Review

Recent Progress on Enyne Metathesis: Its Application to Syntheses of Natural Products and Related Compounds

Miwako Mori

Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan; E-Mail: mori@pharm.hokudai.ac.jp; Tel: +81 11 7876045; Fax: +81 11 7876045.

Received: 28 December 2009; in revised form: 26 February 2010 / Accepted: 16 March 2010 / Published: 19 March 2010

Abstract: Olefin metathesis using ruthenium carbene complexes is a useful method in synthetic organic chemistry. Enyne metathesis is also catalyzed by these complexes and various carbo- and heterocycles could be synthesized from the corresponding enynes. Dienyne metathesis, cross enyne metathesis and ring-opening enyne metathesis have been further developed. Various complicated compounds, such as the natural products and the related biologically active substances, could be synthesized using these metatheses reactions. Skeletal reorganization using the transition metals and metallotropic rearrangement are also discussed.

Keywords: enyne metathesis; ring-closing enyne metathesis; dienyne metathesis; cross metathesis; ring-opening metathesis; natural product

Table of Content

Introduction
1. Ring-Closing Enyne Metathesis
2. Ring-Closing Dienyne Metathesis
3. Cross Enyne Metathesis
4. Ring-Opening Enyne Metathesis
5. Skeletal Reorganization Using Transition Metals
6. Metallotropic Rearrangement
Perspective
Introduction

Since the discovery of molybdenum and ruthenium carbene complexes by Schrock and Grubbs in 1990 [1] and 1992 [2], synthetic organic chemistry has made rapid progress using metathesis reactions. Grubbs et al. found that molybdenum carbene complex 1a was effective for olefin metathesis [3]. They then synthesized ruthenium-carbene complex 1b for olefin metathesis [2], and synthesized carbo- and heterocyclic compounds using ring-closing olefin metathesis [4–6]. In 1995, Grubbs found that ruthenium-carbene complex 1c has the same reactivity as that of 1b [7], and it is now commercially available. Complexes 1b and 1c are stable and easy to handle (Figure 1). Thus, many researchers were able to use these catalysts, and various cyclic compounds were synthesized from dienes using ring-closing metathesis (RCM).

**Figure 1.** Ruthenium catalysts for alkene metathesis.

![Figure 1](image1)

**Figure 2.** Ruthemium catalysts for alkene metathesis.

![Figure 2](image2)
In 1999, Herrmann [8–9], Nolan [10–11] and Grubbs [12–16] found novel ruthenium-carbene complexes 1d-1g having a heterocyclic carbene as a ligand. Since these catalysts, called as the second-generation ruthenium carbene complex, are very effective for olefin metathesis compared with 1b and 1c [14], olefin metathesis has been further progressed by use of these catalysts. Furthermore, cross-metathesis (CM) of alkene and ring-opening metathesis (ROM) have been developed using these complexes. Later, many ruthenium carbene complexes 1h-k [17–22] having various ligands were synthesized (Figure 2).

Metathesis of enynes having alkene and alkyne moieties in a molecule is an extremely interesting reaction [23–27]. In this reaction, the double bond of enyne 2 is cleaved and 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 3 having a 1,3-diene moiety (Scheme 1).

**Scheme 1.** Ring-opening enyne metathesis.

![Scheme 1](image)

The first enyne metathesis was reported by Katz [28–30], who used a Fischer tungsten-carbene complex. Then Mori reported a chromium-catalyzed enyne metathesis [31–34]. It was later found that the ruthenium-carbene complex 1b or 1c was very effective for enyne metathesis [35–36]. The reaction would proceed via a [2+2] cycloaddition of a ruthenium-carbene complex with an alkyne part to produce ruthenacyclobutene 4, and ring-opening of this affords a ruthenium carbene complex 5, which reacts with an alkene part to produce ruthenacyclobutane 6, and ring-opening of this gives a cyclized compound 3 and a ruthenium-carbene complex is regenerated (Scheme 2, Route 1). In some cases, metathesis products via complexes 4' were obtained. The other mechanism also considered involves at first reaction of the alkene part of enyne 2 with ruthenium carbene complex to afford a new ruthenium carbene complex 7. The latter species reacts with the alkyne part to produce ruthenacyclobutene 8 and its subsequent ring-opening gives ruthenium carbene 9, that undergoes intermolecular [2+2] cycloaddition with the alkene part of enyne 2 to produce ruthenacyclobutane 10. Ring-opening of this gives cyclic compound 3 and ruthenium carbene complex 7 is regenerated (Scheme 2, Route 2).

Later, the detailed study on the reaction mechanism was shown by Lippstreu and Straub, who described that the reaction would proceeds via Route 2, and ruthenacyclobutene 4, generated from an alkyne part of enyne 2 and ruthenium carbene complex, do not exist as local minimum in the catalytic cycle [37].

Using ruthenium carbene complexes 1b and 1c, various carbo- and heterocycles could be synthesized from the corresponding enynes [35–36]. Furthermore, diyne metathesis, cross enyne metathesis and ring-opening enyne metathesis have been developed. As the results, the novel route for the synthesis of various complicated compounds, such as the natural products and the related biologically active substances, were pioneered. Skeletal reorganization using the transition metals and metallotropic rearrangement will be discussed.
1. Ring-Closing Enyne Metathesis (RCM)

Mori reported the synthesis of heterocycles having a diene moiety using enyne metathesis [35–36]. Enynes 11 were treated with 1 mol % of Grubbs catalyst 1b at room temperature to afford heterocycles 12 in high yields. Using this procedure, five- to nine-membered heterocycles could be synthesized (Scheme 3).

Scheme 3. Synthesis of heterocycles using ruthenium catalyst.

In this reaction, enynes 11 (R = H), having a terminal alkyne, did not give a satisfactory result [38]. For example, RCM of enyne 11h afforded cyclic compound 12h in only 21% yield. It is reasoned that an alkene part in product 12h further reacts with ruthenium carbene methylidene complex 1l to afford
ruthenium carbene 14, which would be coordinated by the alkene part to produce 15. Thus, the catalytic activity would decrease (Scheme 4). In fact, when the reaction of 11h using 1c was carried out under ethylene gas, the catalytic activity was much larger to afford 12h in 90% yield, even with the use of 1 mol % of the ruthenium catalyst 1c. The higher reactivity observed in enyne metathesis in the presence of ethylene gas has often been advantageous in applications to natural product synthesis.

Scheme 4. Metathesis of enyne having terminal alkyne under ethylene gas.

