
Enyne Metathesis

Miwako Mori

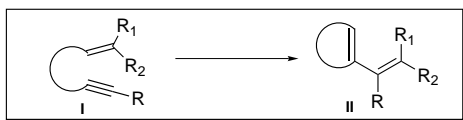
Enyne metathesis is unique and interesting in synthetic organic chemistry. Since it is difficult to control intermolecular enyne metathesis, this reaction is used as intramolecular enyne metathesis. There are two types of enyne metathesis: one is caused by [2+2] cycloaddition of a multiple bond and transition metal carbene complex, and the other is an oxidative cyclization reaction caused by low-valent transition metals. In these cases, the alkylidene part migrates from alkene to alkyne carbon. Thus, this reaction is called an alkylidene migration reaction or a skeletal reorganization reaction. Many cyclized products having a diene moiety were obtained using intramolecular enyne metathesis. Very recently, intermolecular enyne metathesis has been developed between alkyne and ethylene as novel diene synthesis.

Keywords: Enyne metathesis, Enyne, Metathesis, Carbene complex, [2+2] Cycloaddition

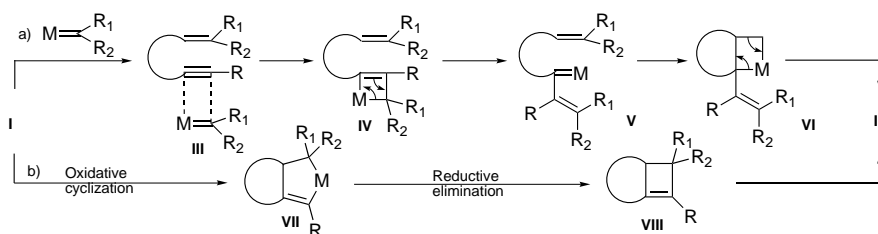
1	Introduction	133
2	Intramolecular Enyne Metathesis	135
2.1	Enyne Metathesis Using Fischer Carbene Complexes (W, Mo, Cr) .	135
2.2	Pd- and Pt-Catalyzed Enyne Metathesis	139
2.3	Ru-Catalyzed Enyne Metathesis	142
3	Intermolecular Enyne Metathesis	146
4	Utilization of Enyne Metathesis for the Synthesis of Natural Products and Biologically Active Substances	150
5	Perspective	152
6	References	153

1 Introduction

The metathesis reaction is a powerful strategy in synthetic organic chemistry [1], and it is generally accepted that this reaction is catalyzed by highly efficient transition metal alkylidenes [2, 3]. Intermolecular diene metathesis produces



Scheme 1. Enyne metathesis



Scheme 2. Reaction proceeding by a low-valent transition metal complex

many olefins [4], and it has usually been used as intramolecular diene metathesis [5]. Enyne metathesis is also quite interesting, and this reaction occurs between alkene and alkyne. Since it is difficult to control this reaction, we also used it as intramolecular enyne metathesis. This reaction is designated as an alkylidene migration reaction from the alkene part to the alkyne carbon (Scheme 1). Thus, enyne metathesis is also called a skeletal reorganization or alkylidene migration.

Enyne metathesis is caused by transition metals. There are two types of enyne metathesis: one is caused by a carbene complex, as is olefin metathesis, via [2+2] cycloaddition; and the other type is a reaction that proceeds via oxidative cyclization by a low-valent transition metal complex (Scheme 2).

Enyne metathesis was discovered by Katz [6] in 1985. Katz demonstrated this reaction as a methylene migration reaction using Fischer tungsten carbene complex. The same types of reactions were subsequently reported using Fischer molybdenum and chromium carbene complexes. Recently, very reactive carbene complexes for olefin metathesis were discovered by Grubbs and Schrock. Grubbs synthesized many cyclic compounds using his ruthenium carbene complex. This methodology is now a useful synthetic method for cycloalkenes in the field of natural product synthesis, especially macrocyclic compounds. It has become apparent that the ruthenium carbene complex acts as a catalyst for dienyne- and enyne metathesis. On the other hand, Trost discovered a very interesting palladium-catalyzed enyne metathesis during the course of his study on enyne cyclization. This reaction proceeds through oxidative cyclization by a low-valent metal complex. It is now known that many metals are effective for enyne metathesis.

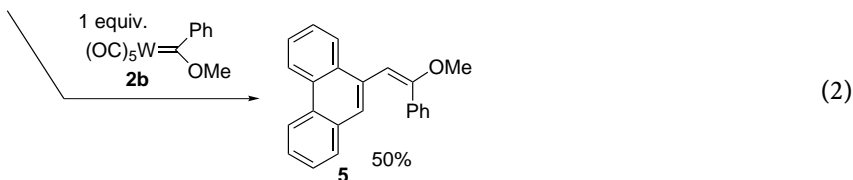
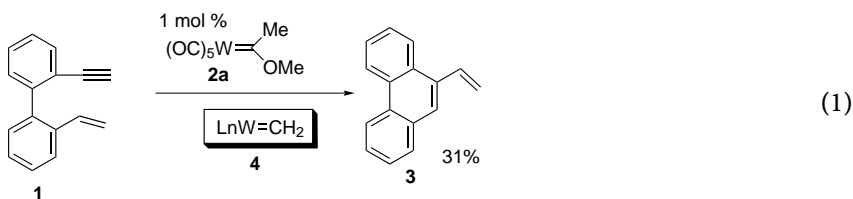
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Intramolecular Enyne Metathesis

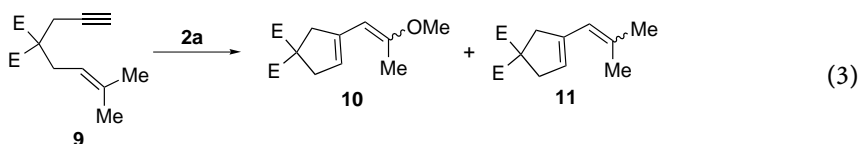
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Enyne Metathesis Using Fischer Carbene Complexes (W, Mo, Cr)

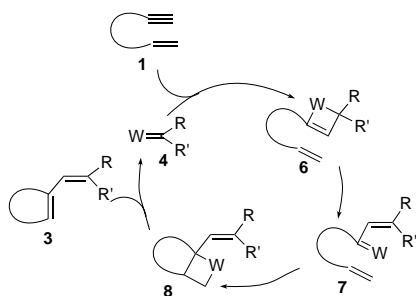
Katz [6] reported a very interesting methylene migration reaction using a Fischer tungsten carbene complex. The reaction of enyne **1** and 1 mol% of tungsten carbene complex **2a** gave methylene migration product **3** in 31% yield (Eq. 1). However, when an equimolar amount of complex **2b** was used for this reaction, a different metathesized product **5** was obtained in 50% yield (Eq. 2). This is the first example of intramolecular enyne metathesis. In the former reaction, the real catalyst is methylene tungsten complex **4** ($R=R'=H$). In this reaction, the alkyne part of enyne **1** reacts with methylene tungsten complex **4** generated from **1** and **2a** via [2+2] cycloaddition to form metalacyclobutene **6** (Scheme 3). Retrocycloaddition occurs to give vinyl carbene complex **7**, which reacts with the alkene intramolecularly to produce metalacyclobutane **8**. Retrocycloaddition occurs to give **3** and methylene tungsten complex **4**.



