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Review

Ruthenium-catalyzed ROM, RCM and CM of enyne

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Abstract

Ruthenium-catalyzed ROM–RCM and CM were carried out. In the case of ROM–RCM of cycloalkene-yne, various cyclized compounds were reconstructed from the corresponding cycloalkene having alkyne in a tether using the second-generation ruthenium–carbene complex.

Keywords: Enyne metathesis; Cross-metathesis; Ring-opening metathesis; Ring-closing metathesis; Ruthenium–carbene complex

A metathesis reaction using a metal–carbene complex is interesting because multiple bonds are cleaved and, at the same time, multiple bonds are formed [1]. Enyne metathesis is a very attractive reaction because the double bond of enyne is cleaved and the alkylidene parts of alkene migrate to the alkyne carbons [2] (Scheme 1).

Thus, in intermolecular enyne metathesis, the alkynes afford 1,3-dienes, and in intramolecular enyne metathesis, a cyclized compound having a diene moiety is formed. Second-generation ruthenium–carbene complexes, **1b** [3], **1c** [4–6] and **1d** [7], having heterocyclic carbene as a ligand have recently been developed, and various interesting results have been obtained by using these complexes. Here, we report our recent results of enyne metathesis reactions using these second-generation ruthenium–carbene complexes **1** (Fig. 1).

1. Synthesis of 1,3-diene from alkyne and ethylene

Although cross-enyne metathesis is very interesting, it is difficult to use cross-enyne metathesis in synthetic organic chemistry because diene metathesis, enyne metathesis and diyne metathesis would occur simultaneously in this reaction and various compounds would be formed. During the course of our study on enyne metathesis [8], we developed a novel method for synthesizing 1,3-diene **3** from alkyne **2** and ethylene [9] using **1a** [10]. The reaction procedure is very simple: a CH_2Cl_2 solution of alkynes **2** and a catalytic amount of ruthenium–carbene complex **1a** was stirred at room temperature under ethylene gas (1 atm) for 1–2 days to give 1,3-dienes **3** in good to moderate yields. The possible reaction course is shown in Scheme 2.

In this reaction, if alkynes **2** had acetoxy, benzoyloxy or tosylamide groups at the propargylic position, 1,3-dienes **3** were obtained in good yields. However, alkynes **2** that did not have these groups at the propargylic position afforded 1,3-dienes **3** in poor yields [11]. The effect of a heteroatom at the propargylic position is thought to arise because the carbonyl oxygen of the acyl or sulfonyl moiety coordinates to the ruthenium metal and then the reaction proceeds (Fig. 2, Scheme 3).

Thus, we reinvestigated this 1,3-diene synthesis using the second-generation ruthenium carbene complex **1d** [12]. At first, the effect of the acetoxy group at the propargylic position was examined. When a CH_2Cl_2 solution of alkyne **2b** with 5 mol% of **1a** was stirred under 1 atm pressure of ethylene (balloon) at room temperature for 48 h, the desired 1,3-diene **3b** was obtained in 75% yield (Table 1, run 1). However, when alkyne **2c** having no acetoxy group at the propargylic position was treated with **1a** in a similar manner at room temperature, the desired 1,3-diene **3c** was obtained in only 16% yield (run 2). It is clear that the presence of an acetoxy group at the propargylic position is important in the reaction of alkyne and ethylene using **1a**. On the other hand, when **2b** was treated with 5 mol% of **1d** in toluene at 80 °C, **3b** was obtained in quantitative yield after only 30 min (run 3). In a similar manner, **2c** having no acetoxy

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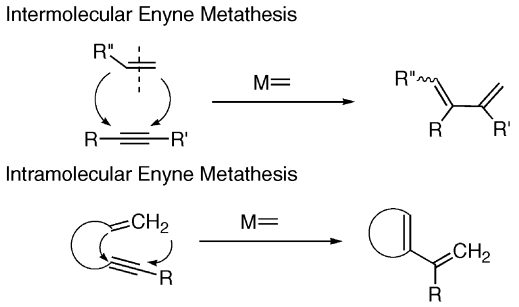


Scheme 1. Intra- and Intermolecular enyne metathesis.

