DOI: 10.1002/adsc.200600484

Synthesis of Natural Products and Related Compounds using Enyne Metathesis

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Received: September 21, 2006

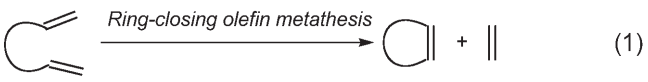
Abstract: Since the molybdenum and ruthenium carbene complexes **1a** and **1b** were discovered by Schrock and Grubbs in 1990 and 1992, synthetic organic chemistry has progressed with the use of these complexes as the catalyst for olefin metathesis. It was found that the ruthenium carbene complex was 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, dienyne 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
2 Syntheses of Natural Products and Related Compounds using Ring-Closing Enyne Metathesis (RCM)
3 Synthesis of Natural Products and Related Compounds using Dienyne Metathesis
4 Synthesis of Natural Products and Related Compounds using Cross-Metathesis
5 Synthesis of Natural Products and Related Compounds using Ring-Opening Metathesis (ROM) and Ring-Closing Metathesis–Cross Metathesis (RCM-CM)
6 Perspectives

Keywords: enyne metathesis; Grubbs' catalyst; natural products; ruthenium carbene complexes

1 Introduction

Metathesis is one of the most useful reactions in recent synthetic organic chemistry.[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)].



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Since the discovery of molybdenum and ruthenium carbene complexes by Schrock and Grubbs in 1990[2] and 1992,[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.[4a] They then prepared the ruthenium carbene complex **1b** for olefin metathesis,[3a] and synthesized carbo- and heterocyclic compounds using this process.[4] In 1995, Grubbs found that ruthenium carbene complex **1c** has the same reactivity as **1b**,[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,[5] Nolan[6] and Grubbs[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**,[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.[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,[10] who used a Fischer tungsten carbene complex. Our group has reported a chromium-catalyzed

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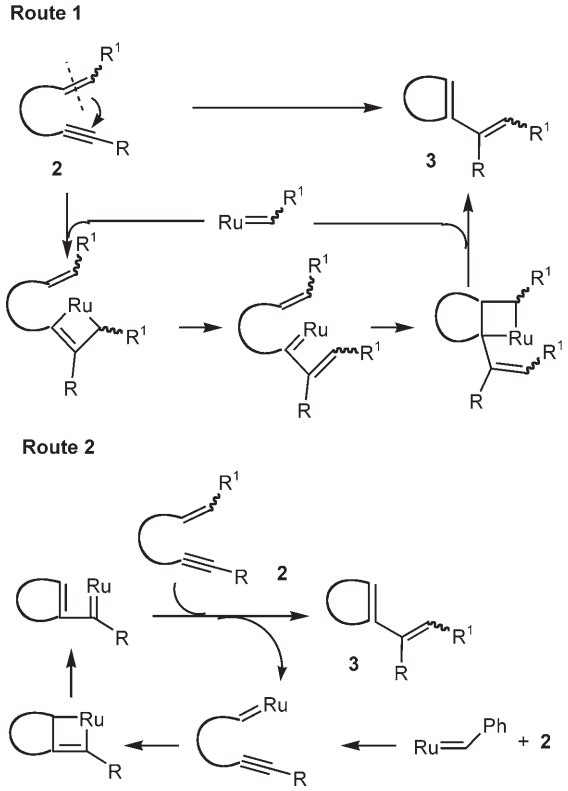


Scheme 1. Ring-closing enyne metathesis.

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).

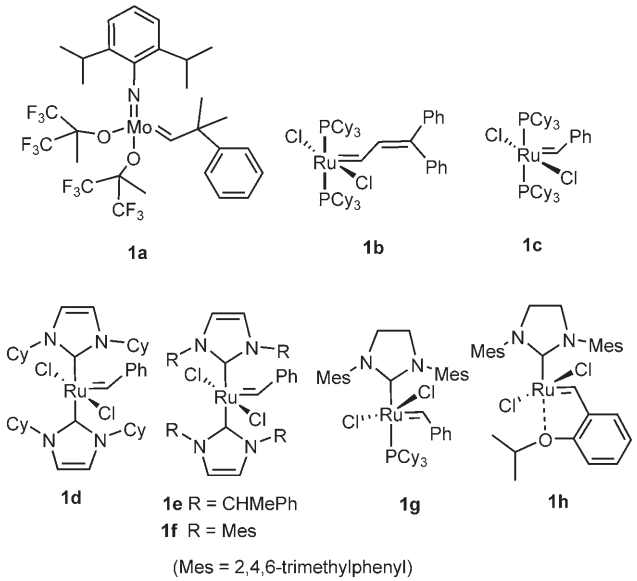
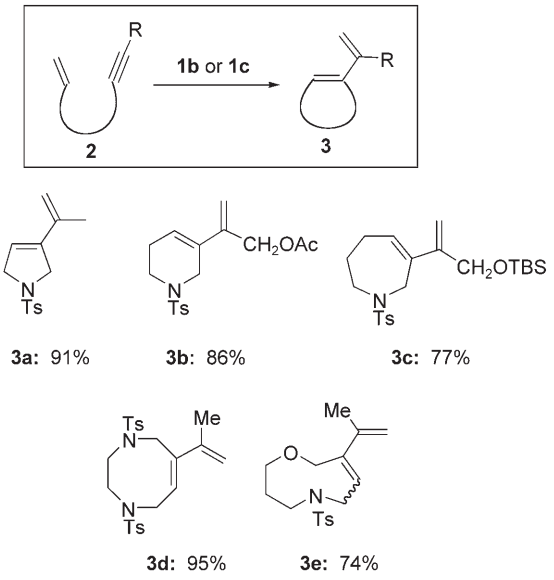


Figure 1. Mo and Ru carbene catalysts.