When the second-generation ruthenium carbene complexes were used for enyne metathesis, unprecedented results were shown [39–40]. The reaction of enyne 16a or 16b was carried out using 5 mol % of 1f to afford expected metathesis product 17a or 17b along with six-membered compound 18a or 18b. Use of other second-generation ruthenium carbene complex 1g to the reaction of 16a gave a similar result. Presumably, when ruthenium carbene methylidene complex 1l reacts with the alkyne moiety in 16, two regiochemically different pathways are possible (Scheme 5, path A and B). Each carbene complex 19 or 20 gives a different product 17 or 18, respectively. On the other hand, if 1l reacts with an alkene moiety (path A'), compound 17 is formed. In this case, the path B' is a non-productive process. Thus, compound 18 should be formed via path B. However, it is not clear why two products 17 and 18 were formed when the second-generation ruthenium carbene complexes were used.

Recently, it was reported that cyclobutene derivative 22 could be synthesized from enyne 21 using ruthenium carbene complex 1g under microwave irradiation conditions with 58% yield (Scheme 6) [41].

Two synthetic methods of highly functionalized conjugated diene 26 using ring-closing enyne metathesis were reported (Scheme 7). The reaction of propargyl alcohol 23 and allylboronate 24 in the presence of 1c gave cyclic boronic ester 25a. In this reaction, enyne 27a should be formed as an intermediate. Treatment of cyclic boronic ester 25a with H$_2$O$_2$ in aqueous NaOH gave diol 26a [42–43]. Silicon-tethered ring closing enyne metathesis of 27b by ruthenium carbene catalyst 1c gave 25b, which was subjected to Tamao oxidation to afford diol 26b [44–45].
Scheme 5. Enyne metathesis using second generation ruthenium catalysts.

\[
\text{E}=\text{CO}_2\text{Et} + 1\text{f} \quad \text{toluene, } 80 \, ^\circ\text{C} \quad 1\text{f} \quad \text{43\%}
\]

Scheme 6. 1,5-Enyne metathesis.

\[
\text{Ph} + 1\text{g} \quad \text{CH}_2\text{Cl}_2, 70 \, ^\circ\text{C} \quad \text{microwave} \quad \text{58\%}
\]
Scheme 7. Synthesis of functionalized diene.

Enyne 28a having a silyl ynoyl ether on the alkyne gave cyclic compound 29a having a silyl enol ether moiety, which was converted into 1-acetylcyclopentene 30a by desilylation. In a similar manner, enyne 28b afforded bicyclic methyl ketone 29b in 68% yield after deprotection of the silyl group [46]. However, ynoate 28c and yne-phosphonate 28d did not give cyclized compounds. Ene-alkynyl ether 31a or 31b afforded cyclic enol ethers 32a or 32b in good to moderate yield (Scheme 8) [47].

Scheme 8. Metathesis of ene-alkynyl ether.

RCM of ene-alkynyl amide 33a using 1g gave pyrrolidine derivative 34a, which afforded indole derivative 35a by Diels–Alder reaction [48–49]. In a similar manner, one-pot RCM of ene-alkynyl
amide $33b$, a one carbon-elongated homolog, followed by Dield–Alder reaction, gave quinoline derivative $35b$ in a high yield (Scheme 9) [48–51].

Metathesis of enyne $36a$ containing conjugated ene-yne using ruthenium catalyst $1k$ gave cycloheptene derivative $37a$ having a triene unit. This reaction did not proceed by first or second-generation ruthenium catalyst $1c$ or $1g$ (Scheme 10) [52]. Enynes $36b$ and $36c$ having internal alkyne and diene afforded eight-membered ring compounds $37b$ and $37c$ in high yields [53].

The synthesis of substituted styrene $39$ was achieved by ring-closing enyne metathesis (Scheme 11). As an application of this method, 1,1’-binaphthyl derivative $41$ was prepared [54–55].

Metathesis of allene-yne $42$ using molybdenum catalyst $1a$ gave cyclic compound $43$ having an allene moiety. RCM of $42-D$ gave $43-D$, which indicates that the vinylallene skeleton was constructed by a metathesis-type reaction between the alkyne moiety and the proximal carbon-carbon double bond of the allene moiety (Scheme 12) [56].

**Scheme 9.** Ring-closing metathesis of ene-alkynyl amide.

![Scheme 9](image1)

**Scheme 10.** Reaction of enyne containing diene-yne.

![Scheme 10](image2)
**Scheme 11.** Synthesis of carbocyclic aromatic ring-closing metathesis.

\[
\begin{align*}
\text{Pr} & \quad \text{OAc} \\
\text{Pr} & \quad \text{toluene, 80 °C, 2 h} \\
\text{Ph} & \quad 1g \\
\text{Pr} & \quad \text{Ph} \\
\text{38} & \quad \text{39} \quad 99\%
\end{align*}
\]

\[
\begin{align*}
\text{F} & \quad \text{OH} \\
\text{F} & \quad \text{O} \\
\text{O} & \quad \text{OH} \\
\text{40} & \quad \text{41} \\
\text{1g} & \quad 7,5 \text{~mol~%} \\
\text{toluene, 80 °C, 2 h} & \quad 89\%
\end{align*}
\]

**Scheme 12.** Ring-Closing Enyne Metathesis (RCM) of allene-yne

\[
\begin{align*}
\text{TsN} & \quad \text{=N=Ts} \\
\text{R} & \quad \text{H} \\
\text{42} & \quad \text{42-D} \\
\text{R=D} & \quad \text{15 mol ~%} \\
\text{toluene, rt, 3 h} & \quad \text{43} \\
\text{R=H} & \quad 71\% \\
\text{R=D} & \quad 73\% \quad (> 82\% \text{ D})
\end{align*}
\]

**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 ring-closing enyne metathesis is the synthesis of (-)-stemoamide [57–58]. (-)-Pyroglutamic acid was converted into enyne 44 having an ester group on the alkyne, and RCM of enyne 44 was carried out in the presence of 4 mol % of ruthenium-carbene complex 1c to afford bicyclic compound 45 in 87% yield. Conversion of 45 into 46 smoothly proceeded. From this compound 46, (-)-stemoamide could be synthesized (Scheme 13).

**Scheme 13.** Total synthesis of (-)-stemoamide.

\[
\begin{align*}
\text{HO}_2\text{C} & \quad \text{N} \quad \text{H} \\
\text{(-)-pyroglutamic acid} & \quad \text{MeO}_2\text{C} \\
\text{44} & \quad \text{45} \\
\text{4 mol ~%} & \quad \text{1c} \\
\text{CH}_2\text{Cl}_2, \text{rt} & \quad 87\%
\end{align*}
\]

\[
\begin{align*}
\text{NaBH}_4 & \quad \text{MeOH} \\
\text{85\%} & \quad \text{MeO}_2\text{C} \\
\text{46} & \quad \text{46} \\
1. \text{NaOH} & \quad 1. \text{NaOH} \\
2. \text{CuBr}_2 \text{ on Al}_2\text{O}_3 & \quad 2. \text{CuBr}_2 \text{ on Al}_2\text{O}_3 \\
3. \text{NEt}_3 & \quad 3. \text{NEt}_3 \\
4. \text{NiCl}_2 \cdot 6\text{H}_2\text{O} & \quad 4. \text{NiCl}_2 \cdot 6\text{H}_2\text{O} \\
\text{NaBH}_4 & \quad \text{NaBH}_4 \\
\text{(-)-Stemoamide} & \quad \text{(-)-Stemoamide}
\end{align*}
\]

76% from 46
Carbacephem 49a and carbapenem 49b were synthesized from enynes 48a and 48b, which were prepared from 4-acetoxy-azetidinone 47. The yield of the latter compound 49b is lower compared with that of 49a because of the highly strained fused 4,5-membered ring system (Scheme 14) [59–60].