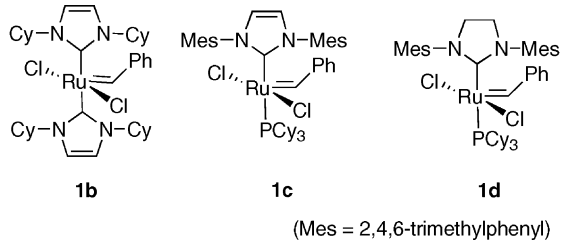
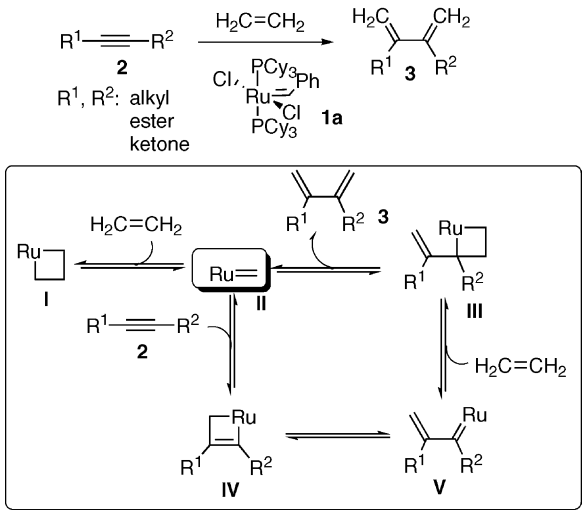
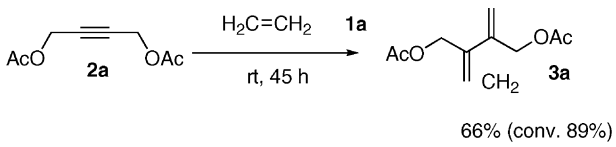


Fig. 1. Second generation ruthenium–carbene complexes.



Scheme 2. Novel diene synthesis from alkyne and ethylene.



Scheme 3. 1,3-Diene synthesis from alkyne and ethylene using 1.

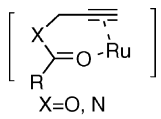
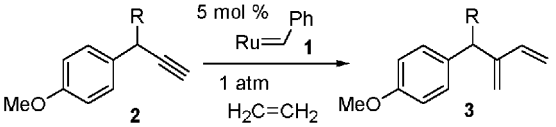


Fig. 2. Coordination of hetroatom at the propargylic position to ruthenium.

Table 1
Comparison of the reactivities of ruthenium catalysts **1a** and **1d**.



Run	*R*		Ru	Solvent	Temperature (°C)	Time (h)		Yield (%)
1	OAc	**2b**	**1a**	CH_2Cl_2	RT	48	**3b**	75
2	H	**2c**	**1a**	CH_2Cl_2	RT	48	**3c**	16
3	OAc	**2b**	**1d**	Toluene	80	0.5	**3b**	100
4	H	**2c**	**1d**	Toluene	80	0.5	**3c**	83

group at the propargylic position gave **3c** in 83% yield after 30 min (run 4). These results indicate that even in the absence of an acetoxy group at the propargylic position, ruthenium–carbene complex **1d** is quite effective for the synthesis of 1,3-diene from alkyne and ethylene.

Various 1,3-dienes were synthesized from alkyne **2** and ethylene using **1d**, and the results are shown in Table 2. In each case, the desired 1,3-diene **3** was obtained in high yield, respectively. The desired 1,3-diene **3i** or **3j** was obtained in the case of alkyne **2i** or **2j** having a trimethylsilyl or carbomethoxy group, though the use of **1a** did not give these desired compounds.

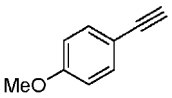
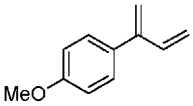
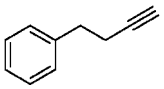
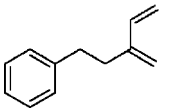
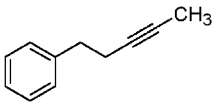
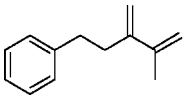
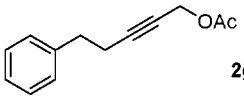
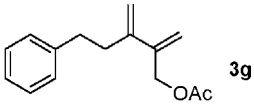
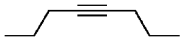
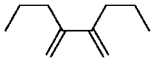
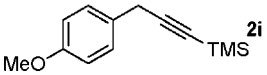
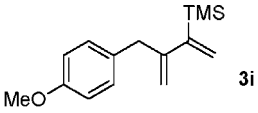
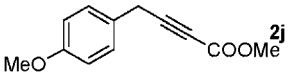
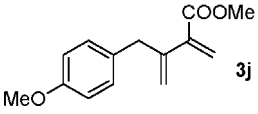
2. ROM–RCM of cycloalkene-yne

In general, ROM of cycloalkene affords a polymer via ruthenacyclobutane **VI**. Therefore, ROM of cycloalkene-yne **4** would afford a polymer via **X** as shown in Scheme 4. However, when this reaction is carried out under ethylene gas, ROM–RCM of **4** would occur to give **5**.