Following the report by Katz, Hoyer [7] reported that enyne **9** having a dimethyl group on the alkene gave metathesis products **10** and **11** using a stoichiometric amount of a Fischer carbene complex (Eq. 3, Table 1).



The substituent effects on the alkene were investigated in the reaction of enyne **12** and chromium carbene complex **2c** [8]. In the reaction of enyne *E*-**12a** having a phenyl group on the alkene with Fischer chromium carbene complex **2c**, metathesis product **13a** was obtained as a main product along with cyclopropane **14** and cyclobutanone **15** (Eq. 4). The reaction of *Z*-**12a** with **2c** gave only

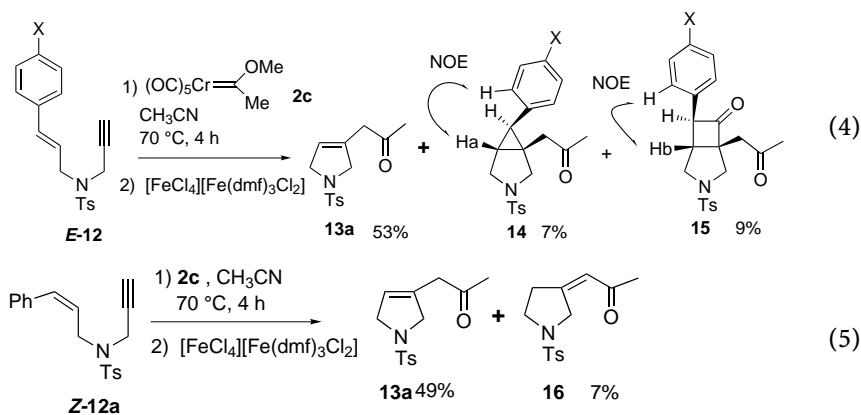


Scheme 3. Reaction mechanism

Table 1. Reaction of enyne **9** with **2a**

M	Yield (%) of 10	Yield (%) of 11
Cr	30	–
Mo	28	50
W	6	34

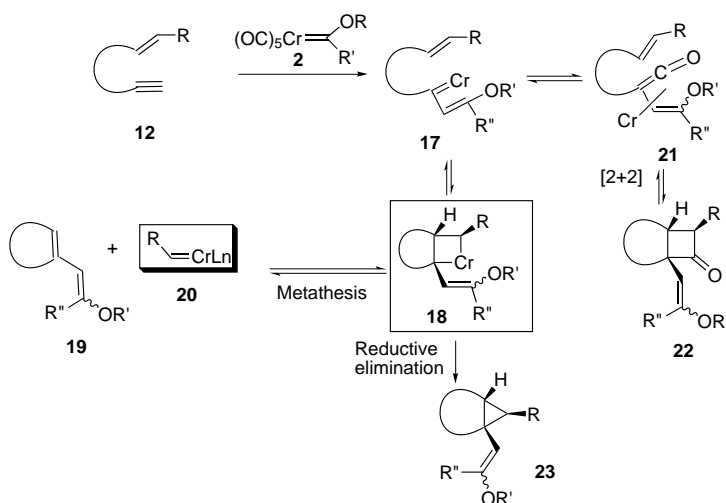
metathesis products **13a** and **16** (Eq. 5). Investigation of the substituent effects on the alkene showed that an electron-withdrawing group accelerates the formation of cyclopropane **14**, while the enyne having an electron-donating group gave the metathesis product as a main product (Table 2).



The reaction course is shown in Scheme 4. Enyne **12** reacts with **2** to give vinyl carbene complex **17**, which is in a state of equilibrium with vinyl ketene complex **21**. [2+2]Cycloaddition of the ketene moiety and alkene part in **21** gives cyclobutanone **22**. On the other hand, the vinyl carbene complex **17** reacts with the alkene intramolecularly to produce metalacyclobutane **18**. From metalacyclobutane **18**, reductive elimination occurs to give cyclopropane derivative **23**. Ret-

Table 2. Reaction of enyne **12** with Cr-carbene complex **2c**

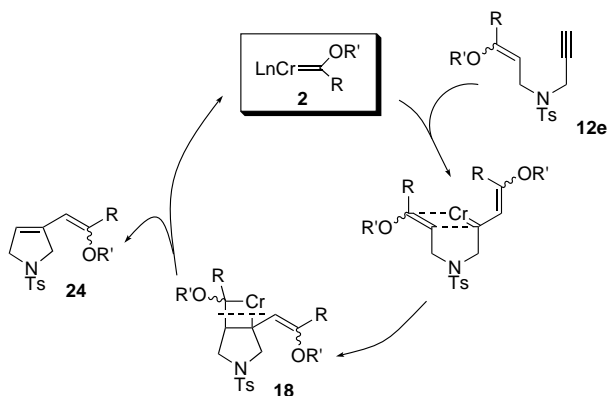
X	Substrate	13a (%)	14 (%)	15 (%)	13a:14
NO ₂	12b	4	75	–	1:19
Cl	12c	46	18	8	3:1
H	<i>E</i> - 12a	53	7	9	7.7:1
Me	12d	62	–	6	1:0

**Scheme 4.** Reaction mechanism of enyne with Fischer carbene complex

rocycloaddition occurs from **18** to give metathesis product **19** and alkylidene carbene complex **20**. Since the [2+2]cycloaddition is controlled by HOMO-LUMO interactions, the cycloaddition in this instance should be retarded by a lack of activation of the double bond. Thus, **12b** would afford only the chromacycle **18b**, which gives the cyclopropane **23b** (namely, **14b**) in good yield because of the instability of the alkylidene carbene complex **20b**. On the other hand, the electron donating groups on the double bond would favor the metathesis process because alkylidene carbene complex **20** generated from chromacycle **18** is stabilized by these substituents.

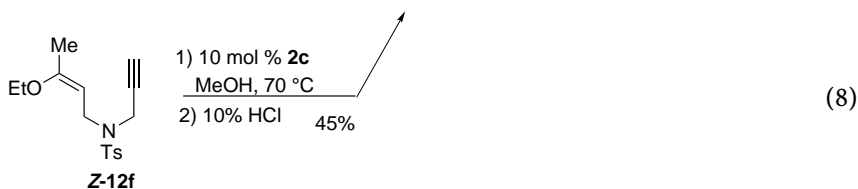
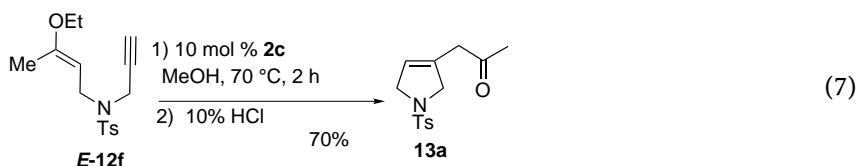
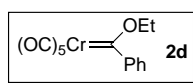
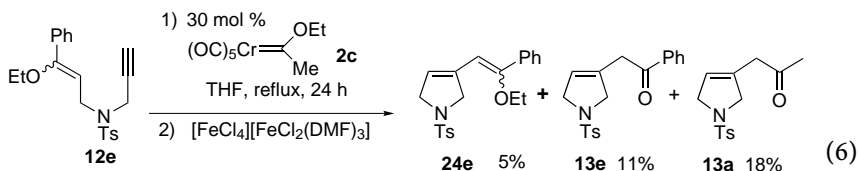
If the substituents on generated carbene complex **20** are the same as those on the alkene, this reaction must proceed by a catalytic amount of chromium carbene complex **2** (Scheme 5) [9].

