CHEMCOMM
Communication
www.rsc.org/chemcomm

Unexpected results of enyne metathesis using a ruthenium complex containing an *N*-heterocyclic carbene ligand

Tsuyoshi Kitamura, Yoshihiro Sato and Miwako Mori*

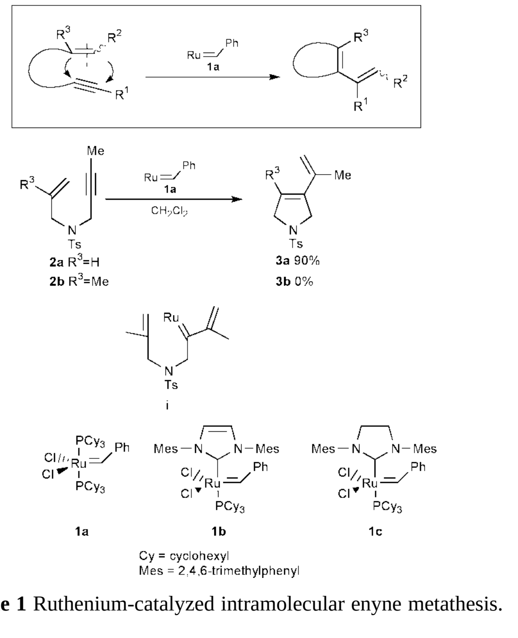
Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

Received (in Cambridge, UK) 14th February 2001, Accepted 24th May 2001
First published as an Advance Article on the web 20th June 2001

Metathesis of enyne having 1,1-substituted alkene, carried out with the new generation of a ruthenium carbene complex containing an *N*-heterocyclic carbene ligand, gave five- and six-membered cyclic compounds in high yield.

In recent synthetic organic chemistry, transition metals play an important role and enable bond cleavage of multiple bonds, such as a double bond or triple bond. A metathesis reaction[1] using a metal carbene complex is quite interesting because multiple bonds are cleaved and, at the same time, a multiple bond is formed. Enyne metathesis[2,3] is particularly attractive, since the double bond of enyne is cleaved and the alkylidene part of the alkene migrates to the alkyne carbon to give a cyclized compound. However, in this reaction, the substituents on the alkyne or the alkene are important. It has been shown that the reaction rate of an enyne having a terminal alkyne is slow because the generated diene moiety coordinates to the ruthenium carbene complex.[3a] On the other hand, the effect of the substituent on the alkene is also important. In the case of an enyne having a mono- or 1,2-disubstituted alkene, the metathesis reaction proceeded smoothly and the desired product was obtained.[3a]

However, when enyne **2b** (R^3 = Me) having 1,1-disubstituted alkene was treated in a similar manner, no cyclized product was obtained and the starting material was recovered (Scheme 1). This means that ruthenium carbene complex **i** formed by the reaction of the alkyne part of enyne and **1a**[4a] does not react intramolecularly with a 1,1-disubstituted alkene. Recently, a new generation of ruthenium carbene complexes containing *N*-heterocyclic carbene ligands was reported.[4b,c] The reactivity of these complexes is greater than that of **1a**, and the metathesis of an olefin having a 1,1-disubstituted alkene proceeded smoothly using **1b** or **1c** to give a cyclized product having tri- or tetra-substituted olefin. Thus, we decided to use the novel ruthenium carbene complex **1b** or **1c** for enyne metathesis.†



Scheme 1 Ruthenium-catalyzed intramolecular enyne metathesis.

