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Ruthenium-Catalyzed ROM–RCM of Cycloalkene-yne

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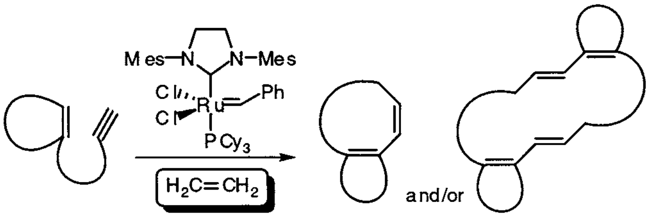
ABSTRACT



ROM–RCM (ring-opening and ring-closing metatheses) of cycloalkene-yne was demonstrated using a second-generation ruthenium complex. When cycloalkene bearing the alkyne moiety at the C-1 position was reacted with a ruthenium–carbene complex under an atmosphere of ethylene, ROM–RCM proceeded smoothly to give bicyclic compound and/or dimeric compound in good yields.

A metathesis reaction[1] using a metal carbene complex is quite interesting because multiple bonds are cleaved and, at the same time, multiple bonds are formed. Enyne metathesis[2−4] is particularly attractive. In the intramolecular enyne metathesis, the double bond of an enyne is cleaved and the alkylidene parts of alkene react with alkyne carbons to give a cyclized compound having the diene moiety. We have already reported enyne metathesis[2] using Grubbs' ruthenium carbene complex **1**[5] and the syntheses of natural products using this method.

ROM−RCM[6] of cycloalkene-yne under an atmosphere of ethylene involves a cleavage of an olefinic bond in a cycloalkene followed by formation of a new ring system.[2k] Herein we report a ring skeletal reorganization of cycloalkene-yne via ROM−RCM. Our initial strategy was envisioned to act according to Scheme 1. Metathesis reaction of cycloalkene-yne **I**, whose alkyne part is connected at the C-1 position of cycloalkene, would give triene **II**. If intra-

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[1] For recent review on metathesis, see: (a) Grubbs, R. H.; Miller, S. J. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (c) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833. (d) Fürstner, A. *Topics in Organometallic Chemistry*; Springer-Verlag: Berlin, 1998; Vol. 1. (e) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (f) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (g) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75. (h) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013. (i) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.

[2] (a) For reviews on enyne metathesis, see; Mori, M. *Top. Organomet. Chem.* **1998**, *1*, 133. (b) Mori, M. *J. Synth. Org. Chem. Jpn.* **1998**, *56*, 115. For reports from our laboratory, see: (c) Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020. (d) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356. (e) Kinoshita, A.; Mori, M. *Heterocycles* **1997**, *46*, 287. (f) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082. (g) Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388. (h) Kinoshita, A.; Sakakibara, N.; Mori, M. *Tetrahedron* **1999**, *55*, 8155. (i) Mori, M.; Kitamura, T.; Sakakibara, N.; Sato, Y. *Org. Lett.* **2000**, *2*, 543. (j) Mori, M.; Kitamura, T.; Sato, Y. *Synthesis* **2001**, 654. (k) Kitamura, T.; Mori, M. *Org. Lett.* **2001**, *3*, 1161. (l) Kitamura, T.; Sato, Y.; Mori, M. *Chem. Commun.* **2001**, 1258. (m) Mori, M.; Tonogaki, K.; Nishiguchi, N. *J. Org. Chem.* **2002**, *67*, 224. (n) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803. (o) Tonogaki, K.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 2235. (p) Kitamura, T.; Sato, Y.; Mori, M. *Adv. Synth. Catal.* **2002**, *344*, 678.