Using first-generation ruthenium catalyst **1a**, we succeeded in ROM–RCM of cycloalkene-ynes **4** as shown in Table 3 [13]. Formally, in this reaction the double bonds of cycloalkene and ethylene are cleaved and each methylene part of ethylene is introduced onto the cycloalkene and alkyne carbons respectively, and a carbon-carbon bond is formed between the carbons of cycloalkene and alkyne to give a pyrrolidine ring as shown in Fig. 3. The ring size of cycloalkene corresponds to the chain lengths of the substituent at the 2-position of pyrrolidine.

In the case of cyclopentene derivatives **4d** and **4e** having substituents, pyrrolidine derivatives were formed in high yields (Table 4, runs 1 and 2). On the other hand, in the case of cyclohexene-yne **4f** having *trans*-substituents on the cyclohexene ring, the desired product **5f** was formed in high yield (run 3). However, cyclohexene-yne **4g** having *cis*-substituents on the cyclohexene ring did not afford the desired product **5g**, and intermolecular metathesis product **6** with ethylene was produced because of the steric hindrance between the ruthenium metal and the silyloxy group of the cyclohexene ring (Fig. 4).

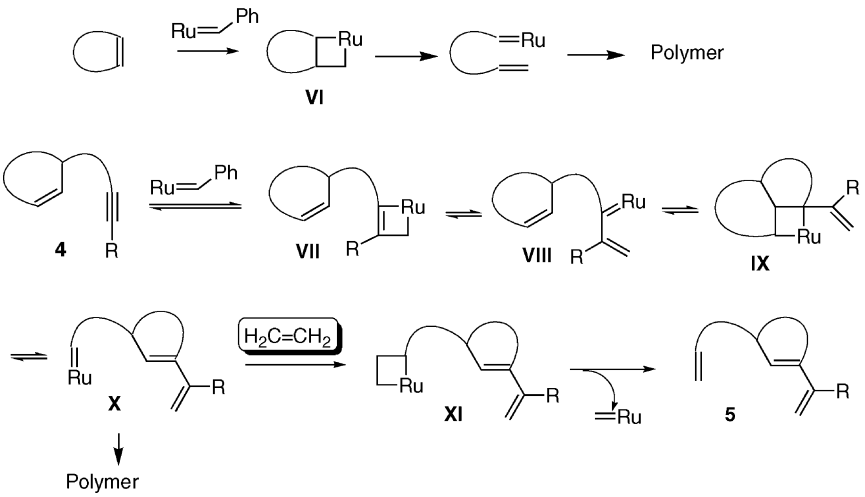
Table 2
Synthesis of various 1,3-dienes using **1d**

Run	Alkyne	Diene	(mol%)	Time (h)[a]	Yield (%)
1	 **2d**	 **3d**	5	0.5	88
2	 **2e**	 **3e**	5	0.5	71
3	 **2f**	 **3f**	5	0.5	85
4	 **2g**	 **3g**	5	0.5	100
5	 **2h**	 **3h**	5	24[b]	80
6	 **2i**	 **3i**	5	16	87[c]
7	 **2j**	 **3j**	10	16	43[c]

[a] All reactions were carried out in toluene at 80 °C.
[b] In CH_2Cl_2, reflux.
[c] **2i** or **2j** was recovered in 10 or 34% yield, respectively.

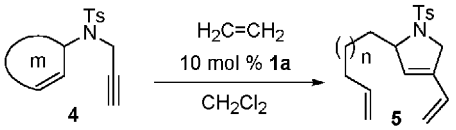
Deprotection of metathesis product **5f** followed by oxidation gave **7**, which produced tricyclic compound **8** in high yield after being allowed to stand at room temperature. The stereochemistry of **8** was determined by NOE experiments as shown in Scheme 5.

Subsequently, ROM–RCM of an alternative cycloalkene-yne was planned. If cycloalkene-yne **9**, whose substituent is placed on the alkene carbon, is treated with a ruthenium–carbene complex, highly strained ruthenacycle **XVI** should be formed via **XV**. Ring opening of **XVI** would



Scheme 4. ROM–RCM of cyclohexene-yne.

