Synthesis of Natural Products and Related Compounds using Enyne Metathesis

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Abstract: Since the molybdenum and ruthenium carbene complexes 1a and 1b were discovered by Schrock and Grubbs in 1990 and 1992, synthetic organic chemistry has progressed with the use of these complexes as the catalyst for olefin metathesis. It was found that the ruthenium carbene complex was also effective for enyne metathesis, which occurs between an alkene and an alkyne. Intramolecular enyne metathesis gives various cyclic compounds having a 1,3-diene moiety and cross-metathesis of an alkene with an alkyne is a useful method for the synthesis of a compound having a diene moiety. Furthermore, dienyn metathesis, ROM of cycloalkenynes or tandem reactions of enyne metathesis have been developed. Using these various enyne metatheses, complicated natural products have been synthesized via novel routes. The syntheses of natural products and related compounds using enyne metathesis are described.

1 Introduction

Metathesis is one of the most useful reactions in recent synthetic organic chemistry\textsuperscript{[1]} In ring-closing olefin metathesis, fission of two double bonds occurs and a new double bond is formed at the same time to produce a cyclic compound [Eq. (1)].

\begin{equation}
\text{Ring-closing olefin metathesis} \quad \text{Cu} + \text{Cu} \quad (1)
\end{equation}

Since the discovery of molybdenum and ruthenium carbene complexes by Schrock and Grubbs in 1990\textsuperscript{[2]} and 1992\textsuperscript{[3a]} synthetic organic chemistry has made rapid progress using metathesis reactions. Grubbs et al. found that molybdenum carbene complex 1a is effective for olefin metathesis\textsuperscript{[4a]} They then prepared the ruthenium carbene complex 1b for olefin metathesis\textsuperscript{[4a]} and synthesized carbo- and heterocyclic compounds using this process\textsuperscript{[4]} In 1995, Grubbs found that ruthenium carbene complex 1c has the same reactivity as 1b\textsuperscript{[3b]} and it is now commercially available. Complexes 1b and 1c are stable and easy to handle. Thus, many researchers can use these catalysts, and various cyclic compounds have been synthesized from dienes using ring-closing metathesis (RCM). In 1999, Herrmann\textsuperscript{[5]} Nolan\textsuperscript{[6]} and Grubbs\textsuperscript{[7]} found the novel ruthenium carbene complexes 1d–g having a heterocyclic carbene as a ligand. Since these catalysts are very effective for olefin metathesis compared with the first-generation ruthenium catalysts 1b and 1c\textsuperscript{[8]} olefin metathesis has been further developed by use of these catalysts. These catalysts (Figure 1) have been found to be particularly effective for metathesis of olefins having substituents on the alkene. Furthermore, cross-metathesis (CM) reactions of alkenes and ring-opening metathesis (ROM) reactions have been developed\textsuperscript{[9]}

The metathesis of enynes having alkene and alkyne moieties in the molecule is an extremely interesting reaction. The first enyne metathesis was reported by Katz\textsuperscript{[10]} who used a Fischer tungsten carbene complex. Our group has reported a chromium-catalyzed
enyne metathesis.\[11\] It was later found that the ruthenium carbene complex 1b or 1c was very effective for enyne metatheses.\[12,13a\]

In this reaction, the double bond is cleaved, a carbon-carbon bond is formed between the double and triple bonds, and the cleaved alkylidene part of the double bond migrates onto the alkyne carbon to produce a cyclic compound having a diene moiety (Scheme 1). The reaction may proceed by a [2+2] cycloaddition of a ruthenium carbene complex with an alkyne part to produce a ruthenacyclobutene, and ring opening of this affords a ruthenium carbene complex, which reacts with an alkene part to produce a ruthenacyclobutane, and ring opening of this gives a cyclized compound and a ruthenium carbene complex is regenerated (Route 1). Another mechanism is also considered by which an alkene part of the enyne reacts at first with the ruthenium carbene complex (Route 2).