[3] Ruthenium carbene systems, see: (a) Kim, S.-H.; Bowden, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801. (b) Stragies, R.; Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2518. (c) Barrett, A. G. M.; Baugh, S. P. D.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Giles, M. R.; Marshall, E. L.; Procopiou, P. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1998**, *63*, 7893. (d) Hoye, R. T.; Donaldson, S. M.; Vos, T. *Org. Lett.* **1999**, *1*, 277. (e) Renaud, J.; Graf, C.-D.; Oberer, L. *Angew. Chem., Int. Ed.* **2000**, *39*, 3101. (f) Stragies, R.; Voigtmann, U.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 5465. (g) Bentz, D.; Laschat, S. *Synthesis* **2000**, 1766. (h) Schramm, M. P.; Reddy, D. S.; Kozmin, S. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4274. (i) Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem. Eur. J.* **2001**, *7*, 3236. (j) Timmer, M. S. M.; Ovaa, H.; Filippov, D. V.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **2001**, *42*, 8231. (k) Yao, Q. *Org. Lett.* **2001**, *3*, 2069. (l) Smulik, J. A.; Giessert, A. J.; Diver, S. T. *Tetrahedron Lett.* **2002**, *43*, 209. (m) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773. (n) Poulsen, C. S.; Madsen, R. *J. Org. Chem.* **2002**, *67*, 4441.

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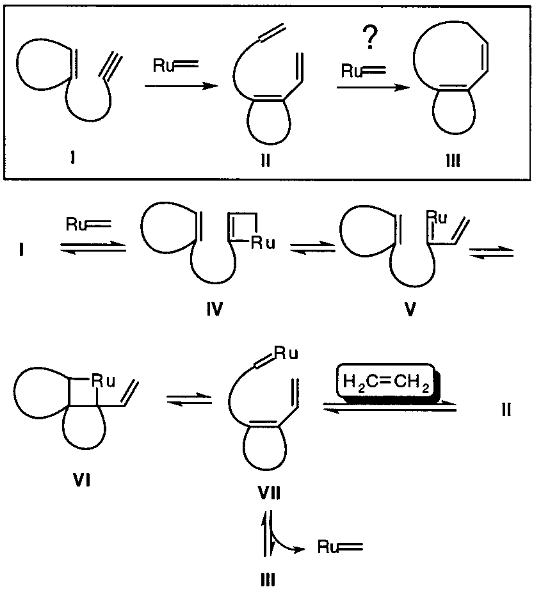
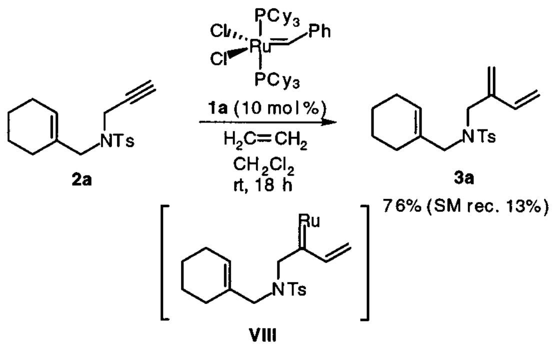
Scheme 1. Plan for ROM−RCM of Cycloalkene-yne



molecular diene metathesis of **II** occurs, bicyclic compound **III** would be formed. That is, the alkyne part of **I** would react with the ruthenium−carbene complex to give ruthenacyclobutene **IV**, which would be converted into ruthenium−carbene complex **V** by ring opening.[7] Then, intramolecular [2 + 2] cycloaddition would occur to afford ruthenacyclobutane **VI**, which would then be converted into ruthenium−carbene complex **VII**. This would react with ethylene intermolecularly to afford triene **II**. On the other hand, if complex **VII** can react with an alkene part of the diene moiety intramolecularly, bicyclic compound **III** would be obtained.

When a CH_2Cl_2 solution of cyclohexene-yne **2a** and 10 mol % first-generation ruthenium carbene complex **1a**[5a] was stirred at room temperature for 18 h under an atmosphere of ethylene, cross enyne metathesis[2g] product **3a** was obtained in 76% yield instead of the ring-opening metathesis product (Scheme 2). Presumably, carbene complex **VIII** cannot react with the cyclohexene moiety.

Scheme 2. Reaction of Cycloalkene-yne **2a** Using **1a**



On the other hand, when a toluene solution of **2a** and 10 mol % second-generation ruthenium carbene complex **1b**[5b−e] was stirred at 80 °C for 16 h under an atmosphere of ethylene, two ring-opening metathesis products were obtained (Scheme 3). Surprisingly, ^{1}H NMR and mass spectra revealed that one is compound **4b** having a 5,7-fused ring system, not a 5,8-fused ring system, obtained in 46% yield. The structure was confirmed by X-ray crystallographic analysis[8] (Figure 1).