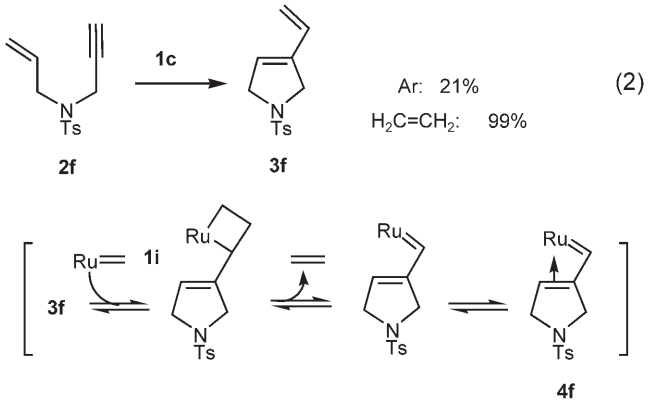
Using ruthenium carbene complex **1b** or **1c**, five- to nine-membered heterocycles could be synthesized from the corresponding enynes (Scheme 2).[13]

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]

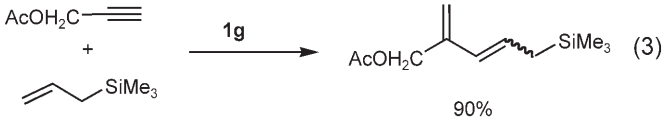


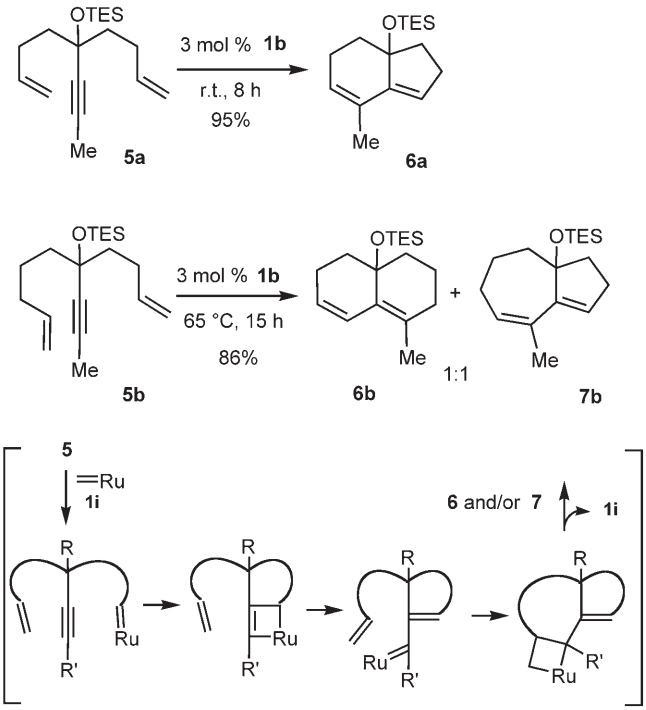
Scheme 2. Synthesis of heterocycles using enyne metathesis.



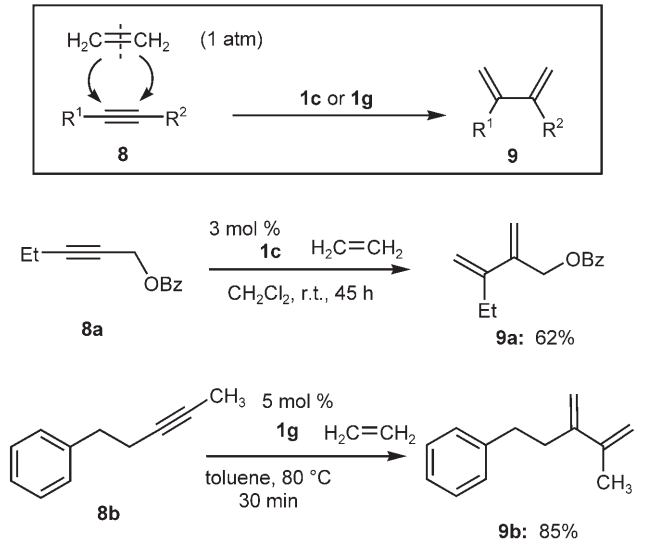
On the other hand, the cross-metathesis of an alkyne and ethylene was developed in 1997.[16] When a CH_2Cl_2 solution of alkyne **8** was stirred under an atmosphere of ethylene at room temperature in the presence of **1c**, 1,3-diene **9** was obtained. It is interesting that, formally, the double bond 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-disbstituted diene was formed [Eq. (3)].[18]





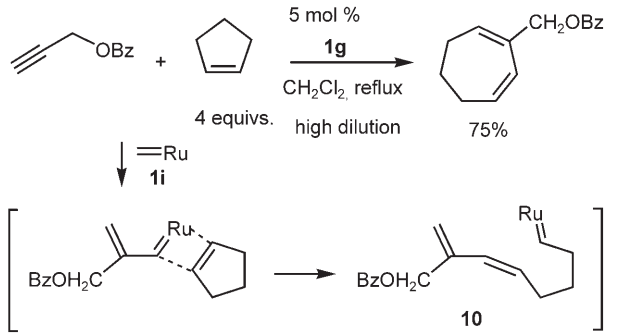
Scheme 3. Dienyne metathesis using ruthenium catalysts.



Scheme 4. Enyne cross-metathesis of an alkyne and ethylene.

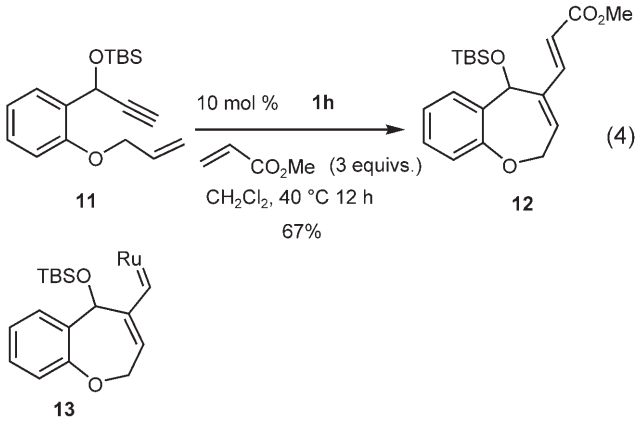
Diver reported the cross-metathesis of a terminal alkyne and cyclopentene using **1g**.[19] at first, the ruthenium carbene complex **1i** reacts with the terminal alkyne to produce a ruthenium carbene complex. The formed carbene complex reacts with cycopentene to produce the ruthenium carbene complex **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



Scheme 5. Cross-metathesis of an Alkyne and cyclopentene.