Using ruthenium carbene complex 1b or 1c, five- to nine-membered heterocycles could be synthesized from the corresponding enynes (Scheme 2).\[13\]

However, enyne 2f having a terminal alkyne did not give a good result. Presumably, the terminal alkene part of product 3f further reacts with the ruthenium carbene complex 1i to form complex 4f and the ruthenium carbene complex could not work. To regenerate the ruthenium carbene complex 1i, the reaction was carried out under ethylene gas and the desired compound 3f was obtained in high yield [Eq. (2)].\[14\]

In 1994, Grubbs discovered an ingenious dienyne metathesis and synthesized various bicyclic compounds 6 from dienynes 5 in one step (Scheme 3).\[15\]

![Figure 1. Mo and Ru carbene catalysts.](image1.jpg)

![Scheme 1. Ring-closing enyne metathesis.](image2.jpg)
On the other hand, the cross-metathesis of an alkyne and ethylene was developed in 1997. When a CH3Cl solution of alkyne 8 was stirred under an atmosphere of ethylene at room temperature in the presence of 1c, 1,3-diene 9 was obtained. It is interesting that, formally, the double bond of ethylene is cleaved and each methylene part is introduced onto the alkyne carbon to produce the 1,3-diene 9. When the second-generation ruthenium carbene complex 1g was used, the reaction time was shortened and functional groups on the alkyne were tolerated (Scheme 4).[17]

Cross-metathesis between a terminal alkyne and a terminal alkene was developed by Blechert, and the 1,3-disubstituted diene was formed [Eq. (3)].[18]

Diver reported the cross-metathesis of a terminal alkyne and cyclopentene using 1g.[19] at first, the ruthenium carbene complex 1i reacts with the terminal alkyne to produce a ruthenium carbene complex. The formed carbene complex reacts with cyclopentene to produce the ruthenium carbene complex 10, which then reacts with the alkene part to afford a cycloheptadiene derivative (Scheme 5).

Furthermore, RCM-CM and ROM-CM were developed using the second-generation ruthenium carbene...
complex. Royer reported on RCM-CM: enyne 11 was reacted with 1h\(^{[20]}\) in the presence of 3 equivalents of methyl acrylate to give 12 in 67\% yield, while the catalysts 1c and 1g were not effective for this reaction [Eq. (4)].\(^{[21]}\) In this reaction, the generated ruthenium carbene complex 13 would further react with methyl acrylate to produce 12 [Eq. (4)].

The ROM-CM of a cycloalkyne was reported by our group (Scheme 6).\(^{[22]}\) Reactions of five- to seven-membered cycloalkenes 14 having the substituent at the 3-position of the cycloalkene with 1c under ethylene gas afforded the cyclic compounds 15 in good yields. This reaction could proceed via the highly strained ruthenacarbobutane 16. In each case, the pyrrolidine derivative 15 was formed, and the initial ring size of the cycloalkene corresponds to the carbon chain length at the 2-position of the pyrrolidine ring. Formally, in this reaction, the double bonds of cycloalkene and ethylene were cleaved and each methylene part of ethylene was introduced onto the alkyne and cycloalkene carbons, respectively, and a carbon-carbon bond was formed between the alkyne and cycloalkene carbons to form a pyrrolidine ring (Table 1).

Blechert reported the same type of ROM-CM. Reaction of cyclopentene derivative 17 having a propargyloxy group at the 3-position with 1c in the presence of diethyl malonate afforded compound 18 in 75\% yield.\(^{[23]}\) In this reaction, the cleaved alkylidene part of diethyl malonate is introduced onto the cyclohexene carbon and the methylene part is introduced onto the alkyne carbon to form furan derivative 18 (Scheme 7).

Skeletal reorganization using a metal catalyst is very interesting. The product from this reaction is the same as that obtained from enyne metathesis, but the reaction mechanism is different with regard to the metal used. Trost et al. found an interesting skeletal reorganization of enynes using a palladium catalyst.\(^{[24,25]}\) In 1994, Murai and Chatani reported skeletal reorganization of 1,6-enynes using [RuCl\(_2\)(CO)]\(_2\) as a catalyst.\(^{[26]}\) Then they found that GaCl\(_3\) was effective for skeletal reorganization.\(^{[27]}\)

Using these various enyne metatheses, complicated natural products have been synthesized via a novel route and the synthetic routes are completely different from that described in the literature.\(^{[28]}\) In this report, the syntheses of natural products and related compounds using enyne metathesis reactions are described.