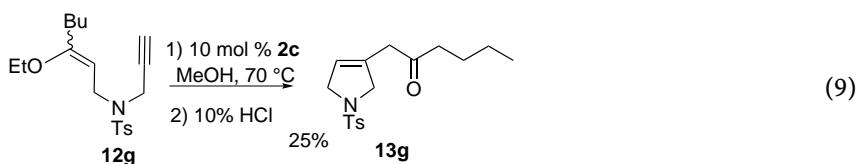
To confirm this, enyne **12e** was reacted with 30 mol% of chromium carbene complex **2c** to give the metathesized products **24e**, **13e**, and **13a** (Eq. 6). Although compound **13a** was the reaction product of **12e** and **2c**, the former two products **24e** and **13e** were formed from enyne **12e** and **2d**, respectively. This indicates that chromium carbene complex **2d** was generated in this reaction. On the basis of



Scheme 5. Plan for chromium-catalyzed enyne metathesis

these results, enyne *E*-12f was reacted with 10 mol% of chromium carbene complex **2c** in MeOH to give metathesis product **13a** in 70% yield (Eq. 7). The reaction of *Z*-12f with 10 mol% of **2c** also gave **13a** in 45% yield (Eq. 8). In a similar manner, enyne **12g** gave **13g** in 25% yield (Eq. 9).

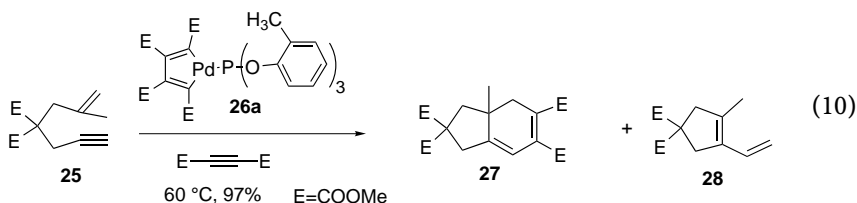




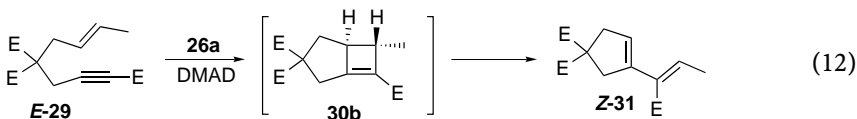
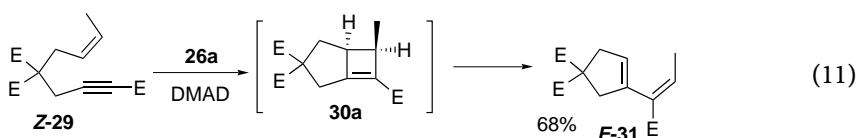
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Pd- and Pt-Catalyzed Enyne Metathesis

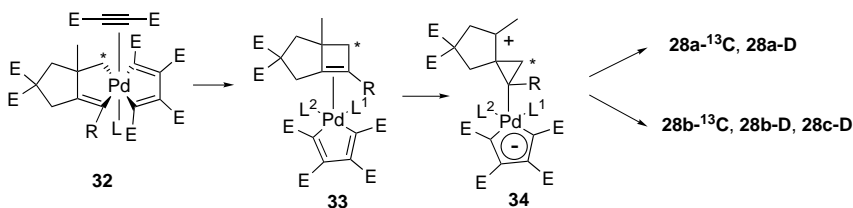
Trost [10] discovered a palladium-catalyzed enyne metathesis during the course of his study on palladium-catalyzed enyne cyclization. Treatment of the 1,6-enyne **25** with palladacyclopentadiene (TCPT, **26a**) in the presence of tri-*o*-tolylphosphite and dimethyl acetylene dicarboxylate (DMAD) in dichloroethane at 60 °C led to cycloadduct **27** and vinylcyclopentene **28** in 97% yield in a ratio of 1 to 1 (Eq. 10). The latter compound **28** is clearly the metathesis product.



This reaction proceeds in a highly stereospecific manner. Thus, enyne **Z-29** gave a 68% yield of the diene product **E-31** (Eq. 11). Similarly, the *E*-substrate **29** gave predominantly **Z-31** (Eq. 12).

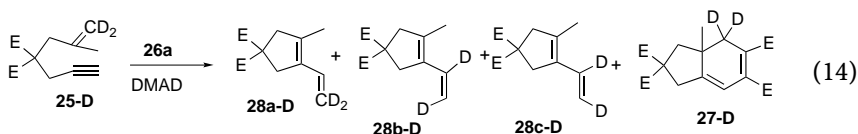
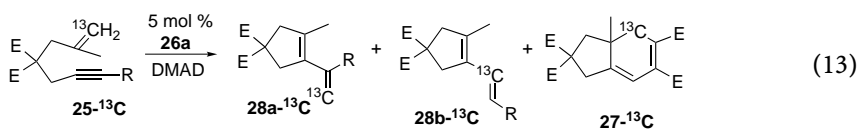


The reaction mechanism was considered to be oxidative cyclization, and palladacyclopentene **32** was formed. Reductive elimination then occurs to give cyclobutene **33**, whose bond isomerization occurs to give diene **28**. The insertion of alkyne (DMAD) into the carbon palladium bond of **32** followed by reductive elimination occurs to give [2+2+2]cycloaddition product **27**. Although the results of the reactions of *E*- and *Z*-isomers of **29** with palladium catalyst **26a** were accommodated by this pathway, Trost considered the possibility of migration of substituents. Therefore, ^{13}C -labeled substrate **25- ^{13}C** was used for this reaction.

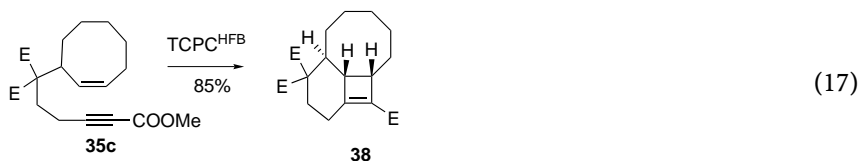
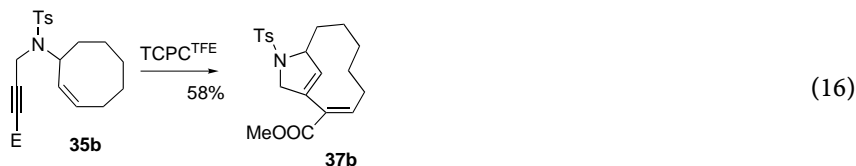
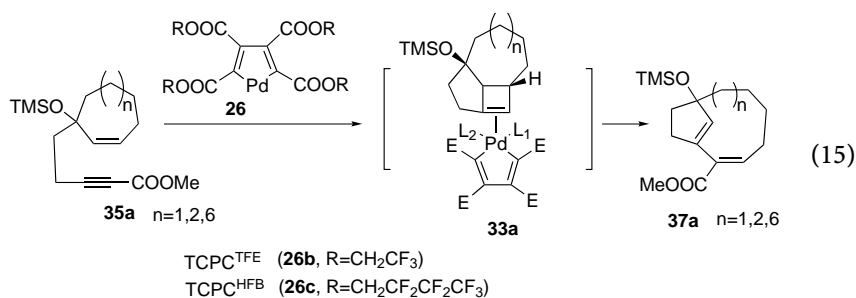