(+)-Differolide could be easily synthesized by enyne metathesis [61]. Enyne 50 was reacted with 1c to give lactone 51, which was spontaneously dimerized to afford (+)-differolide (Scheme 15).

**Scheme 14. Construction of carbacephem and carbapenem skeleton.**

![Scheme 14](image1)

**Scheme 15. Synthesis of (+)-differolide.**

![Scheme 15](image2)

An enantioselective biomimetic synthesis of longithorone A was accomplished on the basis of the proposed biosynthesis [62]. Two [12]-paracyclophanes 52 and 53 were synthesized from common intermediate 54 by applying enyne metathesis macrocyclization in 42% and 31% yields, respectively. Intermolecular Diels-Alder reaction of 52 and 53 provided 59. Deprotection followed by oxidation gave 60, which spontaneously gave longithorone A via transannular Diels-Alder reaction (Scheme 16).

The total synthesis of (+)-anatoxin-a was achieved by Martin [63–64] and Mori [65–66] by the same strategy. The key step is the construction of an azabicyclo[4.2.1]nonene ring system. For that purpose, the 2,5-cis-disubstituted pyrrolidine derivative 61 having cis-substituents was synthesized from (+)-pyroglutamic acid. Enyne metathesis of 61 was carried out using 1g to form this ring system. From this azabicyclic compound 62, anatoxin-a could be synthesized (Scheme 17).
Scheme 16. Total synthesis of (-)-longithorone A.

Longithorone A

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Longithorone A
Scheme 17. Total synthesis of anatoxin-A.

By a similar procedure, (+)-ferruginine was synthesized from (-)-pyroglutamic acid [67]. Construction of the azabicyclo[3.2.1] octane ring system was carried out using enyne metathesis of 64. Wacker oxidation to the resultant diene 65 afforded methyl ketone, and then deprotection followed by methylation gave (+)-ferruginine (Scheme 18).

Scheme 18. Synthesis of (+)-ferruginine.

Kozmin developed a highly efficient synthesis of cyclic compound bearing the methyl ketone functionality from enyne having a silyloxy group on the alkyne (Scheme 8) [46]. As an application of this method, they succeeded in the synthesis of eremophilane [68]. RCM of enyne 66a having a silyloxy group on the alkyne followed by treatment with HF gave cycloalkene 68b having the methyl ketone functionality. Hydrogenation of the double bond in compound 68b gave 69. From this compound 69, α- and β-eremophilane could be synthesized (Scheme 19).

New allocolchinoids functionalized at C10 or C11 in the C ring were synthesized using the RCM of enyne 70 for the construction of the seven-membered ring. The reaction proceeded smoothly to give 71 using 1g in 92% yield. Deprotection followed by PCC oxidation gave 72, which was subjected to a Diels-Alder-aromatization sequence to form 73. Amination of 73 followed by acetylation gave allocholchicines (Scheme 20) [69].
Scheme 19. Total synthesis of eremophilane.

Scheme 20. Synthesis of allo-colchicine.

The agalacto-spirolactone B subunit of quartromicins has been synthesized using the Claisen-Ireland/RCM of enyne approach by Haudrechy et al. [70]. Enyne 74 was treated with 1g in toluene at 80 °C to afford 75 in 73% yield. From this compound 75, subunit B of quartromicin was synthesized (Scheme 21).

An enantioselective synthesis of (-)-galanthamine was realized in 11 steps starting from isovanillin (Scheme 22). The enyne 76 (92% ee) underwent an efficient RCM reaction in the presence of 3 mol % of 1c to give diene 77 in 85% yield. Hydroboration of the terminal alkene of 77 followed by oxidation gave homoallylic alcohol 78 in excellent yield, and palladium-catalyzed cyclization followed by SeO₂ oxidation gave 79. Mesylation of 79 followed by deprotection afforded (-)-galanthamine [71].
Scheme 21. Synthesis of subunit of quartromicin.

For the synthesis of angucyclinone-type natural products, a concise and highly enantioselective route was developed (Scheme 23). Chiral vinylcyclohexene derivative 81 was synthesized using RCM of enyne 80 under an atmosphere of ethylene in high yield. Intermolecular Diels-Alder reaction of 81 and 82 followed by aromatization gave compound 83 having benz[a]anthraquinone skeleton. Utilization of this strategy, total synthesis of YM-181741, (+)-ochromycinone, (+)-rubiginone B have been accomplished [72].

Stereoselective total synthesis of (+)-valienamine was reported utilizing ring-closing enyne metathesis (Scheme 24) [73].
Scheme 23. Synthesis of benz[a]anthraquinone skeleton.

Scheme 24. Synthesis of (+)-valienamine.

An interesting acceleration effect of an allylic hydroxy group on ring-closing enyne metathesis has been demonstrated. Ring-closing enyne metathesis of terminal alkynes possessing an allylic hydroxy group proceeded smoothly. The synthesis of (+)-isofagomine with the aid of this efficient reaction has been demonstrated [74].

Grubbs demonstrated the synthesis of various fused polycyclic compounds using tandem metathesis reaction. A steroidal skeleton could be constructed using tandem enyne metathesis. Treatment of polyene 86 having double and triple bonds at the appropriate positions in the carbon chain gave compound 87 in high yield in one step, although many processes were contained in this reaction as shown in Scheme 25 [75].

Tandem ring-closing enyne metathesis followed by cross olefin metathesis is interesting and useful because the reaction process is shortened and the yield is raised compared with that of the stepwise reaction. One-pot RCM–CM reaction was realized by Royer et al. (Scheme 26). The RCM of 88 in the presence of an excess amount of methyl acrylate using ruthenium carbene complex 1g gave cyclic compound 89 in good yield. The reaction would proceed via the formation of 90 and subsequent CM with methyl acrylate to produce 89 [76].
Materials 2010, 3

Scheme 25. Construction of a steroidal skeleton.

Scheme 26. One-pot reaction of RCM-CM.