2 Syntheses of Natural Products and Related Compounds using Ring-Closing Enyne Metathesis (RCM)

The first example of the total synthesis of a natural product using enyne metathesis is the synthesis of (-)-stemoamide.\(^{[29]}\) (-)-Pyroglutamic acid was con-
verted into enyne 19 having an ester group on the alkyne, and RCM of enyne 19 was carried out in the presence of ruthenium carbene complex 1c to afford bicyclic compound 20, which was converted into 21 and then halolactonization was carried out to give 22. From this compound 22, (−)-stemoamide could be synthesized (Scheme 8).

Carbacephem and carbapenem (25 and 27) were synthesized from enynes 24 and 26, which were prepared from 4-acetoxyazetidinone 23. The yield of the latter compound is low compared with that of 25 because of the highly strained fused 4,5-membered ring system (Scheme 9).[30]
Undeheim described the stereoselective synthesis of the unusual chiral amino acid 31. The starting enyne 29 was synthesized in stereochemically pure form by stepwise alkylations of 28. Reaction of enyne 29 with 1c gave the spiro-compound 30, which was treated with TFA to give the desired amino acid 31 (Scheme 10).

The Tic (1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid) derivative 34 was synthesized by enyne metathesis of 32 followed by Diels–Alder reaction of the resultant diene 33 with dimethyl acetylenedicarboxylate (DMAD) and then DDQ oxidation [Eq. (5)].

(±)-Differolide could be easily synthesized by enyne metathesis. Enyne 35 was reacted with 1c to

Scheme 12. Total synthesis of (−)-longthorone A.
give lactone 36, which spontaneously dimerized to afford (±)-differolide (Scheme 11).

An enantioselective biomimetic synthesis of longithorone A was accomplished on the basis of the proposed biosynthesis.[34] The syntheses of two [12]-paracyclophanes 39 and 41 were realized by applying enyne metathesis macrocyclization to 38 and 40, which were synthesized from the common substrate 37. Longitholone A was synthesized using intermolecular and transannular Diels–Alder reactions followed by oxidation (Scheme 12).

The total synthesis of (±)-anatoxin-a was achieved by Martin,[35a,b] and our group[35c,d] by the same strategy. The key step is the construction of an azabicyclo[4.2.1]nonene ring system. For that purpose, the pyrrolidine derivative 42 having cis-substituents was synthesized from (±)-pyroglutamic acid. Enyne metathesis of 42 was carried out using 1g to form the desired ring system. From this compound 43, anatoxin-a could be synthesized (Scheme 13).

By a similar procedure, (±)-ferruginine was synthesized from (−)-pyroglutamic acid.[36] Construction of an azabicyclo[3.2.1]octene ring system was carried out using enyne metathesis. Wacker oxidation of the resultant diene 46 afforded the methyl ketone, and then deprotection of the nitrogen followed by methylolation gave (±)-ferruginine (Scheme 14).

Skeletal reorganization is a useful tool for the synthesis of complicated natural products. Fürstner achieved a formal total synthesis of the antibiotics metacycloprodigiosin and streptorubin B by a platinum-catalyzed skeletal reorganization reaction (Scheme 15).[37] The key step leading to the meta-bridged pyrrole core structure consisted of a metathesis reaction of the electron-deficient enynes 47a and 47b catalyzed by PtCl₂. The skeletal reorganization products 48a and 48b were then converted into the respective target molecules.

Trost succeeded in a formal total synthesis of roseophilin.[38] Macrocyclic compound 54 was synthesized from enyne 53 by platinum-catalyzed skeletal reorganization. From 54, pyrrole derivative 56 was synthesized and was readily converted into roseophilin (Scheme 16).[38]

**Scheme 13.** Total synthesis of anatoxin-a.

**Scheme 14.** Synthesis of (±)-ferruginine.

**Scheme 15.** Synthesis of natural products using enyne metathesis.
framework analogous to the proposed transition state of the isomerization of previtamin D$_3$ to vitamin D$_3$. The starting dienyne 62 was prepared by condensation of indenone 61 with 60. The target molecule 63 was obtained from dienyne 62 as a diastereomeric mixture at the C-10 position in 48% yield (Scheme 18).