The other is 16-membered ring compound **5a**, which was obtained in 4% yield (Table 1, run 1). At first, from the coupling constant of Ha and Hb on a ^{1}H NMR spectrum ($J_{\mathrm{Ha-Hb}}$ = 16.0 Hz), this compound was considered to be trans-**4a**, and one set of peaks corresponding to trans-**4a** was shown on ^{1}H NMR and ^{13}C NMR spectra. However, a MS spectrum of **5a** (*m*/*z* 606 [M^+]) indicated that it should be a dimeric compound. Encouraged by this result, we found that when a solution of **2a** and 10 mol % **1b** in CH_2Cl_2 was refluxed under an atmosphere of ethylene for 24 h, the yields were improved (run 2). Although an expected product **4a** was obtained under these reaction conditions (14% yield), the main product was **5a** (57%).[9]

Next, to determine whether dimeric compound **5a** is converted into fused 5,7- or 5,8-membered ring compounds

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(4) For a review on cycloisomerization of enynes, see: (a) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1. For selected other examples, see: (b) Katz, T. J.; Sivavec, T. M. *J. Am. Chem. Soc.* **1985**, *107*, 737. (c) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636. (d) Mori, M.; Watanuki, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1082. (e) Watanuki, S.; Ochifuji, N.; Mori, M. *Organometallics* **1994**, *13*, 4129. (f) Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049. (g) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785. (h) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863. (i) Ackermann, L.; Bruneau, C.; Dixneuf, P. H. *Synlett*, **2001**, 397. (j) Semeril, D.; Cleran, M.; Bruneau, C.; Dixneuf, P. H. *Adv. Synth. Catal.* **2001**, *343*, 184.

(5) For **1a**, see: (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. For **1b**, see: (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. For other second-generation ruthenium catalysts, see: (c) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2490. (d) Huang, J.; Stevens, E. D.; Nolan, S. P.; Peterson, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (e) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247.

(6) For recent applications 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.; Stamatos, P. J.; Hoveyda, A. H. *J. Org. Chem.* **1999**, *64*, 9690. (f) Voigtmann, U.; Blechert, S. *Synhesis* **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 (l) Choi, T.-L.; Grubbs, R. H. *Chem. Commun.* **2001**, 2648. (m) Rückert, A.; Eisele, D.; Blechert, S. *Tetrahedron Lett.* **2001**, *42*, 5245. (n) Banti, D.; North, M. *Tetrahedron Lett.* **2002**, *43*, 1561. (o) Lee, C. W.; Choi, T.-L.; Grubbs, R. H. *J. Am. Chem. Soc.* **2002**, *124*, 3224. (p) Minger, T. L.; Phillips, A. J. *Tetrahedron Lett.* **2002**, *43*, 5357 and references therein.

(7) If ROM−RCM proceeds from the cycloalkene part of **I**, a similar reaction mechanism would be considered.

(8) Crystallographic data have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 193041.

(9) Reaction of **3a** with **1b** under Ar gas did not afford **5a** or **4b**, although **3a** was completely consumed.

Scheme 3. Metathesis Reaction of Enyne **2a** Using **1b**

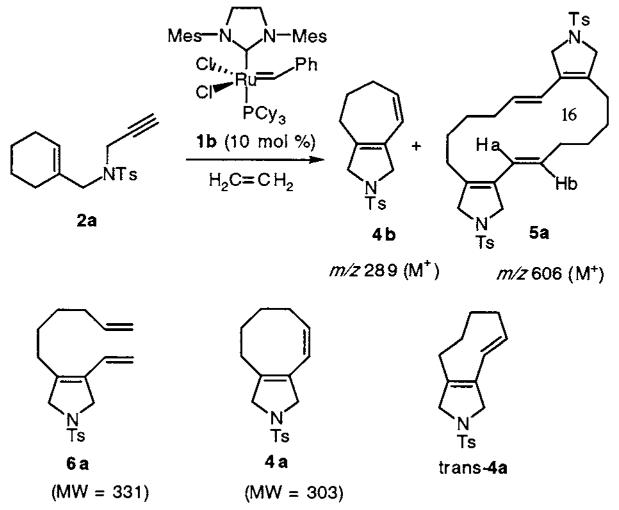


Table 1.