Table 3
ROM–RCM of cycloalkene-yne 4.



Run	Ring size (m)		Time (h)	*n*		Yield (%)
1	6	**4a**	4	1	**5a**	78
2	7	**4b**	1	2	**5b**	70
3	8	**4c**	1	3	**5c**	75

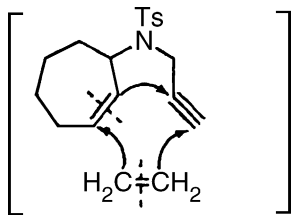


Fig. 3. Formal bond fission and bond formation.

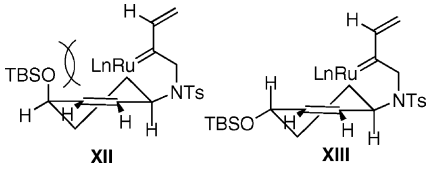
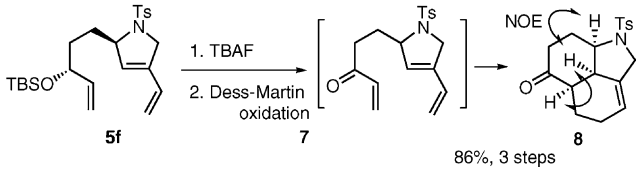


Fig. 4. Steric hindrance between silyloxy group and ruthenium carbene.

give **XVII**, and intramolecular olefin metathesis of **XVII** should give **10** via **XVIII**. If this reaction is carried out under ethylene gas, **XVII** should give **11** (Scheme 6).

When cycloalkene-yne **9a** was treated with 10 mol% of first-generation ruthenium–carbene complex **1a** under ethylene gas, 1,3-diene **12** was obtained in 76% yield (Scheme 7). Presumably, an intermediary ruthenium–carbene complex



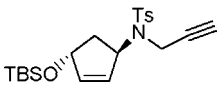
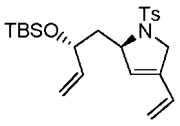
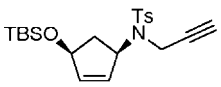
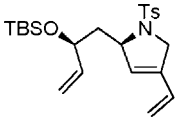
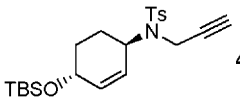
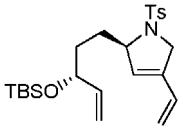
Scheme 5. Diels–alder reaction.

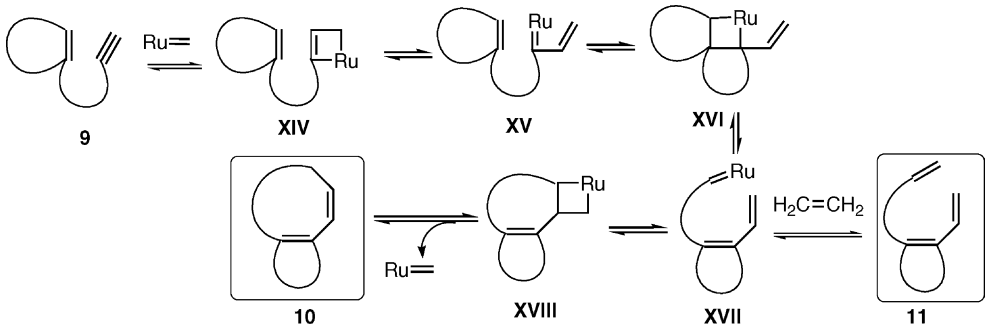
XV′ should be formed, but the ruthenium–carbene could not react with an alkene part on the cyclohexene ring because this olefin is a trisubstituted alkene. Thus, **XV′** reacts with ethylene intermolecularly to give **12**. On the other hand, when **9a** was treated with second-generation ruthenium–carbene complex **1d** in toluene at 80 °C for 16 h, two products were formed. One is the desired bicyclic compound, but ^{1}H NMR and mass spectra indicate that this is a 5–7 fused ring compound **10b**, not a 5–8 fused ring compound **10a**. The structure of **10b** was confirmed by X-ray crystallography. The other is a pyrrolidine derivative **13a** having E-olefin, but mass spectrum analysis indicates that it has a 16-membered ring. When a CH_2Cl_2solution of **9a** and 10 mol% of **1d** was refluxed for 24 h, the yields of them were improved (Table 5, run 2).