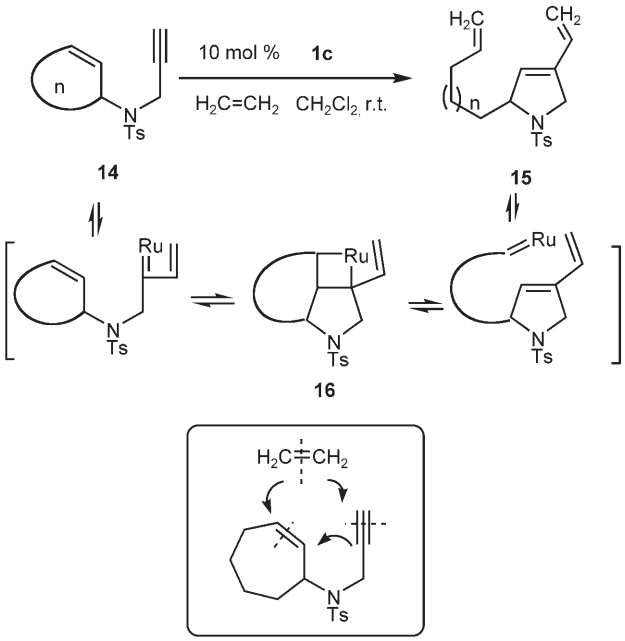
complex. Royer reported on RCM-CM: enyne **11** was reacted with **1h**[20] (see Figure 1) in the presence of 3 equivalents of methyl acrylate to give **12** in 67% yield, while the catalysts **1c** and **1g** were not effective for this reaction [Eq. (4)].[21] In this reaction, the generated ruthenium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



(4)

The ROM-CM of a cycloalkenyne 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 ruthenacyclobutane **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



Scheme 6. ROM of a cycloalkene-yne.

of diethyl allylmalonate afforded compound **18** in 75% yield.[23] In this reaction, the cleaved alkylidene part of diethyl allylmalonate is introduced onto the cyclopentene 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 $[RuCl_2(CO)_3]_2$ as a catalyst.[26] Then they found that $GaCl_3$ was effective for skeletal reorganization.[27]

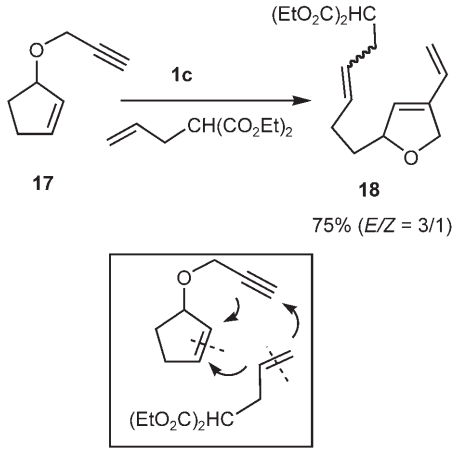
Using these various enyne metatheses, complicated natural products have been synthesized via a novel route and the synthetic routes are completely different from that described in the literature.[28] In this report, the syntheses of natural products and related compounds using enyne metathesis reactions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

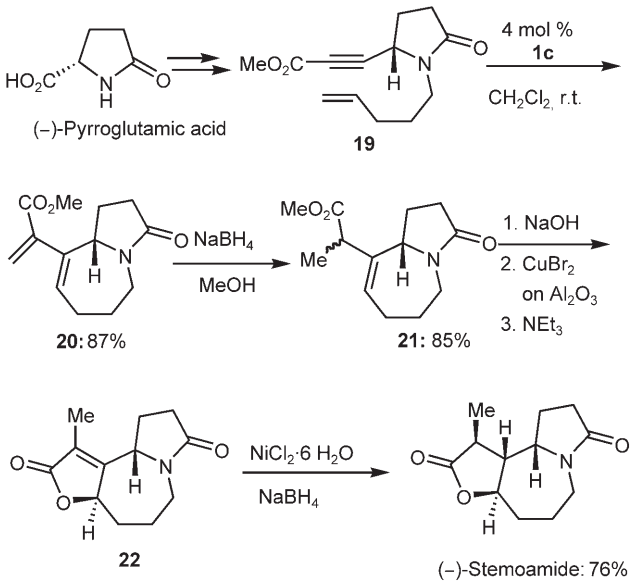
Table 1. ROM of cycloalkenynes.

Entry	Substrate	Ring size	n	Product	Yield [%]
1	**14a**	6	1	**15a**	78
2	**14b**	7	2	**15b**	70
3	**14c**	8	3	**15c**	75



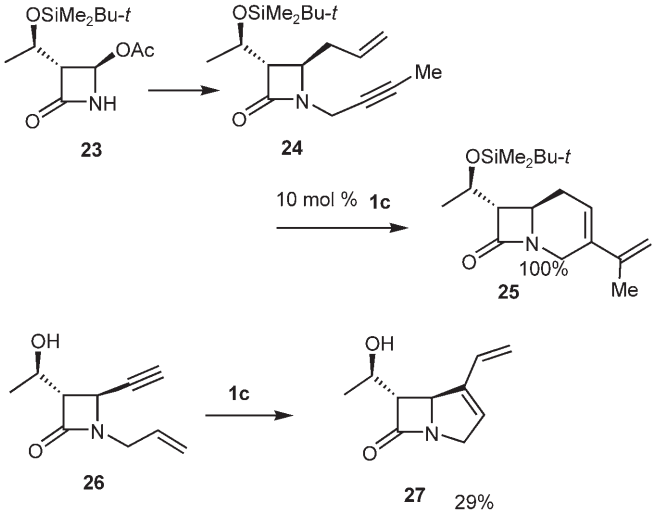
Scheme 7. ROM-CM of an enyne in the presence of an alkene.

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).

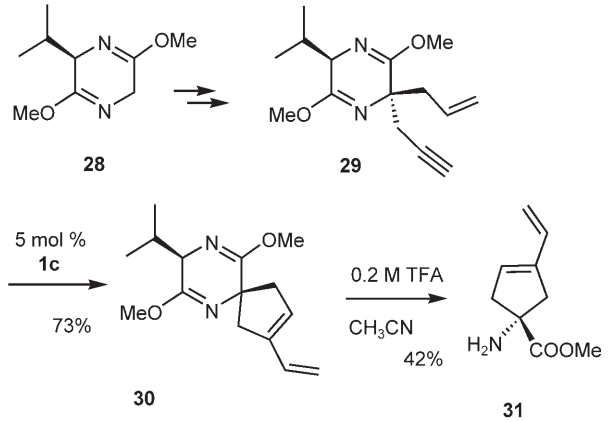


Scheme 8. Total synthesis of (−)-stemoamide.