Total synthesis of (±)-erythrocarine was achieved by our group using dienyne metathesis.$^{[41]}$ Synthesis of trisubstituted alkene 65 was achieved via regio- and stereoselective introduction of carbon dioxide and an alkynyl group onto the terminal alkyne of 64 followed

Scheme 16. Formal total synthesis of roseophilin.

Scheme 17. Construction of a steroidal skeleton.
by deprotection of the Boc group. Hetero-Michael reaction of 65 gave the isoquinoline derivative 66, which was converted into dienyne 67. Since the tertiary amine of 67 coordinates to the ruthenium catalyst and the catalytic activity is decreased, 67 was converted into 67·HCl and dienyne metathesis was carried out using ruthenium catalyst 1c. As a result, tetracyclic compounds 68a and 68b were obtained as a diastereomeric mixture in a ratio of 1 to 1. From the α-isomer 68a, erythrocarine was synthesized (Scheme 19). Hatakeyama succeeded in the total synthesis of erythravine using a similar procedure.[42]

Honda et al. succeeded in a diastereoselective total synthesis of (−)-securinine in an optically pure form by employing RCM of the corresponding dienyne 69 as a key step (Scheme 20). They synthesized dienyne 69 having terminal alkene and disubstituted alkene parts from (+)-pimelic acid, because ruthenium-carbene complex would at first react with the terminal alkene to form a furan ring. Thus, dienyne metathesis of 69 was carried out using 1j[44] to give 70 in good yield. Oxidation of 70 with CrO3 gave lactone 71, which was treated with NBS and then TFA to produce (−)-securinine. They also synthesized viroallosecurinine in a similar manner.[43b]

Scheme 18. Synthesis of a [6.4.0]carbocyclic system.

Scheme 19. Total synthesis of erythrocarine.

Scheme 20. Total synthesis of (−)-securinine.
Hanna developed a concise route to a key intermediate in the total synthesis of guanacastepene A using dienyne metathesis.\[45\] The main feature includes the construction of fused seven- and six-membered rings. Metathesis of dienyne 74, prepared from cyclopentanone derivative 72, was carried out using 1g, and a mixture of tricyclic compound 75 was obtained in a ratio of 1 to 1. Selective epoxidation followed by introduction of an allyloxy group in the presence of Yb(OTf)\(_3\), gave 76 and 77 in a ratio of 3 to 2. From 76, compound 79 could be synthesized, which had previously been converted into \((\pm)\)-guanacastepene A (Scheme 21).

Dienyne metathesis of \(\beta\)-carboline derivative 80 afforded the oxidized pentacyclic compound 82 that is related to alkaloids containing a \(\beta\)-carboline unit. The starting material 80 was readily synthesized from tryptamine (Scheme 22).\[46\]

### 4 Synthesis of Natural Products and Related Compounds using Cross-Metathesis

Anolignanes were synthesized using cross-metathesis of an enyne as a key step. 1,3-Diene 84 could be synthesized from alkyne 83 under ethylene gas using 1g. Deacetoxylation using a palladium catalyst followed by deprotection gave anoliganane A. Anolignane B could be synthesized in a similar manner. It was interesting that the two methylidene parts of the anolignane skeleton could be introduced at the last stage of the total synthesis using cross-metathesis (Scheme 23).\[47\]

A short and efficient synthesis of highly substituted tetrahydropyridines 85 was achieved from a monosubstituted alkyne, a terminal alkene, and an imine by a combination of enyne cross-metathesis and aza-Diels–Alder reaction under high pressure. Cross-metathesis of a terminal alkyne and an alkene afforded diene
86a, which was reacted with imine to give the pipercolinic acid derivative 85a in high yield (Scheme 24).

The reaction was further extended to an intramolecular Diels–Alder reaction, and cis-hexahydro-1H-indene 87 was synthesized from a diene and a terminal alkyn in one step. The intermediate would be 89, which was spontaneously converted into 87. Deprotection of the silyl group followed by PCC oxidation gave indanone 88 (Scheme 25).

A new method for the synthesis of phenylalanine derivative 90 was developed using the same strategy. A terminal alkyn, prepared from a glycine derivative and propargyl bromide, was reacted with allyl acetate using 1g to give a diene, which was heated with DMAD and then the resultant product was oxidized with DDQ to give 90 (Scheme 26).

Scheme 24. Synthesis of pipercolinic acid from alkyn, alkene and imine.