Scheme 6. Reaction mechanism

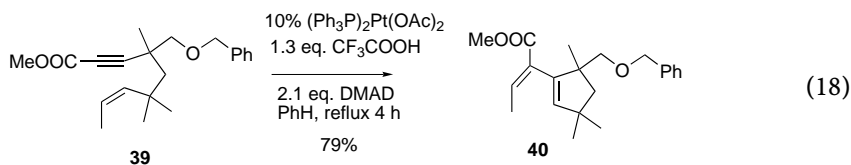
In the reaction of $25\text{-}^{13}\text{C}$, $28\text{a-}^{13}\text{C}$ and $28\text{b-}^{13}\text{C}$ were obtained in 52% yield along with 12% yield of $27\text{-}^{13}\text{C}$ (Eq. 13). On the other hand, when 25-D was treated in a similar manner, 28a-D , 28b-D , and 28c-D were obtained in 42% yield with 19% yield of cycloadduct 27-D (Eq. 14). From these results, one explanation for this reaction is shown in Scheme 6.

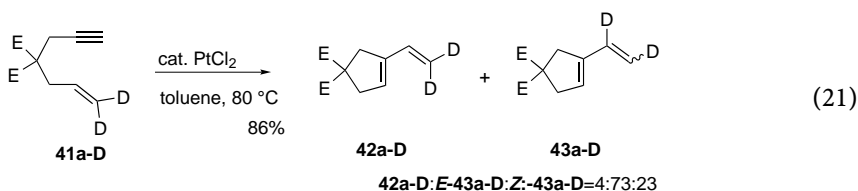
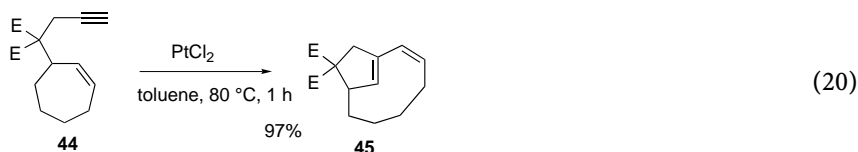
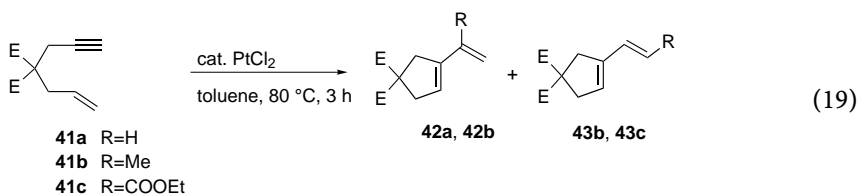


This method provides a very simple route to bridged bicycles possessing bridgehead olefins [11]. When enyne **35a** ($n=1, 2$, and 6) was treated with TCPC^{TFE} **26b**, seven-membered (**37a**, $n=1$, 53%), eight-membered (**37a**, $n=2$, 86%), and twelve-membered (**37a**, $n=6$, 73%) rings were formed (Eq. 15). Incorporation of nitrogen in the tether, as in **35b**, provides the azabicyclic compound **37b** in 58% yield [11a,b] (Eq. 16). In order to obtain further confirmation of the formation of a four-membered ring, a mixture of 4% TCPC^{HFB} , 4% *o*-tri-*o*-tolylphosphate, bis(heptafluorobutyl)-acetylenedicarboxylate, and enyne **35c** in dichloroethane was heated at 80°C , and cyclobutene **38** was obtained in 85% [11c] (Eq. 17). X-ray crystallography of **38** indicates that the stereochemistry of the fused 8,6-membered rings is *trans*. Although this palladium-catalyzed reaction seemed highly selective only in the case of substrates having an electron withdrawing group on the acetylenic terminal carbon and *cis* substituents on the olefin part, the reaction is very synthetically attractive.



A simple platinum complex also effects metathesis of enyoate as outlined in Eq. 18 [12]. The yield is comparable to that of TCPC but the reaction significantly faster. Murai and Chatani [13] also reported platinum-catalyzed conversion of 1,6- and 1,7-enyne to 1-vinylcycloalkenes. The treatment of 1,6-enyne **41a** with 4 mol% of PtCl_2 in toluene at 80°C under nitrogen for 3 h resulted in skeletal reorganization to give **42a** in 86% isolated yield (Eq. 19). The PtCl_2 -catalyzed reaction of **44** (cyclic olefin) gave exclusively bicyclic compound **45** in 97% yield (Eq. 20). The reaction of **41b** with 8 mol% of PtCl_2 at 80°C was completed in 3 h to afford 86% of the two isomers **42b** and **43b** with a ratio of 8:1. The formation of **43** is interesting with respect to the reaction mechanism because it involves an unusual change in the bond relationship. While the olefinic terminal carbon in **41b** migrates onto the alkyne carbon bearing the methyl group to give **42b**, in a formal sense, insertion of the olefinic terminal carbon in **41b** into the C-C triple bond would give **43b**. The enyne **41c** having an ester group on the terminal alkene underwent skeletal reorganization to give exclusively **43c** in 80% yield. The anomalous C-C bond formation also occurred in the reaction of **41a-D**, and **42a-D** and **43a-D** were obtained in 86% yield in a ratio of 4 to 96 (Eq. 21).

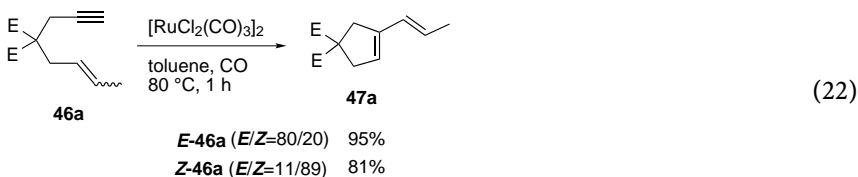


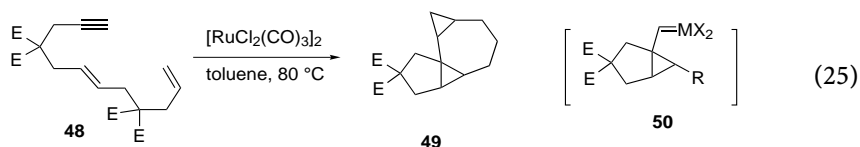
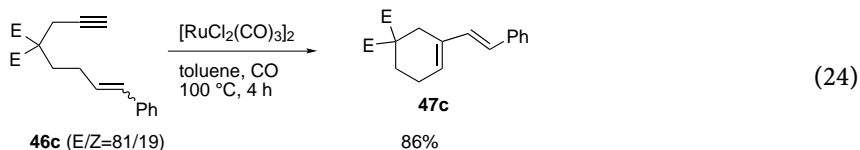
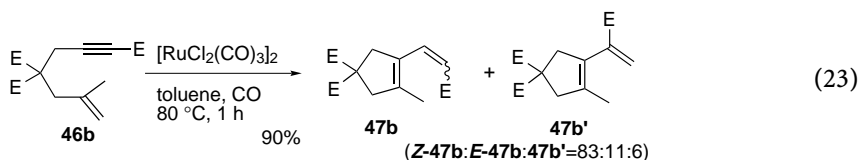