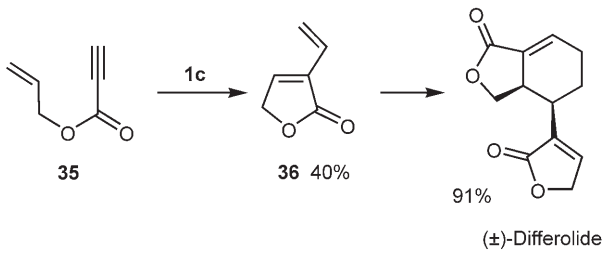
Carbacephem and carbapenem (**25** and **27**) were synthesized from enynes **24** and **26**, which were prepared from 4-acetoxyazetidinone **23**. The yield of the latter compound is low compared with that of **25** because of the highly strained fused 4,5-membered ring system (Scheme 9).[30]



Scheme 9. Construction of the carbacephem and carbapenem skeletons.



Scheme 10. Synthesis of a chiral amino acid.

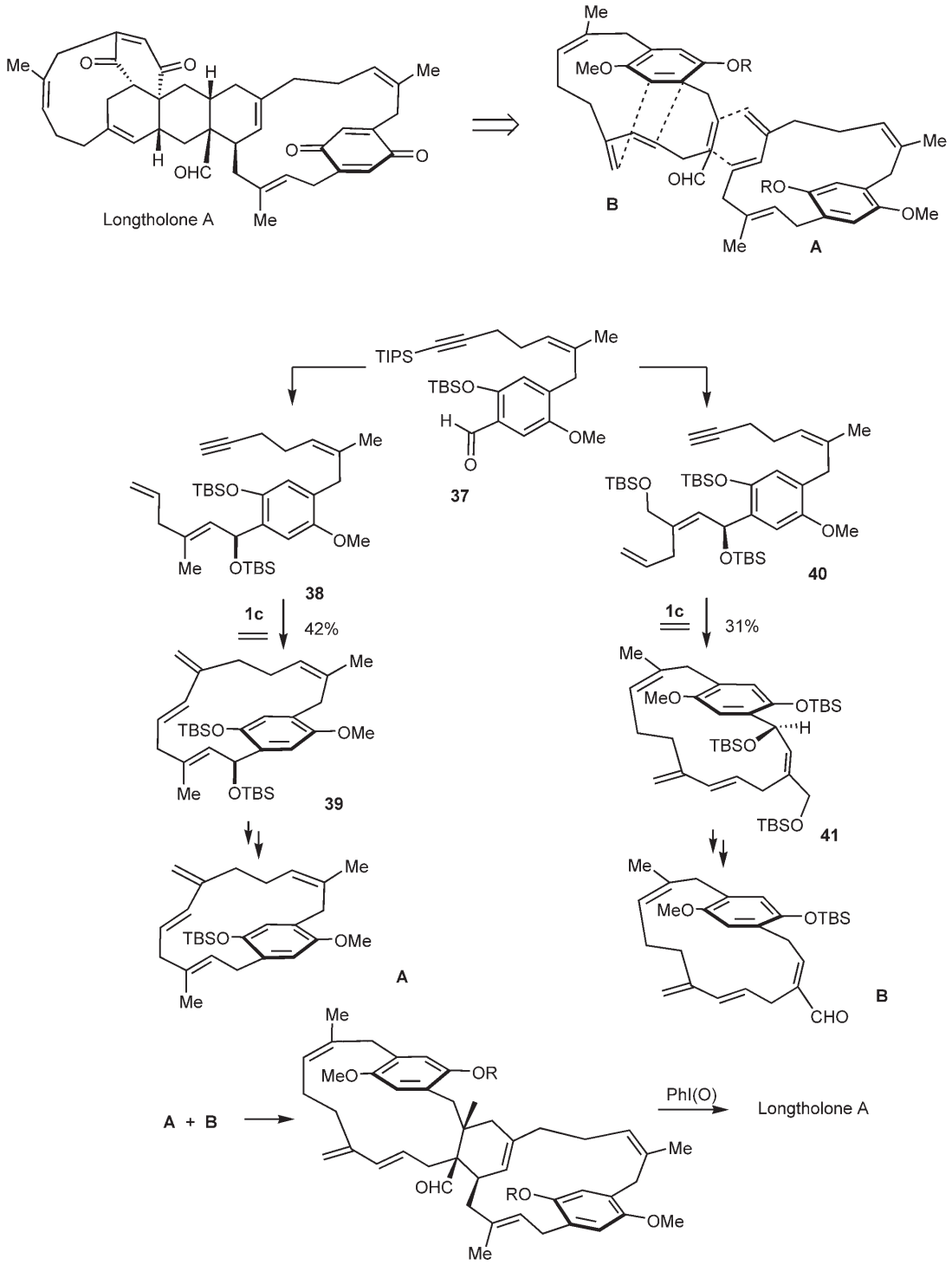


Scheme 11. Synthesis of (±)-differolide.

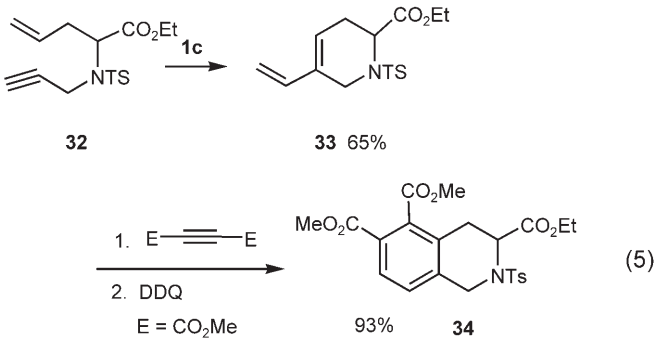
Undeheim described the stereoselective synthesis of the unusual chiral amino acid **31**.[31] The starting enyne **29** was synthesized in stereochemically pure form by stepwise alkylations of **28**. Reaction of enyne **29** with **1c** gave the spiro-compound **30**, which was treated with TFA to give 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)].[32]

(±)-Differolide could be easily synthesized by enyne metathesis.[33] Enyne **35** was reacted with **1c** to



Scheme 12. Total synthesis of (−)-longthorone A.



