from Enynes **11**

Run	Substrate	Product	Condition	Yield (%)^{a,b}
1	 **11a**	 **12a**	15 h, reflux	42 (53)
2	 **11b**	 **12b**	9.5 h, reflux	54 (43)
3	 **11c**	 **12c**	14.5 h, rt	95
4	 **11d**	 **12d**	7 h, rt	99^{c}
5	 **11e**	 **12e**	14.5 h, rt	11 (36)^{d}

a) All reactions were carried out in CH_2Cl_2 using 10 mol % of **1**. b) The yield in parentheses is that of the recovered starting material. c) The ratio of **12d** to **13** was 2 to 1. d) The dimeric product **14** was obtained in 45% yield.

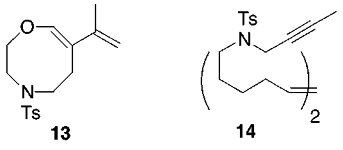


Figure 1.

of eight-membered compounds was accelerated by the two heteroatoms at the 1,4-position, but the reason for this is not clear.

In conclusion, eight-membered ring compounds could be synthesized in high yields using ruthenium-catalyzed intramolecular enyne metathesis. In these cases, the heteroatom plays an important role for the formation of the eight-membered ring. Further studies are in progress.

Supporting Information Available: ^{1}H NMR, ^{13}C NMR IR, and mass spectra of compounds **4a**−**e**, **6** **11a**−**e**, **5a**−**e**, **7**, **8**, **9**, **12a**−**e** **13**, and **14**. This material is available free of charge via Internet at http://pubs.acs.org.

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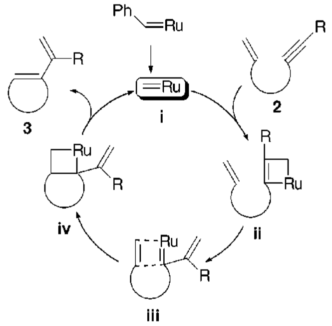
(3) The reaction course for intramolecular enyne metathesis is as shown:

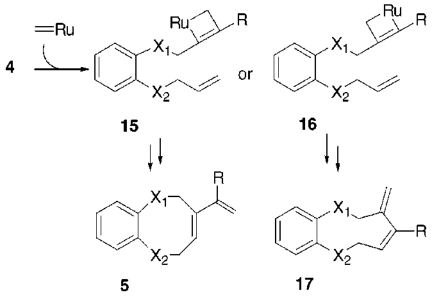


Methylidene ruthenium−carbene complex **i**, which is formed from benzylidene carbene complex, reacts with alkyne to form ruthenacyclobutene **ii** via [2 + 2] cycloaddition. It is then converted into vinylcarbene complex **iii**, which reacts with olefin in a tether to give ruthenacyclobutane **iv**, and then bond fission occurs to give cyclized diene **3** and methylidene ruthenium complex **i**. Thus, the catalytic cycle is established. When **i** reacts first with the olefin moiety of enyne **2**, a similar catalytic cycle would occur. Compare with ref 2a and Hoye, R. T.; Donaldoson, S. M.; Vos, T. *Org. Lett.* **1999**, *1*, 276.

(4) Synthesis of eight-membered ring compounds using olefin metathesis was reported: Miller, S. J.; Kim, S.-H.; Chen, Z.-R. Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108.

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

(6) In the synthesis of an eight-membered ring compound from **4** using enyne metathesis, many pathways, such as the formation of the eight-membered ring compound **5** or nine-membered ring compound **17**, or a medium-sized ring compound having *cis*- or *trans*-olefin, were considered:



However, it is difficult to distinguish which compound is formed in this reaction from the spectral data. Thus, the structure of **5d** was determined by X-ray crystallography, and it is confirmed that an eight-membered ring compound was formed in this reaction.

(7) Under ethylene gas, the yield of **5e** was 67%. In this case, an effect of ethylene gas was not observed.[2l]