Synthesis of anthramycine derivative 99a was achieved using RCM and CM (Scheme 27) [77]. L-Methionine was converted into enyne 91, and RCM of 91 using 1c gave pyrrolidine derivative 92. Deprotection followed by condensation with commercially available acid chloride 93 gave 94. Reductive cyclization of 94 using Zn-AcOH followed by treatment with dilute HCl gave pyrrolo-1,4-benzodiazepinone 95. To convert the vinyl group into an α,β-unsaturated ester group, olefin cross metathesis with ethyl acrylate was carried out using catalyst 1j [20–21]. The reaction proceeded smoothly to give compound 96 in 60% yield. Isomerization of the double bond in the pyrrolidine ring using RhCl₃·H₂O afforded desired compound 97, the amide group of which was converted into aminal
Conversion of 98 into ester 99a was achieved. Stille has already reported the conversion of 99b into (+)-anthramycin.

**Scheme 27.** Synthesis of anthramycin derivative.

Morken and Evans succeeded in the synthesis of (-)-dihydroxanthatin using RCM and CM [78]. Enyne metathesis of 100 using 1g followed by methylation gave bicyclic compound 101. Cross metathesis of 101 and methyl vinyl ketone in the presence of 1g afforded (-)-dihydroxanthatin (Scheme 28).
Martin succeeded in the first total synthesis of the novel sesquiterpene 8-epi-xanthatin [79]. Palladium-catalyzed carbonylation of 102 followed by desilylation gave lactone 104. The total synthesis of 8-epi-xanthatin was directly achieved by tandem RCM-CM of lactone 104 using 1h in the presence of an excess amount of methyl vinyl ketone in one step (Scheme 29).

Scheme 29. Synthesis of 8-epi-xanthatin.

Scheme 30. Construction of ABC ring of lancifodilactone G.
Lancifodilactone G has eight rings with complicated cyclic connectivity. Paquette synthesized ABC segment 109 of lancifodilactones G using ring-closing enyne metathesis and then cross metathesis as the key steps (Scheme 30) [80]. Ring-closing enyne metathesis of 105 using 1g in CH₂Cl₂ gave cycloheptene derivative 106, which was subjected to cross metathesis with methyl acrylate to give α,β-unsaturated ester 107. From this compound 107, target compound 109 was obtained.

2. Ring-Closing Dienyne Metathesis

Grubbs reported an ingenious method for synthesizing bicyclic compounds from dienynes taking advantage of the metathesis reaction (Scheme 31) [81–82]. When a benzene solution of dienyne 110a was stirred in the presence of 3 mol % of 1b, bicyclic compound 111a was obtained in 95% yield in one operation. In the case of 110b, two bicyclic compounds 111b and 112b were formed. Furthermore, dienyne 110c gave tricyclic compound 111c in a quantitative yield. Probably, ruthenium carbene methylidene complex 1l reacts with an alkene moiety in dienyne 110b to give ruthenium carbene complex 113 and/or 116, which reacts with an alkyne part to give ruthenacyclobutene 114 and/or 117. Ring opening of this complex gives ruthenium carbene complex 115 and/or 118, which reacts with the alkene part intramolecularly to give ruthenacyclobutane. Ring opening of this complex gives bicyclic compounds, 111 and/or 112.

Scheme 31. Dienyne metathesis.
The transformation of dienyne into the bicyclic vinylboronate is shown in Scheme 32. Alkynylboronate 119 cleanly underwent ruthenium-promoted metathesis in 70% yield. The resultant bicyclic dialkenylboronic ester 120 was efficiently oxidized to corresponding enoate 121 by treatment with Me$_3$NO in refluxing THF. In the presence of CsF, reaction of 120 with 3-bromobenzonitriile under the catalysis of PdCl$_2$(dpff) furnished cross-coupling product 122 (Scheme 32) [83].

A versatile route for the synthesis of a phosphorus oxide template was presented (Scheme 33). Dienyne metathesis using 1g on substrate 123 led to the formation of bicyclic phosphorus heterocycles 124 [84].

**Scheme 32.** Reaction of eneyne having alkynyl boronate.

**Scheme 33.** Synthesis of phosphorous mono- and bicycles by RCM.

Base-promoted isomerization of propargyl amide 125 gave alkynyl amide 126, dienyne metathesis of which gave bicyclic compounds 127 and 128 in a ratio of 1:1 (Scheme 34) [85].

**Scheme 34.** Base-promoted isomerization of propargyl amide followed by RCM.
Dienyne metathesis of β-carboline derivative 130 afforded oxidized pentacyclic compound 131 related to alkaloids containing a β-carboline unit. The starting material 129 was readily synthesized from tryptamine derivative (Scheme 35) [86].

**Scheme 35.** Dienyne metathesis of β-carboline derivative.

Syntheses of Natural Products and Related Compounds Using Dienyne Metathesis

Dienyne metathesis is a useful method for the synthesis of fused bicyclic or polycyclic compounds in one step, and many bond fissions and bond formations occur during the dienyne metathesis. Therefore, when dienyne metathesis is used for the total synthesis of natural products, retro synthetic analysis for them is unique, and the reaction process is generally shortened.

A new approach to the synthesis of a linearly fused 6–8-6 tricarbocyclic ring system was realized using dienyne metathesis [87]. This ring system is a carbon framework analogous to the proposed transition state of isomerization of previtamin D₃ to vitamin D₃. The starting dienyne 134, which was prepared by condensation of indenone 132 and alkyne 133 followed by deprotection and then introduction of an allyl group, was reacted with 1c to give target molecule 135 as a diastereomeric mixture at the C-10 position in 48% yield (Scheme 36).

**Scheme 36.** Synthesis of a [6.4.0]carbocyclic system.

A concise route to a key intermediate in the total synthesis of guanacastepene A using dienyne metathesis was reported [88]. The main feature includes the construction of fused seven- and six-membered rings. Metathesis of dienyne 136 was carried out using 1g and a mixture of tricyclic compounds 137 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 138a and 138b. Protection of the hydroxyl group of 138a gave 139a, and then it was led to compound 140, which was already converted into (+)-guanacastepene A (Scheme 37).
Scheme 37. Synthesis of (±)-guanacastephene A.

Krishna reported the synthetic study toward the stereoselective total synthesis of ilexlactone, the structure of which was already assigned as 143a. Bicyclic ring system was constructed from dienyne 142a using 5 mol % of 1g in 74% yield. Deprotection of the MOM group afforded the target molecule 143a. However, the spectral data of this compound was found to be different from those of ilexlactone reported in the literature. Thus, the authors further synthesized ent-143a and 143b from 142b in a similar procedure. However, the spectral data of ent-143a and 143b were found to be different from those of ilexlactone. Thus, the authors concluded that the structure proposed ilexlactone was incorrect (Scheme 38) [89].