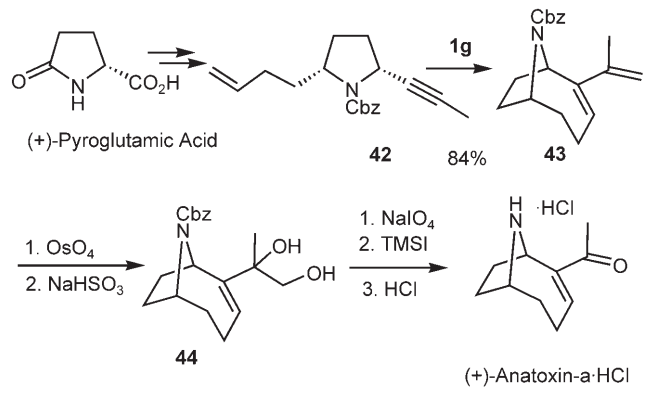
give lactone **36**, which spontaneously dimerized to afford (±)-differolide (Scheme 11).

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**. Longtholone A was synthesized using intermolecular and transannular Diels–Alder reactions followed by oxidation (Scheme 12).

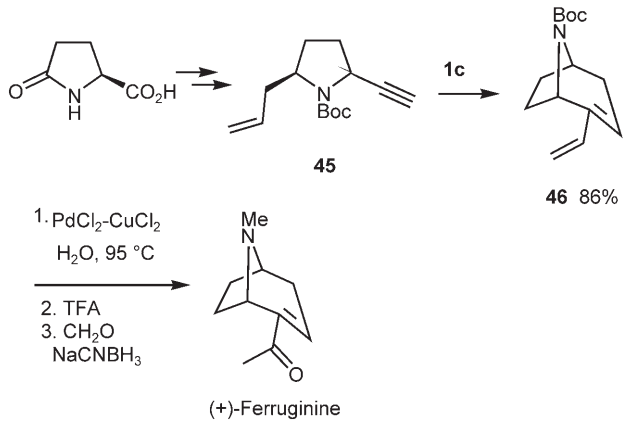
The total synthesis of (+)-anatoxin-a was achieved by Martin[35a,b] and our group[35c,d] by the same strategy. The key step is the construction of an azabicyclo-[4.2.1]nonene ring system. For that purpose, the pyrrolidine derivative **42** having *cis*-substituents was synthesized from (+)-pyroglutamic 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, (+)-ferrunginine 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 methylation gave (+)-ferruginine (Scheme 14).

Skeletal reorganization is a useful tool for the synthesis of complicated natural products. Fürstner ach-



Scheme 13. Total synthesis of anatoxin-a.



Scheme 14. Synthesis of (+)-ferruginine.

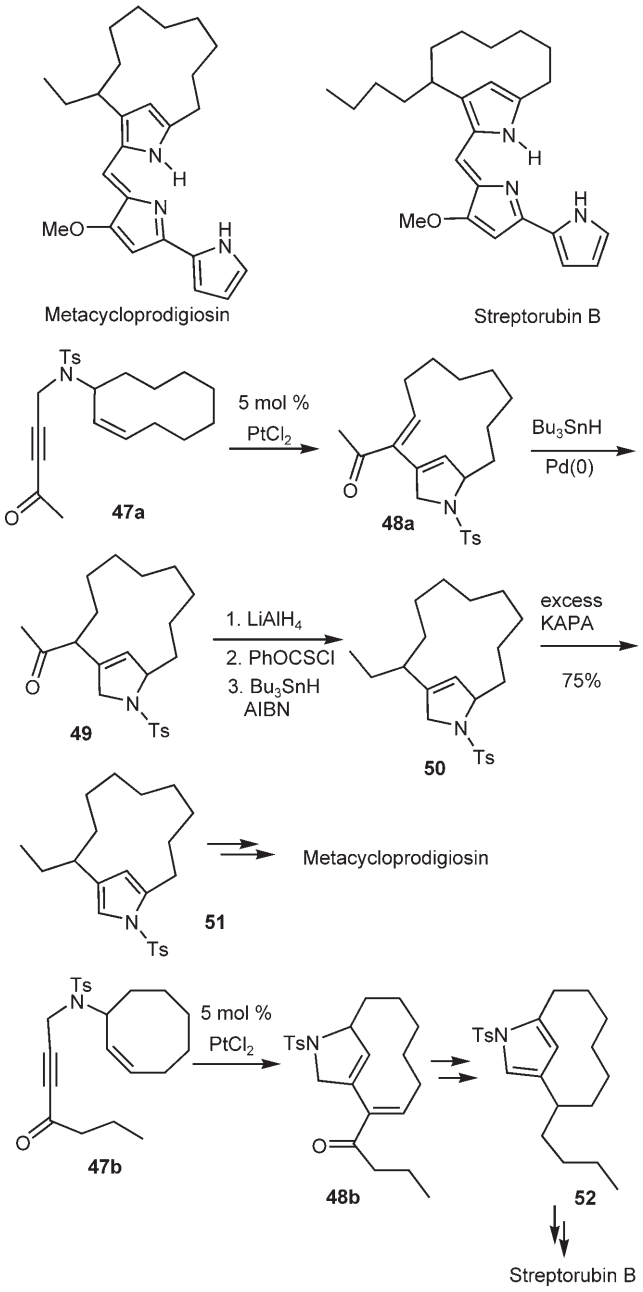
ieved a formal total syntheses of the antibiotics metacycloprodigiosin and streptorubin B by a platinum-catalyzed skeletal reorganization reaction (Scheme 15).[37] The key step leading to the *meta*-bridged pyrrole core structure consisted of a metathesis reaction of the electron-deficient enynes **47a** and **47b** catalyzed by $PtCl_2$. 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]

3 Synthesis 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 process. In the total synthesis of natural products using dienyne metathesis, retro-synthetic analyses are completely different from those of the methods reported previously, and the reaction process was generally shortened. Grubbs demonstrated the synthesis of various fused polycyclic compounds using dienyne metathesis. Double and triple bonds are placed at the appropriate positions in the carbon chain. A steroidal skeleton could be synthesized from polyenyne **57** in high yield in one step, although many processes were involved in this reaction (Scheme 17).[39]