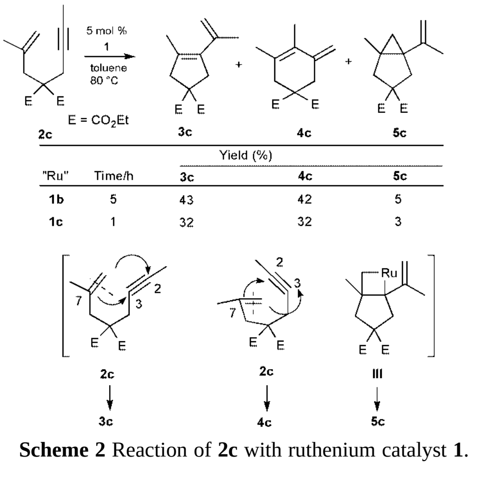
When a toluene solution of enyne **2c** was warmed in the presence of 5 mol% of **1b** at 80 °C for 5 h, two metathesis products, **3c** and **4c**, were obtained in 85% yields along with compound **5c** in 5% yield (Scheme 2). Compounds **3c** and **4c** were obtained as a mixture of two inseparable isomers, and they could be isolated by iterative chromatography on silica gel. Compound **3c** has a five-membered ring, which is usually formed by the reaction of enyne having a mono-substituted alkene and **1a**.[3a] On the other hand, the ^{1}H NMR spectrum of **4c** is similar to that of **3c**, and other spectral data such as ^{13}C NMR, HMQC, HMBC and mass spectra supported this structure. This compound should be produced by C–C bond formation between the disubstituted alkene carbon (C7) and the outside alkyne carbon (C2), and the methylene carbon of the alkene migrates to the inside alkyne carbon (C3).

Compound **5c** is formed by reductive elimination from ruthenacyclobutane **III** as shown in Scheme 2. When ruthenium carbene complex **1c** was used for this reaction, the same compounds **3c** and **4c** were each obtained in 32% yield, along with a small amount of **5c**. This indicates that the six-membered ring **4c** was formed from 1,6-ene-yne using ruthenium carbene complex **1b** or **1c**.

A possible reaction course is shown in Scheme 3. It is thought that there are two pathways in the reaction of the alkyne part of the enyne with the methylidene ruthenium carbene complex.[5] If the reaction proceeds through path A, ruthenium carbene complex **II** would be formed.

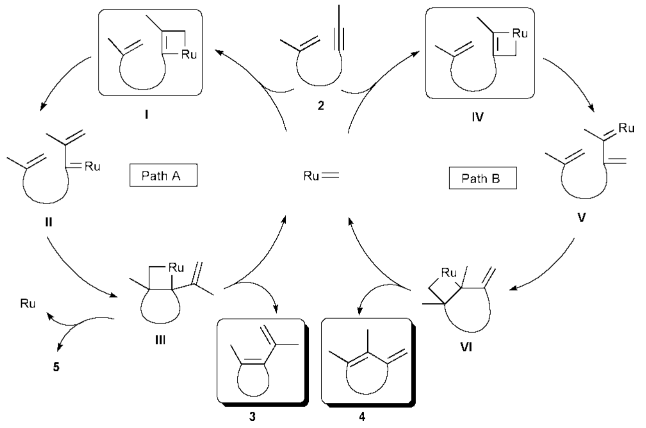
Intramolecular [2 + 2]cycloaddition affords **III**. Thus, a smaller ring-sized product is formed (five-membered ring). However, when ruthenium metal of the carbene complex bonds to the outside carbon of alkyne, ruthenacycle **IV** would be formed and would be converted into ruthenium carbene complex **V** by ring opening. Then the ruthenium carbene complex reacts intramolecularly with the alkene part to give ruthenacyclobutane **VI**, which affords a six-membered ring compound.[6]

Various enynes were treated with **1b** in a similar manner, and the results are shown in Table 1. In all cases, enyne metathesis



		Yield (%)		
"Ru"	Time/h	3c	4c	5c
1b	5	43	42	5
1c	1	32	32	3

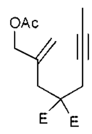
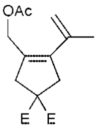
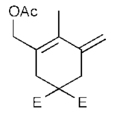
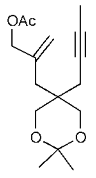
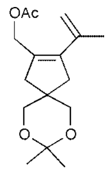
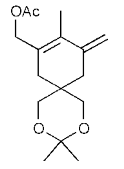
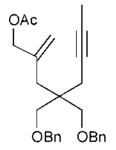
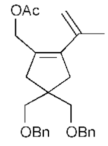
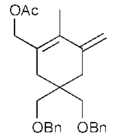
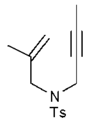
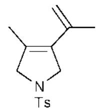
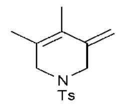
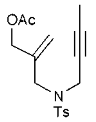
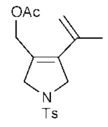
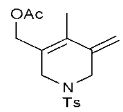
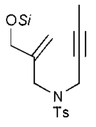
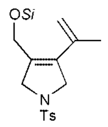
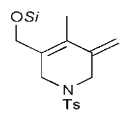
Scheme 2 Reaction of **2c** with ruthenium catalyst **1**.