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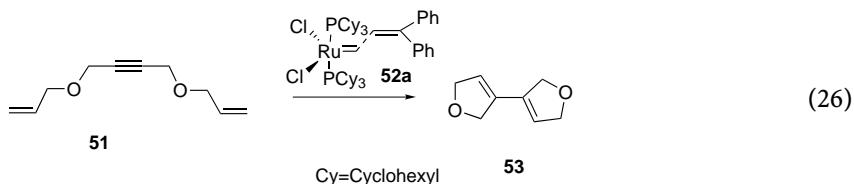
Ru-Catalyzed Enyne Metathesis

Murai and Chatani [14] also reported the ruthenium-catalyzed skeletal reorganization of 1,6-enynes **46** to 1-vinylcyclopentenes **47** (Eq. 22). They used $[\text{RuCl}_2(\text{CO})_3]_2$ as a catalyst, and the reaction was carried out under an atmosphere of CO. $[\text{RuBr}_2(\text{CO})_3]_2$, $\text{RuCl}_2(\text{p-cymene})_2$ and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ can be used for this reaction. The reactions of *E*-**46a** and *Z*-**46a** gave only the *E*-isomer of **47a**. The reaction of **46b** with $[\text{RuCl}_2(\text{CO})_3]_2$ under CO gave *Z*-**47b** as a major product, although the reaction using Trost's catalyst gave a 1:1.4 mixture of **47b'** and bicyclo[3.2.0]heptene derivative, while **47b** was not formed [10] (Eq. 23). From these results, it must be concluded that this reaction differs from Trost's palladium-catalyzed reaction. This catalyst is also applicable to a 1,7-enyne **46c** (Eq. 24). The authors considered carbenoid **50** as an intermediate and attempted to trap this [15]. The reaction of 6,11-dien-1-yne **48** in toluene in the presence of 4 mol% of $[\text{RuCl}_2(\text{CO})_3]_2$ at 80 °C for 4 h under N_2 gave tetra-cyclic compound **49** in 84% yield (Eq. 25). The reaction involves two cyclopropanation reactions where both acetylenic termini formally act as a carbene.

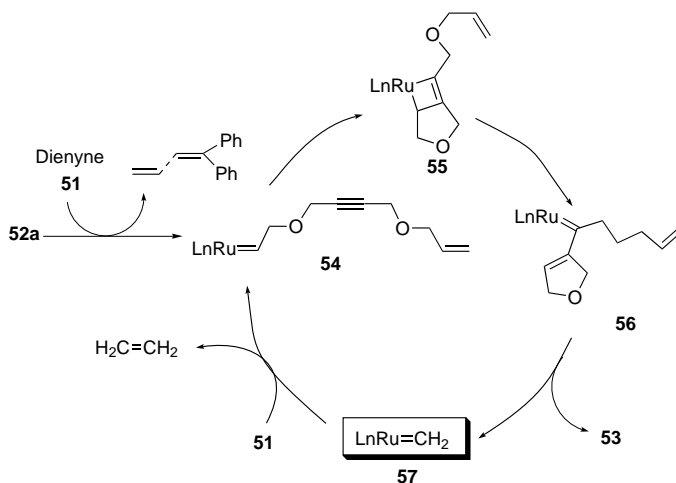




Very reactive carbene complexes for olefin metathesis were recently discovered by Grubbs [2] and Schrock [3]. Grubbs et al. synthesized many cyclic compounds from dienes using his ruthenium carbene complex **52a** [5]. Using this ruthenium catalyst, he developed an elegant dienyne metathesis [16]. When a benzene solution of diene **51** and 3 mol% of **52a** was stirred at room temperature for 4 h, the cyclized product **53** was obtained in 90% yield (Eq. 26). In this reaction, dienyne **51** reacts with carbene complex **52a** to produce ruthenium carbene complex **54**, which reacts with olefin intramolecularly via [2+2] cycloaddition to produce ruthenacyclobutene **55** (Scheme 7). Retrocycloaddition occurs to give vinyl carbene complex **56**, which reacts again with the other olefin group intramolecularly to produce cyclized compound **53** and ruthenium methylene complex **57**, which is the real metathesis catalyst. It then reacts with dienyne **51** to regenerate carbene complex **54** and ethylene.



The symmetrical dienyne **58a** was converted to a fused bicyclo[4.3.0] ring in 95% yield [17] (Eq. 27). With substrate **58c** containing an unsymmetrical diene tether, two different products, **59c** and **59c'**, were obtained in a ratio of 1 to 1 (Eq. 28). The reaction course in the formation of the different bicyclic rings is shown in Scheme 8. This dienyne metathesis is also catalyzed by tungsten or molybdenum complex **62** or **63** (Fig. 1), and a dienyne bearing terminal alkyne **58b** could be cyclized to give **59b** in 97% yield.



Scheme 7. Ruthenium-catalyzed dienyne metathesis

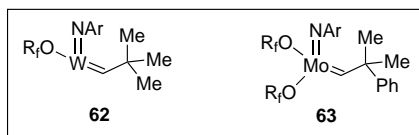
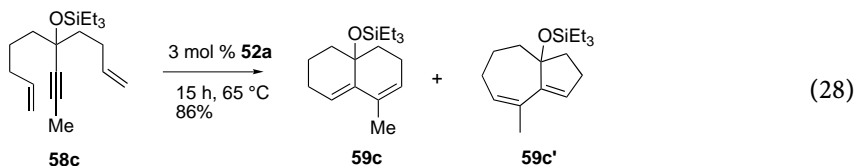
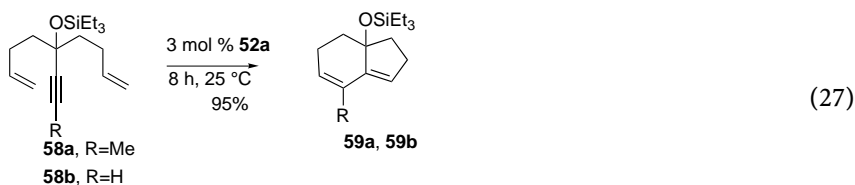
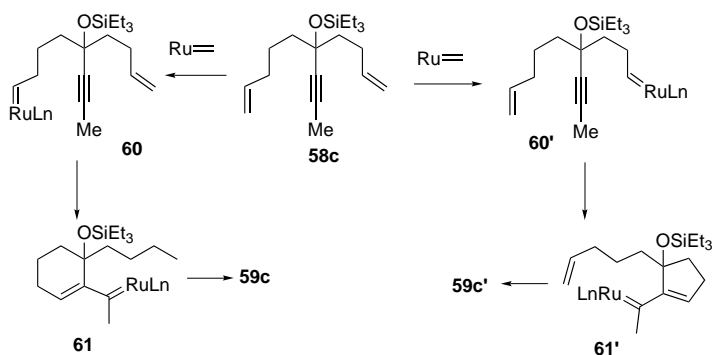