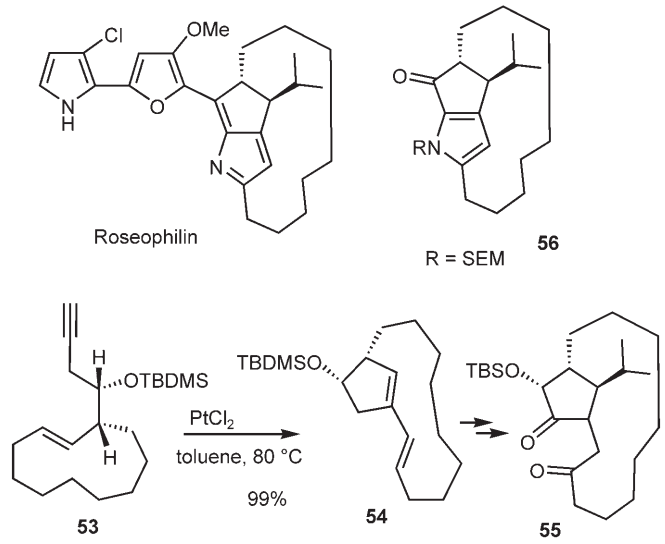
A new approach to the synthesis of a linearly fused 6-8-6 tricarbocyclic ring system was realized using dienyne metathesis.[40] This ring system is a carbon



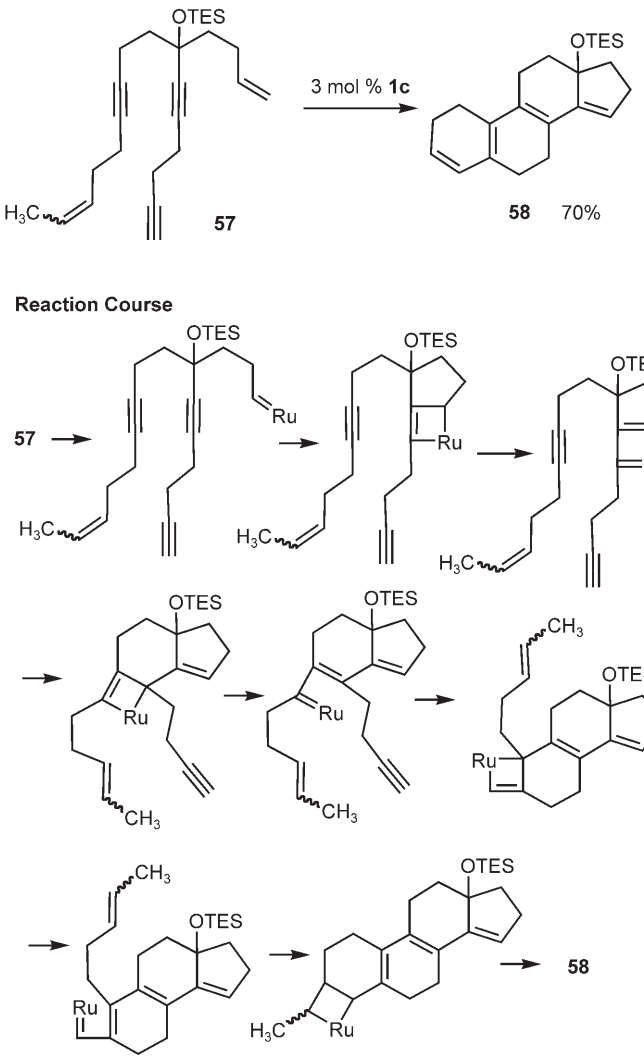
Scheme 15. Formal total syntheses of streptorubin B and metacycloprodigiosin.

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).

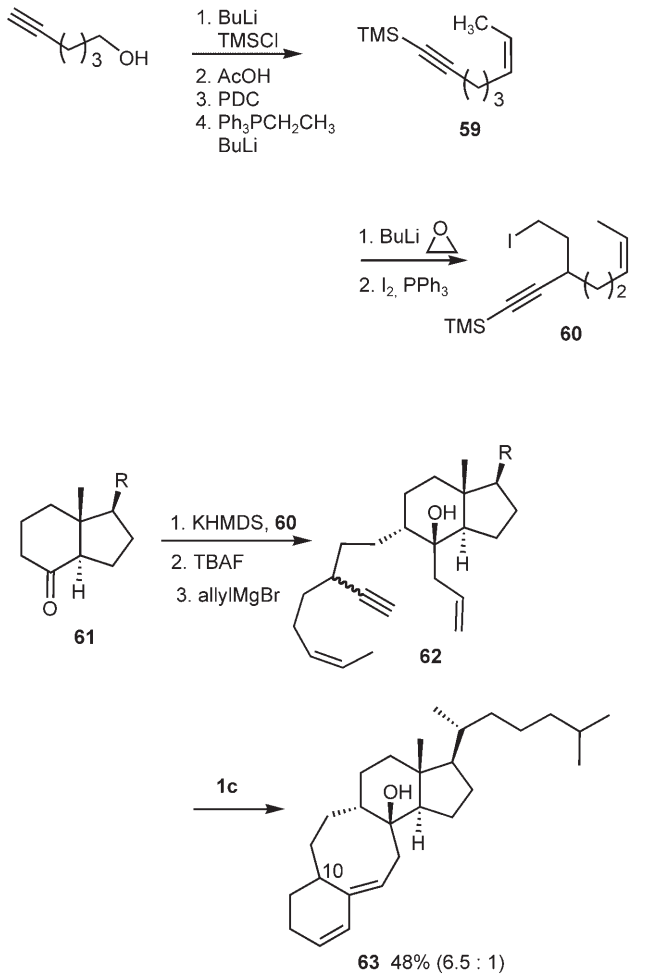
Total synthesis of (±)-erythrocarine was achieved by our group using dienyne metathesis.[41] Synthesis of trisubstituted alkene **65** was achieved *via* regio- and stereoselective introduction of carbon dioxide and an alkynyl group onto the terminal alkyne of **64** followed