run	conditions	yields (%) 4b	4a	5a
1	toluene, 80°C, 16 h	46	0	4
2	CH_2Cl_2, reflux, 24 h	26	14	57

under the metathesis reaction conditions, a solution of **5a** and 20 mol % of **1b** in toluene was stirred at 80 °C for 16 h under an atmosphere of ethylene. Interestingly, **4b**, **4a**, and **6a** were obtained in 39, 9, and 21% yields, respectively (Scheme 4). These results suggest that **5a** reacted with ethylene in the presence of ruthenium complex **1b** to afford **6a**. Since ring-closure to an eight-membered ring is difficult, olefin migration[10] followed by olefin metathesis would occur to give fused 5,7-membered ring compound **4b**.

Subsequently, ROM–RCM of cyclopentene-yne **2b** was investigated (Scheme 5). When a CH_2Cl_2 solution of **2b** and 10 mol % **1b** was refluxed under an atmosphere of ethylene for 2 h, the desired ROM–RCM product **4b** was obtained in 95% yield (Table 2, run 1). Even in the case of longer reaction time (26 h), **4b** was obtained in quantitative yield (run 2). The use of 5 mol % **1b** gave a similar result (run 3). These results suggested that ring closure of **VII** to seven-membered ring compound **4b** proceeds easily and that **4b** is stable under these reaction conditions.

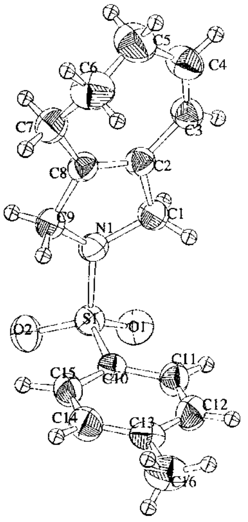
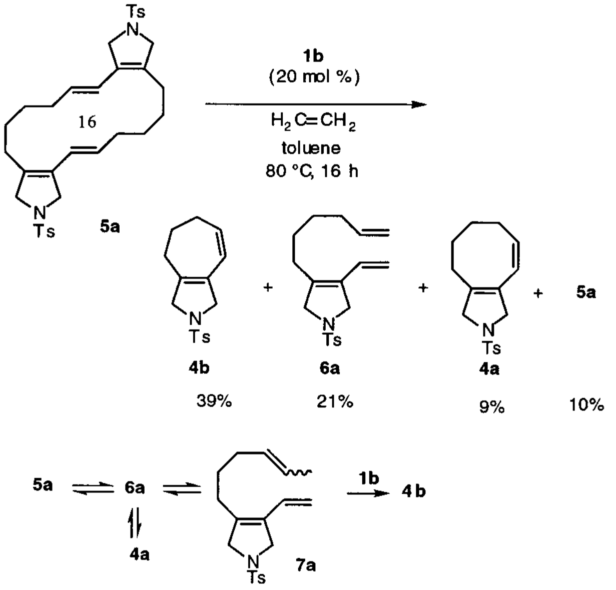


Figure 1. X-ray crystallographic analysis of **4b**.

Scheme 4. Reaction of **5a** with Ethylene in the Presence of **1b**



Scheme 5. ROM–RCM of Cyclopenete-yne **2b** Using **1b**

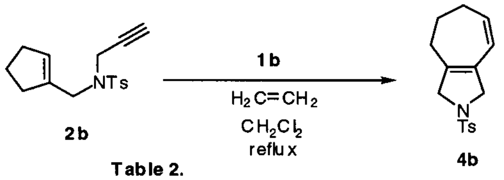


Table 2.

run	**1b** (mol %)	time (h)	yield (%)
1	10	2	95
2	10	26	quant.
3	5	4	90

Furthermore, ROM–RCM of cycloheptene-yne **2c** was investigated (Scheme 6). When the reaction of **2c** was carried out in toluene at 80 °C for 21 h, **4b**, dimeric compound **5c**, and isoindline derivative **8**[11] were obtained in 36, 8, and 6% yields, respectively, along with an inseparable mixture **9** (Table 3, run 1). GC-MS analysis showed that **9** is a mixture