Fig. 1. Tungsten and molybdenum complexes **62** and **63**



Enyne metathesis using ruthenium catalyst **52a** was developed by Mori and Kinoshita [18]. When enyne **62a** was treated with Grubbs's ruthenium catalyst **52a** in benzene at room temperature for 22 h, the cyclized product **63a** was obtained in only 13% yield (Eq. 29). It seems that the catalyst was coordinated by the diene generated in this reaction. This problem was overcome by the study of



Scheme 8. Reaction mechanism

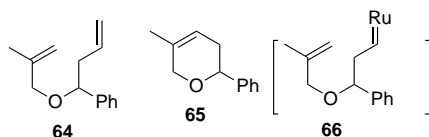
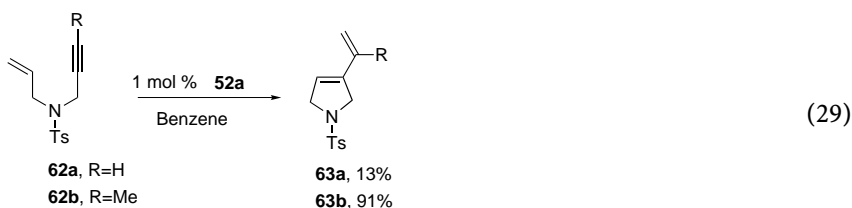


Fig. 2. Diene 64, the cyclized product 65 and the alkyldiene ruthenium complex 66

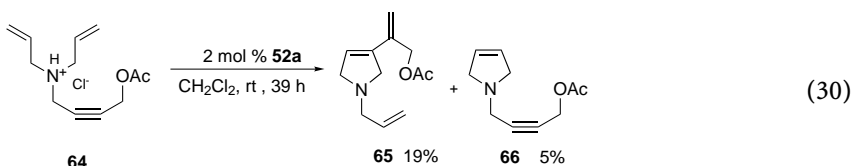
the substituent effects on the olefin metathesis. When diene 64 was treated with 1 mol% of 52a, the cyclized product 65 was not obtained. This means that alkyldiene ruthenium complex 66 could not react with the *exo*-methylene part (Fig. 2). If the diene produced in enyne metathesis has an *exo*-methylene part, the ruthenium catalyst would not be coordinated by the diene moiety. On the basis of this idea, diene 63b was obtained from enyne 62b in 91% yield after only 35 min. Various cyclized products 63c–g were obtained from the corresponding 1,6-, 1,7-, and 1,8-enynes 62c–g having substituents on the alkyne (Table 3).

Table 3. Ruthenium-catalyzed enyne metathesis

Substrates		Time	Products	Yields (%)
	62c R=Ac 62d R=TBDMS	40 min 50 min		63c 86 63d 83
	62e n=1 62f n=1 62g n=2	1.5 h 1.5 h 2.5 h		63e 88 63f 86 62g 77



To investigate if the ruthenium catalyst first reacts with the alkyne part or with the alkene part, the reaction of **64** with ruthenium catalyst **52a** was carried out (Eq. 30). Two metathesized products, enyne metathesis product **65** and diene metathesis product **66**, were obtained in 19% and 5% yields, respectively. This result indicates that the reaction of the alkyne part with **52a** is faster than that of the alkene part with **52a**.

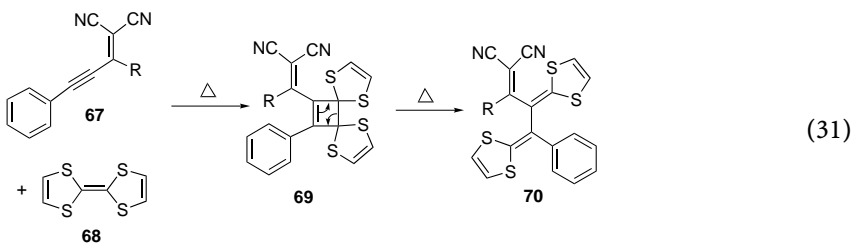


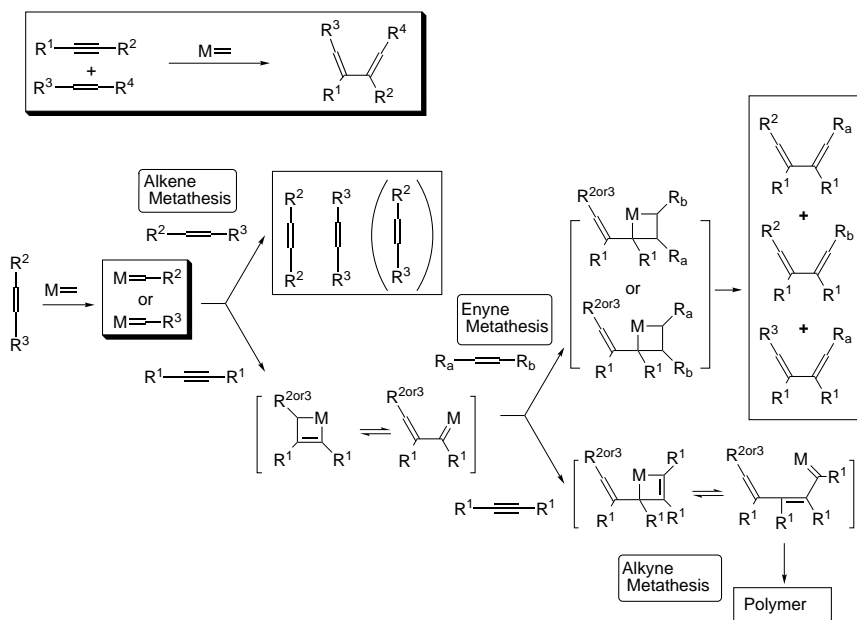
3

Intermolecular Enyne Metathesis

Intermolecular-enyne metathesis, if it is possible, is very unique because the double bond of the alkene is cleaved and each alkylidene part is then introduced onto each alkyne carbon, respectively, as shown in Scheme 9. If metathesis is carried out between alkene and alkyne, many olefins, dienes and polymers would be produced, because intermolecular enyne metathesis includes alkene metathesis, alkyne metathesis and enyne metathesis. The reaction course for intermolecular enyne metathesis between a symmetrical alkyne and an unsymmetrical alkene is shown in Scheme 9. The reaction course is very complicated, and it seems impossible to develop this reaction in synthetic organic chemistry.

Compound **68** is known to form an electrically conducting “organic metal” with a large number of acceptor systems. When a toluene solution of enyne **67** and alkene **68** was refluxed for 2 days, the coupling product **70**, rather than the expected charge transfer complex, was obtained in good yield (Eq. 31, Table 4). This reaction involves a metathetic process [19].