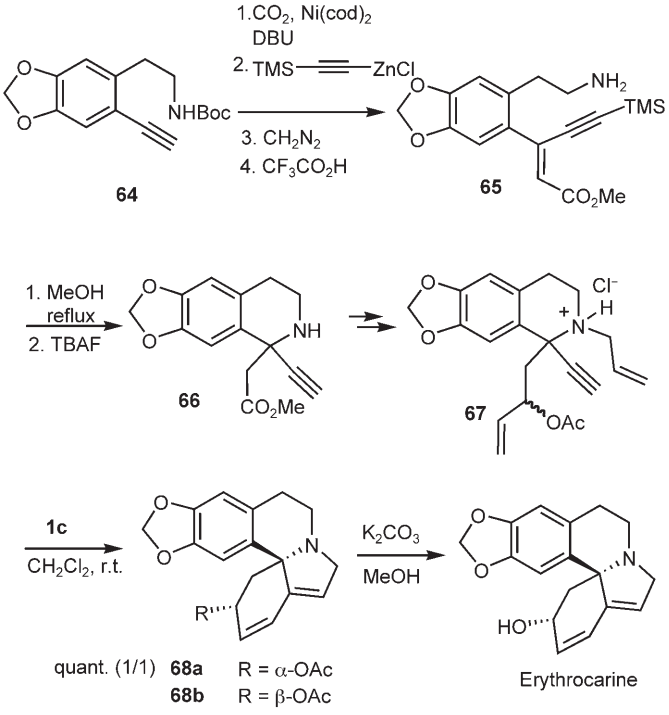
Scheme 16. Formal total synthesis of roseophilin.



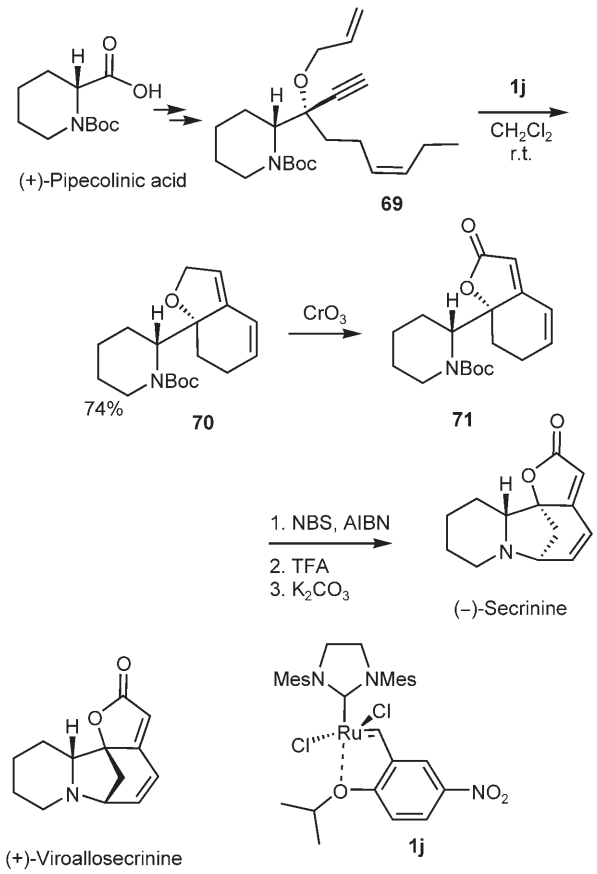
Scheme 17. Construction of a steroidal skeleton.



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



Scheme 19. Total synthesis of erythrocarine.



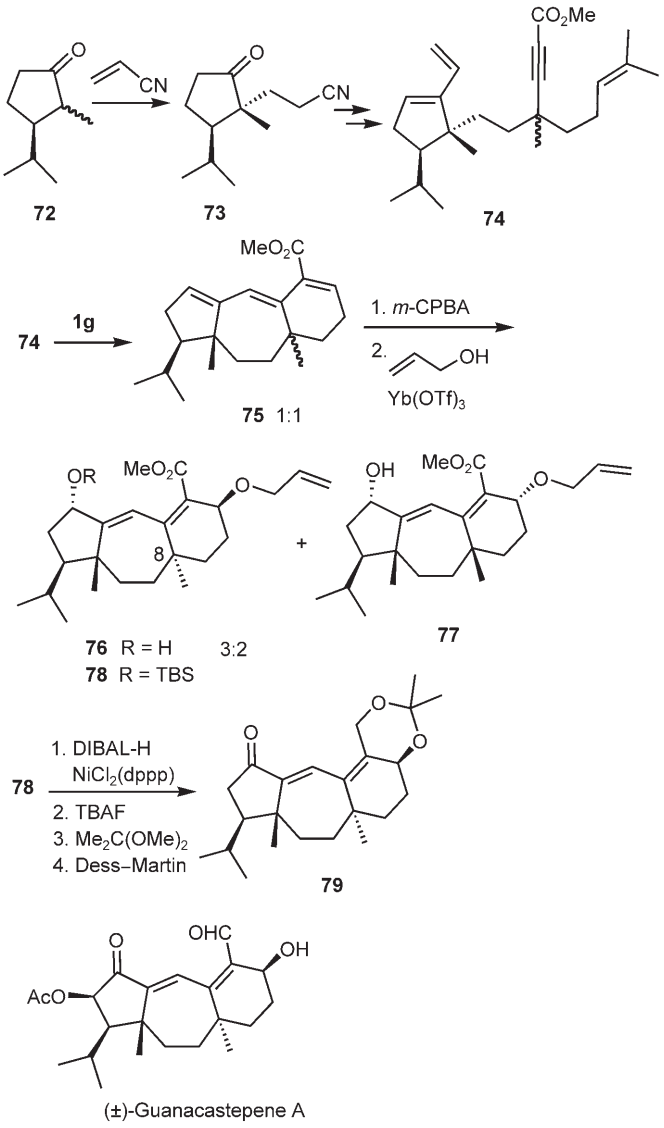
Scheme 20. Total synthesis of (−)-securinine.