Total synthesis of (±)-erythrocarine was achieved by Mori using dienyne metathesis [90]. Synthesis of trisubstituted alkene 146 was achieved with a regio- and stereoselective introduction of carbon dioxide and an alkynyl group onto the terminal alkyne of 145 followed by desilylation. Hetero-Michael reaction of 146 gave isoquinoline derivative 147, which was converted into dienyne 149. Since the tertiary amine of 149 coordinates to the ruthenium catalyst and the catalytic activity is decreased, dienyne metathesis of 149·HCl was carried out using ruthenium catalyst 1c to give tetracyclic compounds as a diastereomeric mixture in a ratio of 1:1 in quantitative yield. Deacetoxylation of α-isomer gave erythrocarine (Scheme 39). Hatakeyama succeeded in total synthesis of erythravine using a similar procedure [91].
Scheme 38. Synthetic study directed toward the total synthesis of ilexlactone.

Scheme 39. Total synthesis of erythrocarine.

Honda et al. succeeded in a diastereoselective total synthesis of (-)-securinine in an optically pure form by employing RCM of the corresponding dienyne 150 as a key step [92]. They synthesized dienyne 150 having terminal alkene and disubstituted alkene parts from (+)-pipecolinic acid, because ruthenium-carbene complex would at first react with the terminal alkene to form a furan ring. Thus, dienyne metathesis of 150 was carried out using 1i [18] to give bicyclic compound 151 in good yield. Oxidation of 151 with CrO3 gave lactone 152, which was treated with NBS and then TFA to produce (-)-securinine (Scheme 40). They also synthesized viroallosecurinine in a similar manner [93].
Scheme 40. Total synthesis of (-)-securinine.

Hatakeyama succeeded in the total synthesis of erythroidine [94]. Construction of C and D rings was begun from amino acid 153, which was led to dienyne 158. Dienyne metathesis was carried out using 1c to give erythroidine in 42% yield along with compound 159 in 4% yield. In this case, 1g turned out to be less effective and gave erythroidine in less than 30% yield (Scheme 41).

Scheme 41. Total synthesis of (+)--erythroidine.

The successful enantioselective syntheses of (-)-acylfulvene and (-)-irofulven was achieved by use of ring-closing metathesis strategy [95]. Synthesis of these compounds began through coupling of readily
available aldehyde (+)-160 and enyne 161. Treatment of 162a with 1g catalyst (15 mol %) in toluene at 90 °C afforded desired 163a in 90% yield, which was readily converted into the key triol 164a (3S/3R = 6:1) after desilylation. When triyne 162b was treated in a similar manner, desired 164b was obtained in 52% yield along with minor by-product 165 in 20% yield. The key triol 164a was converted into triene 166. Diene metathesis of 166 using 1g (15 mol %) proceeded smoothly to give bicyclic compound 167, crude product of which was directly converted into (-)-acylfulvene. According to the known method, (-)-acylfulvene was converted into (-)-irofulven (Scheme 42).

**Scheme 42.** Synthesis of (-)-acylfulvene and (-)-irofulven.

For the synthesis of (-)-cochleamycin, conjugate diene 174 was synthesized from 172 by diyne metathesis as a key step. The reaction of alcohol 168 with trialkyne 169 gave alcohol 170, which was further reacted with alcohol 171 to give diyne 172. A tandem ring-closing metathesis of diyne substrate 172 proceeded to provide a bicyclic siloxane 173. Removal of the silicon tether of 173 afforded
an \((E,Z)\)-1,3-dienediol \(174\), which was converted into the key compound \(177\) for the synthesis of (-)-cochleamycin (Scheme 43) [96].

**Scheme 43.** Formal total synthesis of (-)-cochleamycin A using dienyne metathesis.

3. **Cross Enyne Metathesis**

A novel synthetic procedure of 1,3-diene from alkyne and ethylene using cross enyne metathesis was developed in 1997 by Mori [97–98]. When a \(\text{CH}_2\text{Cl}_2\) solution of alkyne \(178a\) was stirred under an atmosphere of ethylene at room temperature in the presence of \(1c\), 1,3-diene \(179a\) was obtained in 62% yield. It is interesting that, formally, the double bond of ethylene is cleaved and each methylene part of ethylene is introduced onto the alkyne carbon to produce 1,3-diene \(179\) (Scheme 44). The possible reaction course was shown in Scheme 45. Reaction of ruthenium carbene methyldiene complex \(1l\), generated from \(1c\) and ethylene, with alkyne \(178\) gives ruthenacyclobutene \(180\), ring-opening of which gives ruthenium carbene \(181\). It reacts with ethylene to afford ruthenacyclobutane \(182\), ring-opening of which gives 1,3-diene \(179\), and \(1l\) is reproduced. If \(1l\) reacts with ethylene, this is non-productive process.
and 1l would be reproduced. However, this method has a problem, that is: propargyl ester 178a or amide 178b gave good results, while homopropargyl amide 178c led to 1,3-diene 179c in only 11% yield (Scheme 44). Presumably, a heteroatom at the propargylic position is important, and the ruthenium catalyst would be coordinated by the heteroatom at first and then the reaction proceeds.

When the second-generation ruthenium-carbene complex 1g was used for this reaction, an alkyne 178 lacking heteroatoms at the propargylic positions, gave 1,3-dienes 179 in good yield (Table 1) [99–103]. Furthermore, the reaction was more rapid and the functional groups on the alkyne were tolerated.

Cross metathesis between terminal alkynes 178i and terminal alkenes was subsequently developed by Blechert, and 1,3-disubstituted diene 183i was obtained in high yield [104]. Phenylalanine derivative 184 could be synthesized by use of this procedure followed by Diels-Alder reaction (Scheme 46) [104–105].

**Scheme 44.** Synthesis of 1,3-diene using cross metathesis.

**Scheme 45.** Possible reaction course for formation of 1,3-diene.
Table 1. Synthesis of Various 1,3-dienes from alkyne and alkene using 1g,a

| entry | alkyne 178         | 1,3-diene 179       | time (h) | yield (%) |
|-------|--------------------|---------------------|----------|-----------|
| 1     | MeO 178d           | MeO 179d            | 0.5      | 88        |
| 2     | 178e               | 179e                | 0.5      | 71        |
| 3     | CH3 178f           | 179f                | 0.5      | 85        |
| 4     | MeO TMS 178g       | MeO TMS 179g        | 16       | 87        |
| 5     | MeO COOMe 178h     | MeO COOMe 179h      | 16       | 43        |

a All reactions were carried out using 5 mol % of 1 g under 1 atm. pressure of ethylene gas in toluene at 80 °C. b The starting material was recovered in 10% (entry 4) and 34% (entry 5) yields, respectively.

Scheme 46. Synthesis of alanine derivative.