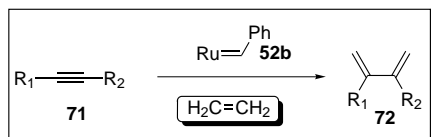


Scheme 9. Intermolecular enyne metathesis

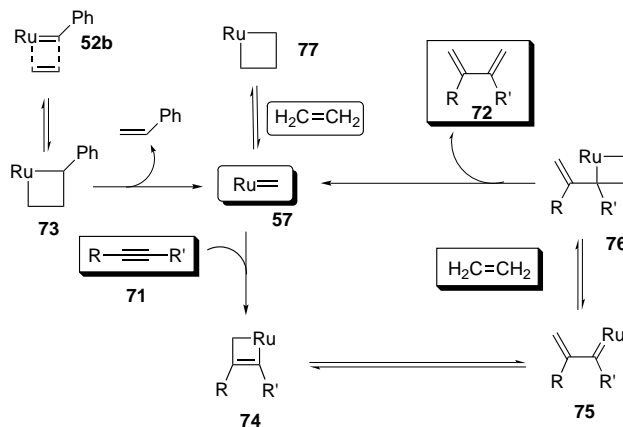
Table 4. Reaction of **67** with **68**

R	Yield (%)
CN	70a 77
Ph-C \equiv C	70b 77
COOEt	70c 47
H	70d 33

Intermolecular enyne metathesis has recently been developed using ethylene gas as the alkene [20]. The plan is shown in Scheme 10. In this reaction, benzyldiene carbene complex **52b**, which is commercially available [16b], reacts with ethylene to give ruthenacyclobutane **73**. This then converts into methylene ruthenium complex **57**, which is the real catalyst in this reaction. It reacts with the alkyne intermolecularly to produce ruthenacyclobutene **74**, which is converted into vinyl ruthenium carbene complex **75**. It must react with ethylene, not with the alkyne, to produce ruthenacyclobutane **76** via [2+2]cycloaddition. Then it gives diene **72**, and methylene ruthenium complex **57** would be regenerated. If the methylene ruthenium complex **57** reacts with ethylene, ruthenacyclobutane **77** would be formed. However, this process is a so-called non-productive process, and it returns to ethylene and **57**. The reaction was carried out in CH_2Cl_2 un-



Pathway of Intermolecular Enyne Metathesis



Scheme 10. Plan for 1,3-diene synthesis using intermolecular enyne metathesis

der an atmosphere of ethylene gas at room temperature with a balloon, and the results are shown in Table 5. Symmetrical and unsymmetrical alkynes bearing functional groups in the tethers, and even the terminal alkynes, can be used in this reaction. In each case, the yield is moderate to good and the conversion yields are high. This procedure is a very useful and unique diene synthesis. Namely, the double bond of ethylene is cleaved and each methylene part is introduced into each alkyne carbon, respectively, as formally shown in Scheme 11.

Takahashi [21] reported a very interesting formal intermolecular enyne metathesis between alkyne and vinyl bromide using an equimolar amount of dibutyl zirconocene. When alkyne **71h** was treated with an equimolar amount of Cp_2ZrBu_2 in the presence of vinyl bromide, diene **72h** was obtained in 95% yield (Eq. 32). Cyclizations of **80** on zirconocene give diene **82** in high yields (Eq. 33). This reaction proceeds by the formation of zirconacycle **83** (Fig. 3) having a bromide at the α -position from alkyne **71h** and vinyl bromide, and bond isomerizations occur to give vinyl zirconium complex **84**, which is hydrolyzed to give diene **72h**.

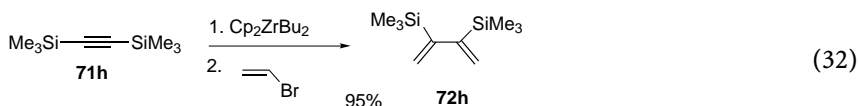
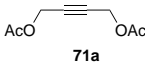
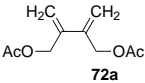
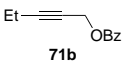
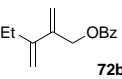
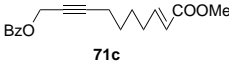
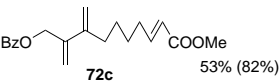
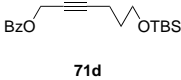
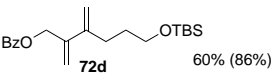
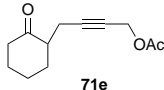
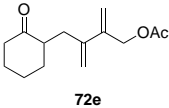
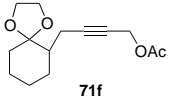
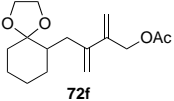
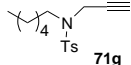
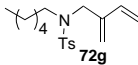


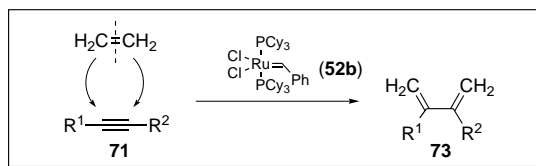
Table 5. 1,3-Diene synthesis of intermolecular enyne metathesis

Run	Substrate	Ru (mol %)	Product	Yield ^{a)}
1	 71a	3 10	 72a	66% (89%) 71% (90%)
2	 71b	3	 72b	62% (100%)
3	 71c	10 ^{b)}	 72c	53% (82%) 53% (82%)
4	 71d	10 ^{b)}	 72d	60% (86%) 60% (86%)
5	 71e	3	 72e	74% (89%) 74% (89%)
6	 71f	3	 72f	48% (84%) 48% (84%)
7	 71g	5	 72g	81% (100%) 81% (100%)

All reactions were carried out in CH_2Cl_2 under ethylene gas using ruthenium catalyst **52b** at room temperature for 45 h.

^a Yields in parentheses are conversion yields.

^b 5 mol% of ruthenium complex catalyst **52b** was used. After 40 h, 5 mol% of **52b** was readded.



Scheme 11. 1,3-Diene synthesis from alkyne and ethylene

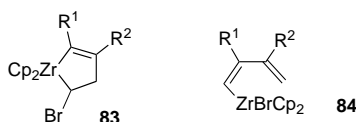
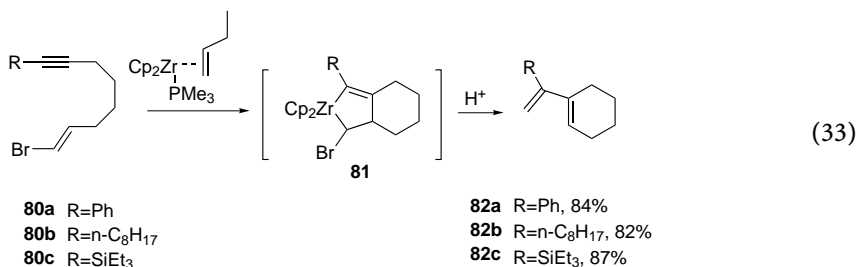


Fig. 3. Zirconacycle **83** and vinyl zirconium complex **84**

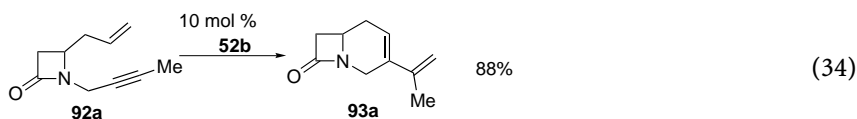


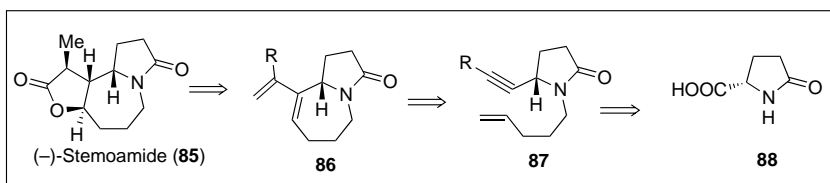
4

Utilization of Enyne Metathesis for the Synthesis of Natural Products and Biologically Active Substances