The dimeric compound **13a** was treated with 20 mol% of **1d** in toluene at 80 °C for 16 h to give **10a**, **10b** and **11a**, in 9, 39 and 21% yields, respectively. The results indicated that 5–7 fused ring compound **10b** is a thermodynamic product under these reaction conditions (Scheme 8).

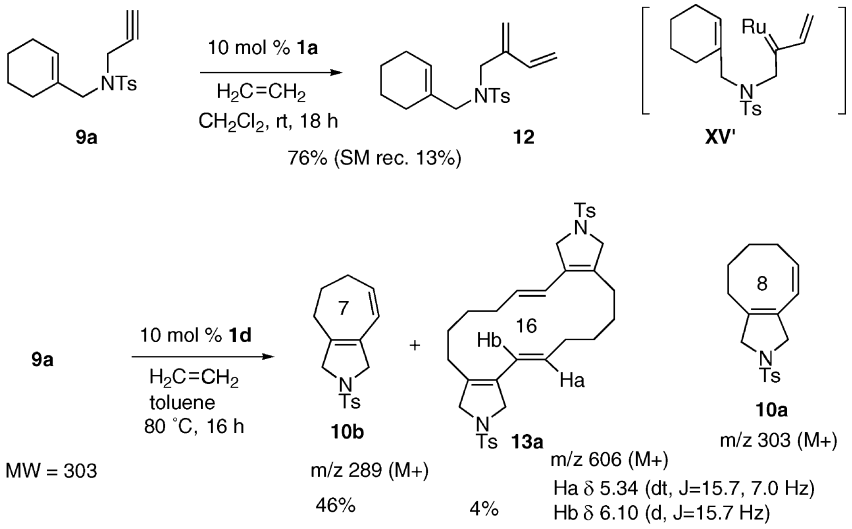
The reaction mechanism was considered on the basis of these results. Reaction of **17a** with **1d** gives **XV′**, which should be converted into ruthenacyclobutane **XVI′**. Ring-opening of **XVI′** gives ruthenium–carbene complex **XVII′**, which should afford dimeric compound **13a** and bicyclic compound **10a**. Reaction of **XVII′** with ethylene gives **11a**, and a terminal alkene of **11a** would migrate by **1d** to afford **14** and then diene metathesis would occur to give **10b** (Scheme 9).

Table 4
ROM–RCM of enyne bearing *cis*- and *trans*-1,4-disubstituted cycloalkene-yne using **1d**

Run	Cycloalkeneoyne	Time (h)	Products	Yield (%)
1	 **4d**	8	 **5d**	88
2	 **4e**	14	 **5e**	93
	Cycloalkene-yne			
3	 **4f**	3	 **5f**	90



Scheme 6. Plan for ROM–RCM of cycloalkene-yne.

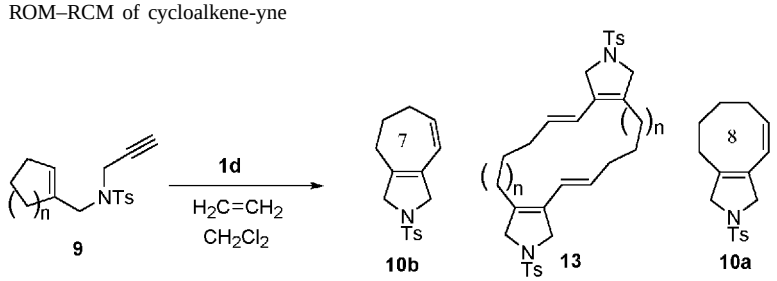


Scheme 7. Reaction of cyclohexene-yne using **1a**.

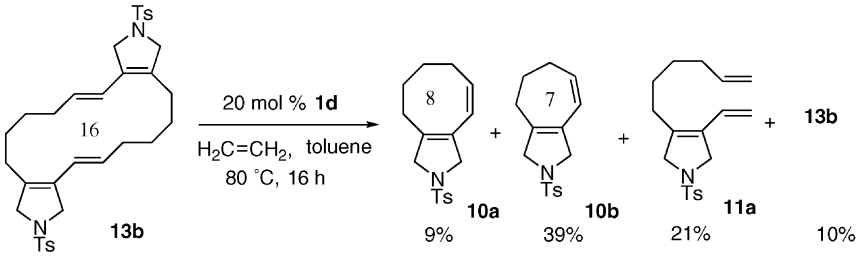
Subsequently, ROM–RCM of cyclopentene-yne **9b** was carried out. In this case, 5–7 fused ring compound **10b** was obtained in 95% yield (run 3). The desired **10b** was produced in quantitative yield by prolonged reaction time (run 4). On the other hand, when cycloheptene-yne **9c** was treated in a similar manner in CH_2Cl_2, dimeric compound **13c** was obtained in 80% yield (run 5). However, the use of toluene as a solvent afforded **10b** and **13** in 36 and 8% yields, respectively.