Scheme 25. Synthesis of cis-fused carbo-bicyclic compounds.

Scheme 26. Synthesis of an alanine derivative from a glycine.
ROM of a cycloalkene having a substituent at the 2-position with \( 1g \) afforded a bicyclic compound via the reaction course shown in Scheme 27.\(^{[22b,51]} \) In this reaction, the formed ring size \((n + 2)\) is the initial ring size \((n)\) plus 2 and the other ring size corresponds to the carbon chain length from an alkyne carbon to an alkene carbon. Cyclopentene derivative 91a was treated with \( 1g \) to give bicyclic compound 92a. Thus, to synthesize an isoquinoline derivative using this method, the initial cycloalkene would be cyclobutene and the chain length containing nitrogen would be six. Treatment of cyclobutene-yne 91b with \( 1g \) afforded isoquinoline derivative 92b in 60% yield in one step. Furthermore, the glycine derivative 91c having a cyclobutene ring in a tether afforded the cyclic amino acid 92c in 76% yield. This procedure was further extended to the synthesis of biaryl compound 92d. It is interesting that the substituent on the alkyne is placed at the 5-position of the isoquinoline (Scheme 27).\(^{[52]} \)

The synthesis of anthramycin derivative 99a was achieved using RCM and CM (Scheme 28).\(^{[53]} \) L-Methionine was converted into enyne 93, and RCM of 93 using \( 1c \) gave pyrrolidine derivative 94. Deprotection followed by condensation with a commercially available acid chloride gave 95. Reductive cyclization of 95 using Zn-AcOH followed by treatment with dilute HCl gave the pyrrolo-1,4-benzodiazepinone 96. To convert the vinyl group into an \( \alpha,\beta \)-unsaturated ester group, cross-metathesis with ethyl acrylate was carried out using catalyst \( 1k \).\(^{[54]} \) The reaction proceeded smoothly to give compound 97 in 60% yield. Isomerization of the double bond in the pyrrolidine ring using \( \text{RhCl}_3 \cdot \text{H}_2\text{O} \) afforded the desired compound 98, the amide group of which was converted into aminal.

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**Scheme 28. Synthesis of anthramycin derivative.**
99a. Conversion of 99b into (+)-anthramycin was achieved by Stille.

Morken succeeded in the synthesis of \((-\text{C}0\)-dihydroxanthatin using RCM and CM.\[55\] Allylic alcohol 100 was converted into tetrahydrofuran 101 by the catalytic Oshima–Utimoto reaction. After olefin homologation and oxidation, lactone 102 could be synthesized. Enyne metathesis of 102 using 1g followed by methylation gave bicyclic compound 103. Cross-metathesis of 103 and methyl vinyl ketone in the presence of 1g afforded \((-\text{C}0\)-dihydroxanthatin (Scheme 29).

Martin succeeded in the first total synthesis of the novel sesquiterpene 8-\textit{epi}-xanthatin.\[56\] Commercially available ester 104 was converted into vinyl triflate 105. Palladium-catalyzed carbonylation followed by desilylation gave lactone 107. The total synthesis of 8-\textit{epi}-xanthatin was directly achieved by RCM-CM of lactone 107 using 1h in the presence of an excess amount of methyl vinyl ketone in one step (Scheme 30).

### 6 Perspectives

Since the discovery of stable and isolable catalysts for metathesis by Schrock and Grubbs, a wide range of olefin metatheses has been reported, and olefin metathesis now occupies an important position in natural product syntheses. A medium-sized ring, a macrocyclic ring and even five- and six-membered rings are now constructed by RCM of an olefin in place of the old methods. Enyne metathesis, dienyne metathesis, enyne cross-metathesis, and ROM reactions of cyclo-alkene-yne have also been developed. The remarkable features of these enyne metatheses are that the double and triple bonds are cleaved and a diene moiety is formed. The recent retrosynthetic analysis of the natural product is completely different from that of the previous syntheses. It is difficult to estimate the structures of the products of tandem enyne metathesis containing enyne, dienyne, ROM, or enyne cross-metathesis reactions. Novel procedures for the synthesis of the natural products, various complex molecules and macrocyclic compounds will certainly be further developed using these various enyne metatheses.

### References