A short and efficient synthesis of highly substituted tetrahydropyridines was achieved from a monosubstituted alkyne, a terminal alkene, and an imine by a combination of cross enyne metathesis and aza-Diels-Alder reaction under high pressure. Cross metathesis of terminal alkyne and alkene afforded diene 185, which was reacted with imine to give pipecolinic acid derivative 186 in high yield (Scheme 47) [106].
Scheme 47. One-step synthesis of pipecolinic acid.

\[
\begin{align*}
\text{AcO} + \text{CH}_2\text{Cl}_2, 24 \text{ h} \\
\text{1c} \\
\end{align*}
\]

The reaction was further extended to intramolecular Diels-Alder reaction, and cis-hexahydro-1H-indene 189 was synthesized from diene 187 and terminal alkyne in one operation [107]. The intermediate would be 190, which was spontaneously converted into 188. Deprotection of the silyl group followed by PCC oxidation gave indanone 189 (Scheme 48).

Scheme 48. Synthesis of cis-fused carbo-bicycles.

One pot synthesis of nitrogen and oxygen heterocycles was reported using intermolecular cross enyne metathesis in the presence of Bronsted acid (Scheme 49) [108].

Scheme 49. One pot synthesis of nitrogen heterocycles using cross metathesis.

Diver reported cross metathesis of terminal alkyne and cyclopentene using 1g [109]. Ruthenium-carbene complex 11 reacts with the terminal alkyne to produce ruthenium-carbene complex
Materials 2010, 3

194, which reacts with cyclopentene to produce ruthenium-carbene complex 195. It reacts with the alkene part to afford a cycloheptadiene derivative 193 (Scheme 50).