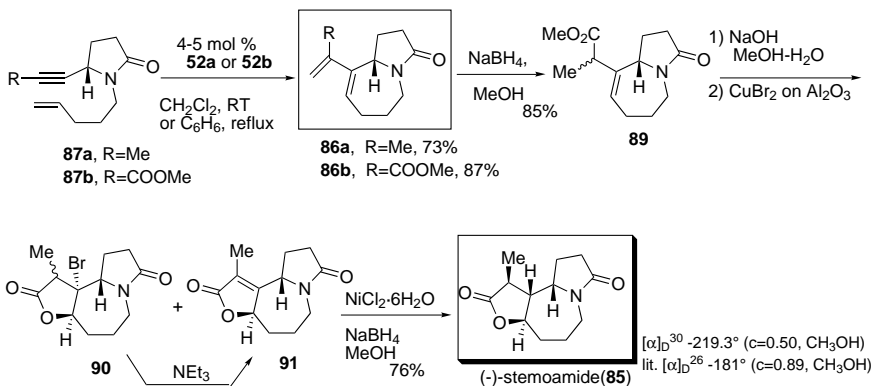
Since enyne metathesis has only recently been developed, there are only a few reports on the utilization of enyne metathesis in synthetic organic chemistry. Mori and Kinoshita [22] succeeded in the total synthesis of (-)-stemoamide (**85**) from (-)-pyrroglutamic acid using ruthenium-catalyzed enyne metathesis as a key step. The retrosynthetic analysis is shown in Scheme 12. The reaction of enyne **87a**, which was prepared from (-)-pyrroglutamic acid, with ruthenium carbene complex **52a** in benzene upon heating provided cyclized diene **86a** in 73% yield (Scheme 13). On the other hand, the reaction of enyne **87b** having a carbomethoxy group on the alkyne with **52b** in CH₂Cl₂ at room temperature gave diene **86b** in 87% yield. Reduction of **86b** followed by halolactonization gave bromide **90** and elimination product **91**. Treatment of **90** with NEt₃ gave **91**, which was reduced with NaBH₄ in MeOH in the presence of NiCl₂·6H₂O to give (-)-stemoamide (**85**).

Barrett [23] reported an ingenious method of synthesizing bicyclic β-lactams **93** using enyne metathesis (Scheme 14). From enynes **92** having various functional groups in the tethers, the desired bicyclic β-lactams **93** were obtained in good yields (Eqs. 34–36). In this reaction, terminal alkyne did not give a good result.

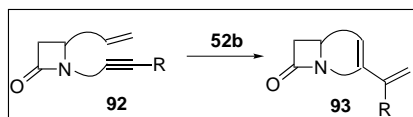
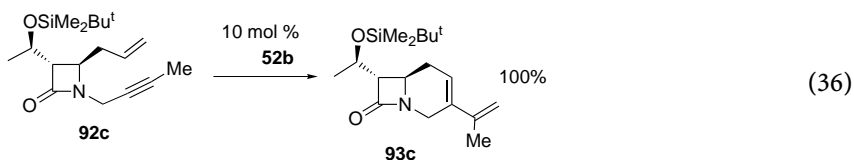
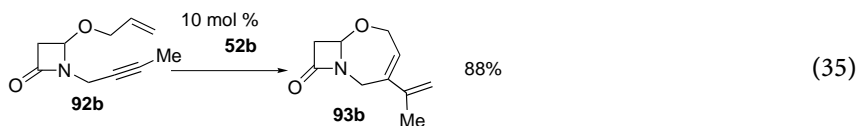




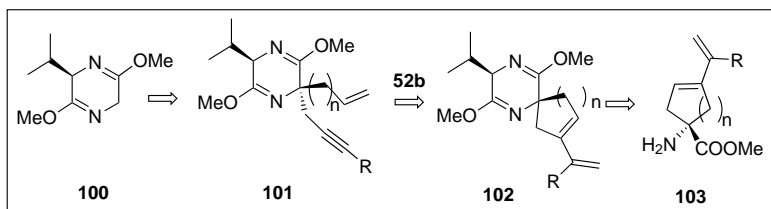
Scheme 12. Retrosynthetic analysis



Scheme 13. Synthesis of (-)-stemoamide

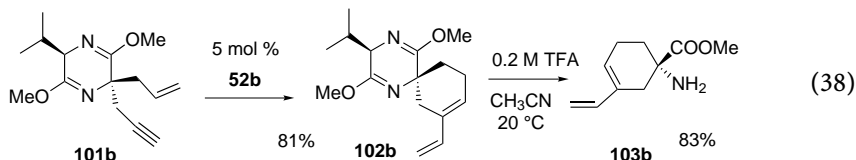
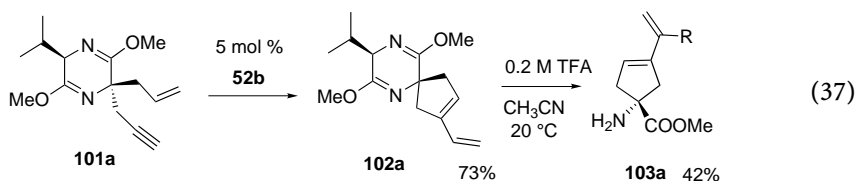
Scheme 14. Synthesis of bicyclic β -lactams

Undheim [24] described the stereoselective synthesis of cyclic 1-amino-1-carboxylic acid using ruthenium-catalyzed enyne metathesis. His plan is shown



Scheme 15. Synthesis of cyclic 1-amino-1-carboxylic acid

in Scheme 15. The starting enyne **101** was prepared in stereochemically pure form by stepwise alkylations of the chiral auxiliary (*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine with bromo-alkenes and -alkynes. The enyne **101** was treated with 5 mol% of ruthenium catalyst **52b** to give spiro compounds **102**, which were cleaved to the desired amino acid methyl ester **103** under mild acidic conditions (0.2 M trifluoroacetic acid in CH_3CN at room temperature) (Eqs 37, 38).



5 Perspective

Although this chemistry was first developed only 13 years ago, in 1985, by Katz, many interesting reactions have been shown in the literature. The main characteristic feature of enyne metathesis is that the double bond of alkene is cleaved and each alkylidene part is introduced onto respective alkyne carbons forming a compound with a diene moiety. Thus, the triple bond of alkyne is converted into a single bond. Among the many enyne metatheses or skeletal rearrangement reactions, ruthenium-catalyzed enyne metathesis is useful because the catalyst is commercially available, the reaction procedure is very simple, the reaction proceeds under very mild conditions, and the reaction mechanism is clear. The mechanisms of enyne metatheses using other metals are less obvious. Thus, many interesting reactions may be developed using various metal complexes.

Despite its difficulty, intermolecular enyne metathesis has been developed and will be a very important reaction in synthetic organic chemistry. It is expected that many interesting and useful applications will be developed in the future.

6

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