Scheme 3 Two possible reaction pathways for enyne metathesis.

products **3** and **4** were obtained as an inseparable mixture of two isomers. In some cases, we could isolate each pure compound after iterative of flash column chromatography on silica gel. In each case, a small amount of **5** was produced. Although all spectral data supported the structures of compounds **4**, the structure of a derivative of **4b** was further confirmed by X-ray crystallographic analysis.[7]

Table 1 Enyne metathesis using **1b**[a]

Run	Substrate	Conditions	Products, yield[b]	
1	 **2d**	80 °C 6 h E = CO_2Me	 **3d** 50%	 **4d** 39%
2	 **2e**	80 °C 15 h	 **3e** 47%	 **4e** 27%
3	 **2f**	80 °C 24 h	 **3f** 50%	 **4f** 42%
4	 **2b**	80 °C 6 h	 **3b** 34%	 **4b** 30%
5	 **2g**[c]	50 °C 3 h	 **3g** 41%	 **4g** 30%
6	 **2h**[c]	50 °C 24 h *Si* = TBDMS	 **3h** 29%	 **4h** 17%

[a] All reactions were carried out using **1b** (5 mol%) in toluene. [b] All yields were calculated from ^{1}H NMR spectra after isolation as a mixture of two isomers. [c] 10 mol% of **1b** was used.

Although the reason why the reaction of enyne **2a** with **1a** gave only **3a**,[3a] but enyne **2b** reacts with **1b** or **1c** gave **3b** and **4b** is not clear, the results are quite interesting.

Further studies of enyne metathesis using **1b** or **1c** are in progress.

Notes and references

† *Typical procedure for the metathesis reaction* of **2d.** To a solution of **2d** (34.2 mg, 115 μmol) in toluene (3.8 ml, 0.03 M) was added **1b** (4.9 mg, 5.8 μmol, 5 mol%), and the solution was heated at 80 °C for 6 h. After the solvent was removed, the residue was purified three times by flash column chromatography on silica gel (C_6H_{12}–C_6H_6–AcOEt 8 : 1 : 2) to yield **3d** (17.1 mg, 58 μmol, 50%), and **4d** (13.3 mg, 46 μmol, 39%) as colorless oils, respectively.

Selected spectral data for **3d** *and* **4d**. *3-Acetoxymethyl-4-isopropenylcyclopent-3-ene-1,1-dicarboxylic acid dimethyl ester (***3d***).* ν/(neat) 1740, 1636, 1603, 1230 cm^{-1}; δ_H(270 MHz, $CDCl_3$) 1.86 (s, 3 H), 2.06 (s, 3 H), 3.15 (s, 2 H), 3.18 (m, 2 H), 3.75 (s, 6 H), 4.73 (s, 2 H), 4.81 (s, 1 H), 5.02 (s, 1 H); δ_C(67.8 MHz, $CDCl_3$) 20.9 (CH_3), 21.9 (CH_3), 42.7 (CH_2), 43.5 (CH_2), 52.9 ($CH_3 \times 2$), 57.0 (C), 60.8 (CH_2), 116.0 (CH_2), 129.3 (C), 139.2 (C), 139.8 (C), 170.9 (C), 172.3 (C × 2); LRMS *m/z* 296 (M$^+$), 236, 204, 191, 177, 145, 131, 117; HRMS calcd for $C_{15}H_{20}O_6$ (M$^+$) 296.1260, found 296.1251. *3-Acetoxymethyl-4-methyl-5-methylenecyclohex-3-ene-1,1-dicarboxylic acid dimethyl ester* (**4d**). ν/(neat) 1738, 1640, 1610, 1230 cm^{-1}; δ_H(270 MHz, $CDCl_3$) 1.85 (s, 3 H), 2.08 (s, 3 H), 2.73 (s, 2 H), 2.88 (s, 2 H), 3.70 (s, 6 H), 4.71 (s, 2 H), 4.99 (s, 1 H), 5.13 (s, 1 H); δ_H(67.8 MHz, $CDCl_3$) 13.7 (CH_3), 20.9 (CH_3), 34.2 (CH_2), 37.2 (CH_2), 52.7 ($CH_3 \times 2$), 53.8 (C), 64.6 (CH_2), 112.8 (CH_2), 127.9 (C), 131.1 (C), 140.6 (C), 171.0 (C), 171.1 (C × 2); LRMS *m/z* 296 (M$^+$), 254, 236, 223, 204, 177, 163, 117; HRMS calcd for $C_{15}H_{20}O_6$ (M$^+$) 296.1260, found 296.1258.