**Scheme 50.** Cross metathesis of cyclopentene and alkyne.

```
-OBz  + 5 mol % 1g
  CH2Cl2, reflux  4 equiv. high dilution
  CH2OBz

[194] 194

[195] 195

[193] 193

Synthesis of Natural Products and Related Compounds Using Cross Metathesis

Synthesis of natural products using cross metathesis is interesting because 1,3-diene moiety is constructed onto the alkyne carbons at the later step. Anolignans were synthesized using cross metathesis of enyne as a key step. 1,3-Diene 197 could be synthesized from alkyne 196 by treatment with 1g under ethylene gas. Palladium-catalyzed deacetoxylation followed by deprotection gave anolignan A. Anolignan B could be synthesized in a similar manner. It was interesting that two methylene parts of the anolignan skeleton could be introduced at a later stage of the total synthesis using cross metathesis (Scheme 51) [110].

**Scheme 51.** Synthesis of anolignan A using cross enyne metathesis.

Novel vitamin D receptor antagonists, 24,24-ethanovitamine D3–26,23-lactones 198a and 198b and their analogs were synthesized (Scheme 52) [111]. The CD-ring precursors 203a and 203b were efficiently synthesized via ruthenium-catalyzed intermolecular enyne metathesis of 200 with ethylene as a key step. Cyclopropanation of resultant enyne metathesis product 201 followed by treatment with DIBAL-H and then deprotection gave compounds 203a and 203b. Oxidation of 203a and 203b followed
by palladium-catalyzed coupling reaction with 204 and then deprotection afforded 198a and 198b, respectively.

**Scheme 52.** Synthesis of 24,25-ethanovitamin D3 lactones.

A versatile strategy for the synthesis of C-aryl glycoside was successfully developed. An intermolecular enyne metathesis of C-alkynyl glycoside 205 with ethylene gave diene 206, which
was followed by Diels Alder reaction and then aromatization to provide C-aryl glycoside 207 (Scheme 53) [112].

Lee succeeded in the total synthesis of (-)-amphidinolide E, whose side chain was constructed using cross enyne metathesis [113–114]. Alkyne 208 was first reacted with ethylene in the presence of 1g to give 209, which was further engaged in situ in a chemoselective cross metathesis with 2-methyl-1,4-pentadiene to give triene 210 in 65% yield along with diene 209 in 19% yield. Isolated diene 209 was further recycled and reacted with 2-methyl-1,4-pentadiene in the presence of 1g to afford triene 210, which was further elaborated into 211. Condensation of 211 and 212 afforded compound 213. From this compound 213, total synthesis of amphidinolide E was achieved (Scheme 54).

Scheme 54. Synthesis of amphidinolide E.
Recently, same group succeeded in the total synthesis of amphidinolide K using intramolecular cross enyne metathesis in the key step [115].

Fürstner succeeded in the total synthesis of amphidinolide V using ring-closing alkyne metathesis for the construction of the macrocycle (Scheme 55). Dialkyne 214 was treated with molybdenum complex 215 to give macrocycle 216 in 84% yield. Then an intermolecular enyne metathesis of the resulting cycloalkyne 216 with ethene was used to set the vicinal exo-methylene branches. From this compound 217, amphidinolide V was synthesized. As the result, the absolute configuration of amphidinolide V was determined to be as $8R, 9S, 10S, 13R$ [116–117].

Scheme 55. Synthesis of amphidinolide V.

4. Ring-Opening Enyne Metathesis

Tandem metathesis of cycloalkene-ynes is a unique reaction because different cyclic compound is formed from the starting cycloalkene via many steps by a one operation. These reactions are contained ring opening metathesis (ROM), ring closing metathesis (RCM) and/or cross metatheses (CM). Mori reported the ROM of cycloalkene-yne [118]. When cycloheptene-yne 220a, the substituent of which was placed at the 3-position of cycloalkene, was reacted with the first generation ruthenium carbene complex 1c in CH$_2$Cl$_2$ under ethylene gas at room temperature for 24 h, pyrrolidine derivative 221a was obtained in 56% yield (Table 2, entry 1). Various cycloalkene-ynes 220 gave pyrrolidine derivatives 221 in high yields by a one-pot operation. Formally, in this reaction, the double bonds of ethylene and cycloalkene
were cleaved and each methylene part of ethylene was introduced onto the alkyne and cycloalkene carbons, respectively, and a carbon-carbon double bond was formed between the alkyne and cycloalkene carbons to form a pyrrolidine ring (Figure 3). In each case, pyrrolidine ring is formed and the length of the substituent corresponds to the initial ring size minus 1. The possible reaction course for formation of 221 from 220 was shown in Scheme 56.

Table 2. ROM-RCM of cycoalkene-yne.

| entry | R     | ring size | n  | time (h) | yield (%) |
|-------|-------|-----------|----|----------|-----------|
| 1     | 220a  | Me        | 7  | 2        | 221a 56   |
| 2     | 220b  | H         | 6  | 1        | 221b 78   |
| 3     | 220c  | H         | 7  | 2        | 221c 70   |
| 4     | 220d  | H         | 8  | 3        | 221d 75   |

\[a\] Yields were calculated from 1H NMR. \[b\] 220a was recovered in 36% yield.

Scheme 56. Possible reaction course for ROM of 220.

Blechert reported the same type of ROM-CM. Reaction of cyclopentene derivative 222a having a propargyloxy group at the 3-position with 1c in the presence of diethyl allyl malonate afforded compound 223a in 75% yield \[119–120\]. In this reaction, the cleaved alkylidene part of diethyl allyl malonate is introduced onto the cyclopentene carbon, and the methylene part is introduced onto the alkyne carbon to form furan derivative 223a (Figure 4). Furthermore, the five-membered ring of estrone 222b or 222c is cleaved using 1c in the presence of an alkene to give 223b or 223c, and an alkene part is introduced onto the C-ring (Scheme 57).
Scheme 57. ROM-CM enyne in the presence of alkene.

\[
\begin{align*}
\text{Scheme 58. Ring-opening metathesis of cycloalkene-yne.}
\end{align*}
\]

Ring-opening metathesis of 1-substituted cycloalkene-yne 224 with 1g afforded bicyclic compound 225 [121–122]. Reaction of an alkyne part of 224 with ruthenium carbene complex 1l gives
ruthenacyclobutene 226. Ring opening of this gives ruthenium carbene complex 227, which reacts with cycloalkene to afford highly strained ruthenacyclobutane 228. Ring opening of this affords ruthenium carbene complex 229 and then it reacts with alkene part to afford ruthenacyclobutane 230, ring-opening of which gives bicyclic compound 225. When a CH₂Cl₂ solution of cyclopentene derivatives 224a was stirred in the presence of 1g under ethylene gas for 26 h, bicyclic compound 225a was obtained in quantitative yield. In a similar manner, cyclopentene-yne 224b, the side chain of which was elongated, was reacted with 1g to give bicyclic compound 225b in 76% yield. These results indicated that the initial ring (n) was enlarged to (n + 2) ring and the size of the other ring corresponds to the carbon chain length from an alkyne carbon to an alkene carbon (Scheme 58).

To synthesize an isoquinoline derivative using this method, the initial cycloalkene would be cyclobutene and the chain length between alkyne and alkene carbons containing nitrogen would be four. Treatment of cyclobutene-yne 231a with 1g afforded isoquinoline derivative 232a in 60% yield in one step. Furthermore, glycine derivative 231b having a cyclobutene ring in a tether afforded cyclic amino acid 232b in 76% yield. This procedure was further extended to the synthesis of biaryl compound 232c from cyclobutene-yne 231c. It was interesting that in this case, an aryl group on the alkyne of 231c is placed at the 5-position of isoquinoline 232c (Scheme 59) [123].

**Scheme 59.** Synthesis of isoquinoline derivatives using ROM of cyclobutene-yne.

Plumet *et al.* described domino metathesis of propargyl (2-endo-7-oxanorborn-5-enyl) ethers 233a–c with allyl acetate in the presence of Grubbs’ ruthenium catalyst 1c (Scheme 60) [124–125]. The reaction
Materials 2010, 3

proceeded stereoselectively to produce substituted cis-fused bicyclic ethers 234a-c. In a similar manner, indolizinidone derivative 234d was obtained from azabicyclo[2.2.1]heptenone 233d in high yield. Later, the substituent effect of this reaction was further investigated and pyrrolizidinone derivative 234e was obtained in 40% yield along with indolizinidone derivative 234e’ in 30% yield when the toluene solution of 233e (R=Me) and 1g was warmed at 80 °C for 30 min under ethylene gas [126].

North and Banti observed double ring-opening metathesis of dialkynyl cycloalkenes 233f affording tricyclic compound 234f in high yield (Scheme 61) [127–128].

Scheme 60. ROM-RCM followed by CM of cycloalkene-yne.

Scheme 61. ROM-RCM of norbornene derivative.

5. Skeletal Reorganization Using Transition Metals

Trost discovered palladium-catalyzed enyne metathesis during the course of his study on palladium-catalyzed enyne cyclization [129–135]. Treatment of Z-235 with palladacyclopentadiene (TCPT, 236a) in the presence dimethyl acetylene dicarboxylate (DMAD) in dichloroethane at 60 °C led to metathesis product E-238 in 68 % yield, which consisted of only E-isomer E-238. Similarly, the E-substrate E-235 gave predominantly Z-238 (Scheme 62) [129].