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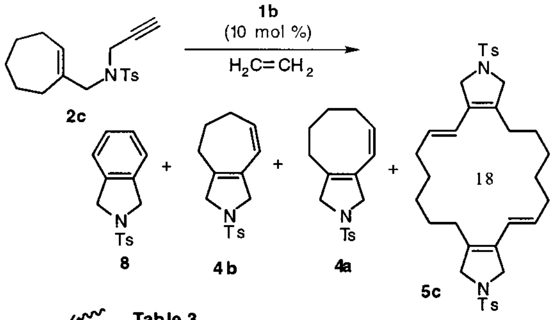
(10) For examples, see: (a) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204. (b) Alcaida, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Org. Lett.* **2001**, *3*, 3781. (c) Cadot, C.; Dalko, P. I.; Cossy, J. *Tetrahedron Lett.* **2002**, *43*, 1839. (d) Huang, J.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P *Org. Lett.* **2002**, *4*, 2417 and references therein.

Scheme 6. Ring-Opening Metathesis of **2c**



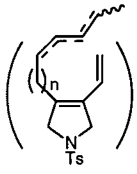


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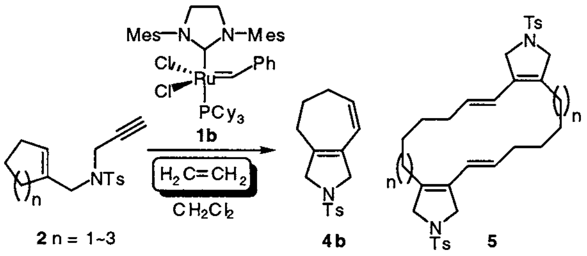
Table 3.

run	conditions	yields (%) 4b	4a	5c	8
1	toluene, 80°C, 21 h	36	0	8	6
2	CH_2Cl_2, reflux, 15 h	trace	trace	58	0
3	CH_2Cl_2, reflux, 1 h	0	0	80	0

of dihydropyrrole derivatives having different carbon lengths and/or having an olefin at various positions in the substituent. On the other hand, when a reaction was carried out in CH_2Cl_2 upon heating for 15 h, dimerization product **5c** was obtained in 58% yield along with a considerable amount of **9** (run 2). In addition, when the reaction was quenched after the spot of the starting material **2c** disappeared on TLC (1 h), only **5c** was obtained in 80% yield (run 3).

ROM−RCM of 5-, 6-, and 7-membered cycloalkene-ynes **2** was demonstrated. The results are summarized in Scheme 7. When the reaction was carried out in CH_2Cl_2, cyclopentene-yne **2b** gave fused 5,7-membered ring compound **4b**, but cycloheptene-yne **2c** afforded dimeric compound **5c**, both in high yields. However, under similar reaction conditions, cyclohexene-yne **2a** gave **4b** and dimeric compound **5a** in 26 and 57% yields, respectively. Since the reaction of **2c** in toluene gave **4b** in moderate yield, bicyclic compound **4b** was obtained in all cases due to the easy formation of seven-membered ring after isomerization of the double bond. Although it is not clear why the dimerization occurred, these results are very interesting.

Scheme 7. Summary of ROM−RCM of Cycloalkene-yne



n = 1	quant	-
n = 2	26%	57%
n = 3	-	80%
n = 3*	36%	8%

* Reaction was carried out in toluene at 80 °C.

Further studies on ROM−RCM of cycloalkene-yne and mechanistic studies for this reaction are in progress.

Supporting Information Available: Typical procedures and spectral data of **2a**−**c**, **3a**, **4a**−**b**, **5a**, **5c**, and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Compound **8** was reported in the literature and was in agreement with reported spectral data. See: Bottino, F.; Grazia, M. D.; Finocchiaro, P.; Fronczek, F. R.; Mamo, A.; Pappalardo, S. *J. Org. Chem.* **1988**, *53*, 3521 and references therein.