These results indicated that 5–7 fused ring compound **10b** was formed from all of the cycloalkene-ynes **9a**, **9b**, and **9c** as a major product because olefin isomerization of **11** should

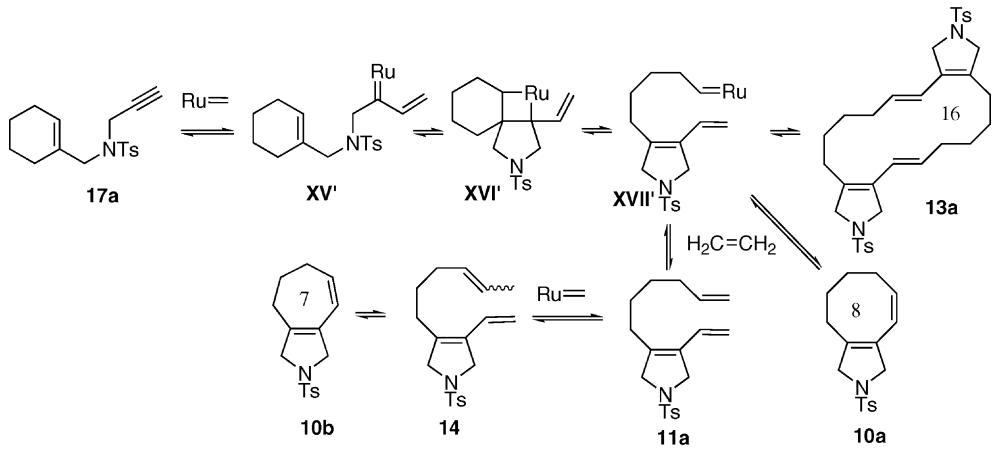
Table 5
ROM–RCM of cycloalkene-yne



Run	*n*	Ring size	Solvent	Temperature (°C)	Time (h)	Yield (%)		
						10b	**13**	**10a**
1	**9a**	2 (6)	Toluene	80	16	46	4	0
2	**9a**	2 (6)	CH_2Cl_2	Reflux	24	26	57	14
3	**9b**	1 (5)	CH_2Cl_2	Reflux	2	95	0	–
4	**9b**	1 (5)	CH_2Cl_2	Reflux	26	100	0	–
5	**9c**	3 (7)	CH_2Cl_2	Reflux	1	0	80	0
6	**9c**	3 (7)	Toluene	80	21	36	8	0

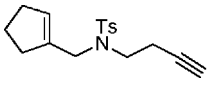
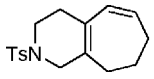
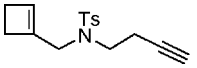
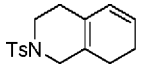
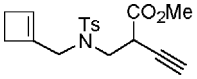
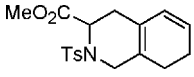


Scheme 8. Reaction of a dimer with ruthenium catalyst **1d**.



Scheme 9. Possible reaction course.

Table 6
Formation of piperidine ring by ROM–RCM using **1d**

Run	Cycloalkene-yne	Time (h)	Product	Yield (%)
1	 **15a**	3	 **16a**	76
2	 **15b**	3	 **16b**	60
3	 **15c**	3	 **16c**	76

easily occur by **1d** and **10b** was formed as the thermodynamic product in each case [14].

Metathesis of various cycloalkene-ynes **15**, in a tether of which one-carbon is elongated, was attempted using **1d**. In this case, a piperidine ring should be constructed. When cyclopentene-yne **15a** was treated in similar manner, the desired cyclized compound **16a** having a piperidine ring was obtained in 76% yield. For the synthesis of quinoline derivatives, cyclobutene-yne was required. Thus, **15b** was synthesized and this was treated in a similar manner to give quinoline derivative **16b** in 60% yield. In the case of **15c**, the desired quinoline derivative **16c** was obtained in 76% yield (Table 6).

ROM–RCM of cycloalkene-ynes is very interesting because the double bond of initial cycloalkene is cleaved and ring reconstruction occurs to give a compound with a different ring compound.

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