This method provides a very simple route to bridged bicycles possessing bridgehead olefins (Scheme 63). When enyne 239a was treated with TCPC^{TFE} 236b, bicyclo[6.2.1]undecadiene 240a was formed in 53% yield. When a mixture of 4% TCPC^{HFB} 236c, 4% tri-o-tolylphosphate, bis(heptafluorobutyl)-acetylenedicarboxylate and enyne 239b in dichloroethane was heated at 80 °C, tricyclic compound 240b was obtained in 85% yield. It means that the reaction proceeds via the formation of the four-membered-ring [132].
The simple platinum complex (Ph₃P)₂Pt(OAc)₂ effected metathesis of enyne. Enyne 241a gave cyclized compound 242a, and the yield was comparable to that of TCPC but significantly faster. Murai and Chatani [136] also reported the PtCl₂-catalyzed reaction of cycloalkene-yne 241b. In this case, exclusively bicyclic compound 242b was obtained in 97% yield (Scheme 64).

In 1994, Murai and Chatani reported skeletal reorganization of 1,6-enyne using [RuCl₂(CO)₃]₂ as a catalyst (Scheme 65) [137–138]. When the reaction of E-243a (E/Z=80/20) was carried out in the presence of [RuCl₂(CO)₃]₂ under carbon monoxide, E-isomer 244a was produced predominantly. It is interesting that from Z-243a (E/Z=11/89), E-244a was formed. An E/Z mixture of 1,7-enyne 243b afforded only E-isomer of 244b in 86% yield.
Scheme 64. Platinum-catalyzed skeletal reorganization.

\[
\begin{align*}
\text{MeOOC} & \quad \text{O} \quad \text{Ph} \\
\text{241a} & \quad \text{10\% (Ph}_3\text{P)}_2\text{Pt(OAc)}_2 \\
& \quad \text{1.3 eq. CF}_3\text{COOH} \\
& \quad \text{2.1 eq. DMAD} \\
& \quad \text{PhH, reflux 4 h} \\
\text{242a} & \quad \text{79\%}
\end{align*}
\]

Scheme 65. Ruthenium-catalyzed skeletal reorganization.

\[
\begin{align*}
\text{243a} & \quad \text{[RuCl}_2\text{(CO)}_3\text{]}_2 \\
& \quad \text{toluene, CO} \\
& \quad \text{80 °C, 1 h} \\
\text{244a} & \quad \text{95\%}
\end{align*}
\]

from \(E\text{-243a} \ (E/Z=80/20)\) \(95\%\) \(E\text{-243a} \ (E/Z=11/89)\) \(81\%\)

\[
\begin{align*}
\text{243b} & \quad \text{[RuCl}_2\text{(CO)}_3\text{]}_2 \\
& \quad \text{toluene, CO} \\
& \quad \text{80 °C, 4 h} \\
\text{244b} & \quad \text{86\%}
\end{align*}
\]

Scheme 66. Trapping of carbenoid intermediate.

\[
\begin{align*}
\text{245} & \quad \text{catalyst} \\
& \quad \text{toluene, 80 °C} \\
\text{E=CO}_2\text{Et} & \quad \text{246} \\
\text{247} & \quad \text{MX}_2
\end{align*}
\]

They speculated that complex 247 having two carbenoid carbons would be generated on the alkyne carbons during the reaction [138]. To trap this intermediate, the reaction of 6,11-dien-1-yne 245, which has an olefin moiety in a tether, was carried out in the presence of [RuCl\(_2\)(CO)\(_3\)]\(_2\) in toluene at 80 °C for
4 h to give tetracyclic compound 246 containing two cyclopropane rings in 84% yield. It is interesting to note that other transition-metal complexes, such as PtCl₂, [Rh(OOCCF₃)₂]₂, [IrCl(CO)₃]₆, and ReCl(CO)₅ also showed catalytic activity for this very complex transformation.

Rh(II)-catalyzed skeletal reorganization of 1,6- and 1,7-enynes through electrophilic activation of alkynes was also reported [139–140]. Surprisingly, in some cases, simple Lewis or Brønsted acids as the catalysts could replace PtCl₂ (Scheme 67). Treatment of 248 with BF₃·Et₂O or HBF₄ gave skeletal reorganization product 249 in good yield [141].

Scheme 67. Lewis and Bronsted acids catalyzed skeletal reorganization.

Murai and Chatani group reported skeletal reorganization of enynes to 1-vinylcycloalkene by GaCl₃ [142]. The reaction of 250a proceeded in methylcyclohexene at 0 °C and was completed within 1 h to give 251a. It is interesting that highly strained cyclobutene derivative 251b was obtained from 1,7-enyne 251a in high yield (Scheme 68).

Scheme 68. Skeletal reorganization by GaCl₃.

Presumably, each skeletal reorganization reaction starts by coordination of the metal to the alkyne part, and then the alkene part would attack the cation center of the alkyne coordinated by metals. However, the reaction mechanism is still not clear, and it is thought that each reaction mechanism differs depending on the metal used [143].
Skeletal reorganization is a useful tool for the synthesis of complicated natural products. Fürstner achieved formal total syntheses of the antibiotics metacycloprodigiosin and streptorubin B by a platinum-catalyzed skeletal reorganization reaction (Scheme 69) [144]. The key step leading to the meta-bridged pyrrole core structures consisted of a metathesis reaction of electron-deficient enynes 252a and 252b catalyzed by PtCl₂. The skeletal reorganization products 253a and 253b were converted into the respective target molecules.

Scheme 69. Formal total synthesis of streptorubin B and metacycloprodigiosin.

Trost succeeded in formal total synthesis of roseophilin [145]. Macrocyclic compound 260 was synthesized from enyne 259 by platinum-catalyzed skeletal reorganization. Compound 260 was converted into 261, which was led to pyrrole derivative 258 and it was already converted into roseophilin (Scheme 70).
Scheme 70. Formal total synthesis of roseophilin.

6. Metallotropic Rearrangement

The bond reorganization processes, defined as metallotropic shift, of various alkynyl carbene complexes with Rh [146], Mn [147], Re [148], Cr [149], Mo [149], and W [149] metals have been already reported. The rearrangement involving Rh, Cr, Mo, and W is a [1,3]-shift, while that with Mn and Re is formally defined as a [1,1.5]-shift. However, the metallotropic shift of ruthenium alkynyl carbene complexes has not been observed until recently (Scheme 71). The metallotropic [1,3]-shift of a transient ruthenium carbene complex is involved in the enyne ring-closing metathesis (RCM) of diyne containing substrates. On the basis of this concept, one-step construction of enediynes and oligoenynes was realized by the uniquely controlled repetitive metallotropic [1,3]-shift of ruthenium carbene species. Reaction of 262a with 1g gave ene-diyne 267a in high yield by one operation. Presumably, reaction of 262a with 1g gives ruthenium carbene complex 263a, which is converted into ruthenium carbene complex 264a via [1,3]-shift. [2+2] Cycloaddition followed by ring opening gives 265a, which is converted into 266a via [1,3]-shift. From this complex 266a, ene-diyne 267a is formed. In a similar manner, 262b and 262c gave oligoenynes 267b and 267c, respectively, in one operation (Scheme 72) [150].

Scheme 71. Metalotropic rearrangement.
Scheme 72. Synthesis of oligoenynes by metathesis of metallocropy.

Synthesis of Natural Products Using Metallotropic Rearrangement

The metallocropic [1,3] shift of a transient ruthenium carbene complex is involved in the enyne ring-closing metathesis of diyne containing substrates. Ring-closing metathesis followed by metallocropic [1,3]-shift and cross metathesis allowed for the development of novel strategy for the total synthesis of conjugated 1,3-diyne-containing natural product (3R,9R,10R)-panaxytriol [151]. When compound 268 was treated with 1g in the presence of 2.0 equiv. of alkene 269, the expected product 270 was obtained in 61% yield as a mixture of Z/E-isomers (5:1) together with 268 (10%). Metathesis of diene in 268 gave ruthenium carbene complex 271, metallocropic [1,3] shift of which gave ruthenium carbene complex 272. Cross metathesis of 272 and alkene 269 afforded compound 270. From this compound 270, (3R,9R,10R)-panaxytriol could be synthesized (Scheme 73).
Scheme 73. Total synthesis of (3R,9R,10R)-panaxytriol.

Total synthesis of (+)-asperpentyn and (-)-tricholomenyn A have been accomplished by implementing this metathesis-based tandem reaction sequence as the key step [152]. Compound 276, which was prepared from 275 and diyne, was treated with 1g under ethylene atmosphere gave 279a and 279b via 277 and 278. From 279a, asperpentyn was synthesized. When compound 280 was reacted with ethylene in the presence of 1g, the reaction did not proceed. In a similar method, compound 281 was treated with 1g under ethylene to give 282, which was led to (+)-tricholomenyn.
Scheme 74. Synthesis of (+)-asperpentyn and (+)-tricholomenyn A using tandem enyne metathesis.

Perspective

Since the discovery of stable and isolable catalysts for metathesis by Schrock and Grubbs, a wide range of olefin metatheses have been reported, and olefin metathesis now plays an important role in natural product syntheses. Enyne metathesis, dienyne metathesis, cross enyne metathesis, and ROM of cycloalkene-yne have also been developed. Furthermore, skeletal reorganization using the transition metals or metallotropic rearrangement is a unique reaction. Novel procedures for the synthesis of the natural products and related compound, various complex molecules and macrocyclic compounds would be further developed using these various enyne metatheses. The retrosynthetic analysis of the natural products using these enyne metatheses would be completely different from that of the previous synthesis and the steps for the synthesis of these compounds would be shortened.

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