1 For recent reviews on metathesis, see R. H. Grubbs and S. J. Miller, *Acc. Chem. Res.*, 1995, **28**, 446; M. Schuster and S. Blechert, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2036; H.-G. Schmalz, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1833; A. Fürstner, *Topics in Organometallic Chemistry, Vol. 1*, Springer-Verlag, Berlin, Heidelberg, 1998; R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4413; S. K. Armstrong, *J. Chem. Soc., Perkin Trans. 1*, 1998, 371; A. J. Phillips and A. D. Abell, *Aldrichimica Acta*, 1999, **32**, 75; A. Fürstner, *Angew. Chem., Int. Ed.*, 2000, **39**, 3013.

2 For a review on enyne metathesis, see M. Mori, *Top. Organomet. Chem.*, 1998, **1**, 133; for recent applications, see; R. T. Hoye, S. M. Donaldoson and T. Vos, *Org. Lett.*, 1999, **1**, 277; A. G. M. Barrett, S. P. D. Baugh, D. C. Braddock, K. Flack, V. C. Gibson, M. R. Giles, E. L. Marshall, P. A. Procopiou, A. J. P. White and D. J. Williams, *J. Org. Chem.*, 1998, **63**, 7893; J. Renaud, C.-D. Graf and L. Oberer, *Angew. Chem., Int. Ed.*, 2000, **39**, 310; A. Fürstner, H. Szillat and F. Stelzer, *J. Am. Chem. Soc.*, 2000, **122**, 6785; R. Stragies, U. Voigtmann and S. Blechert, *Tetrahedron Lett.*, 2000, **41**, 5465; D. Bentz and S. Laschat, *Synthesis*, 2000, 1766.

3 (*a*) A. Kinoshita and M. Mori, *Synlett*, 1994, 1020; (*b*) A. Kinoshita and M. Mori, *J. Org. Chem.*, 1996, **61**, 8356; (*c*) A. Kinoshita and M. Mori, *Heterocycles*, 1997, **46**, 287; (*d*) M. Mori, N. Sakakibara and A. Kinoshita, *J. Org. Chem.*, 1998, **63**, 6082; (*e*) A. Kinoshita, N. Sakakibara and M. Mori, *J. Am. Chem. Soc.*, 1997, **119**, 12 388; (*f*) A. Kinoshita, N. Sakakibara and M. Mori, *Tetrahedron*, 1999, **55**, 8155; (*g*) M. Mori, T. Kitamura, N. Sakakibara and Y. Sato, *Org. Lett.*, 2000, **2**, 543.

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

5 If this reaction proceeds by the reaction of the methylene carbene complex and the olefin part of the enyne, a similar reaction pathway is described.

6 In the synthesis of an eight-membered ring compound using ruthenium catalyst **1a**, we considered the same possibility, but no other products were observed. See ref. 3*g*.

7 Treatment of compound **4d** with K_2CO_3 in MeOH followed by Dess–Martin oxidation (D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4156) afforded an aldehyde, which was converted into 2,4-dinitrophenylhydrazone, whose X-ray crystallography shows that a six-membered ring is formed. CCDC 161214. See http://www.rsc.org/suppdata/cc/b1/b101453f/ for crystallographic data in CIF or other format.