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]

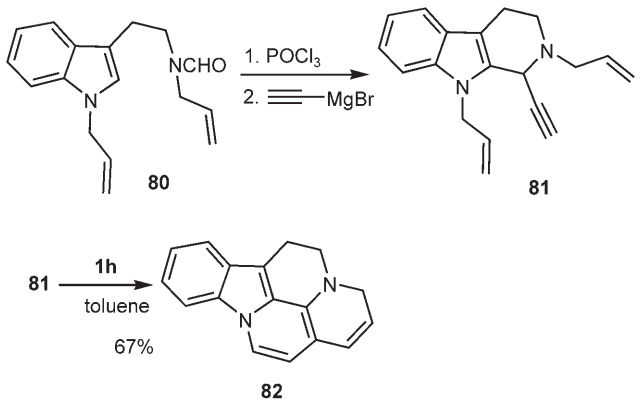
Honda et al. succeeded in a diastereoselective total synthesis of (−)-securinine in an optically pure form by employing RCM of the corresponding dienyne **69** as a key step (Scheme 20).[43a] They synthesized dienyne **69** having terminal alkene and disubstituted alkene parts from (+)-pipecolinic acid, because ruthenium-carbene complex would at first react with the terminal alkene to form a furan ring. Thus, dienyne metathesis of **69** was carried out using **1j**[44] to give **70** in good yield. Oxidation of **70** with CrO_3 gave lactone **71**, which was treated with NBS and then TFA to produce (−)-secrinine. They also synthesized viroallosecurinine in a similar manner.[43b]

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 (±)-guanacastepene A (Scheme 21).

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



Scheme 21. Synthesis of (±)-guanacastepene A.

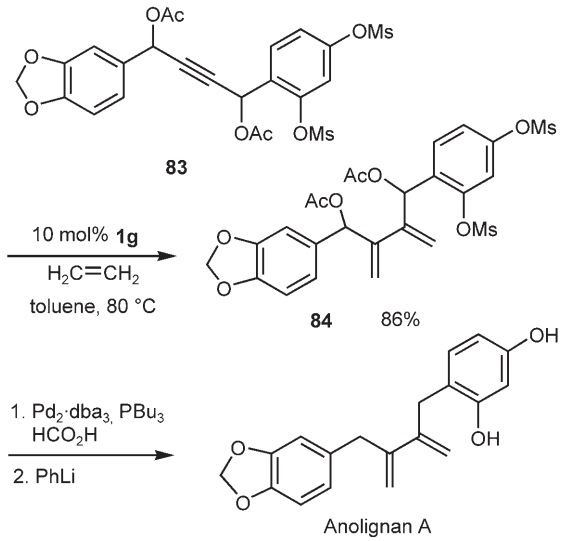


Scheme 22. Dienyne metathesis of a β-carboline derivative.

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

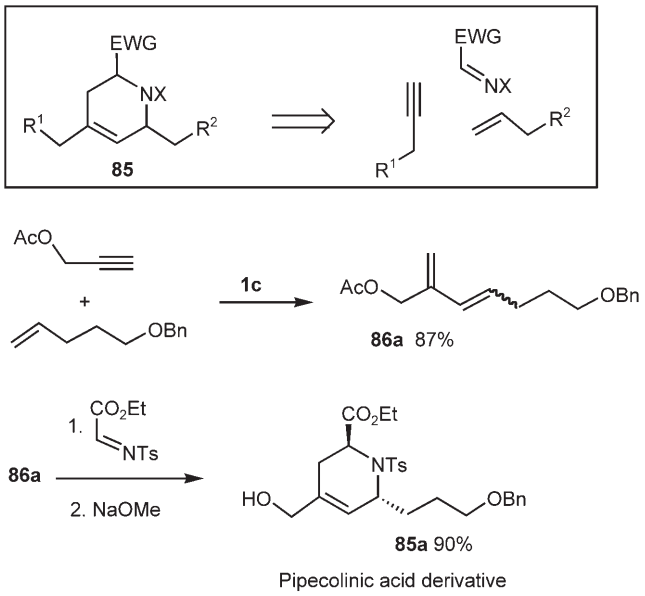


Scheme 23. Synthesis of anolignan A using enyne cross-metathesis.

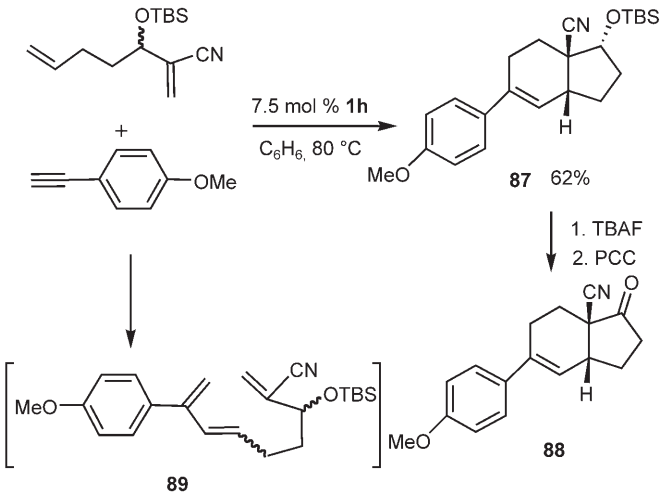
86a, which was reacted with imine to give the pipecolinic acid derivative **85a** in high yield (Scheme 24).[48]

The reaction was further extended to an intramolecular Diels–Alder reaction, and *cis*-hexahydro-1*H*-indene **87** was synthesized from a diene and a terminal alkyne 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).[49]

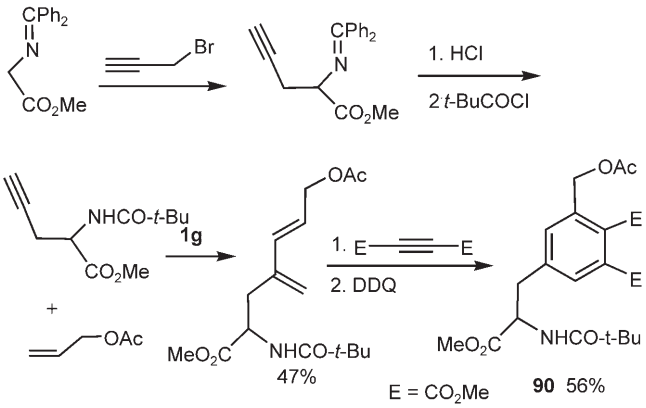
A new method for the synthesis of phenylalanine derivative **90** was developed using the same strategy.[50] A terminal alkyne, prepared from a glycine derivative and propargyl bromide, was reacted with allyl acetate using **1g** to give a diene, which was heated with DMAD and then the resultant product was oxidized with DDQ to give **90** (Scheme 26).



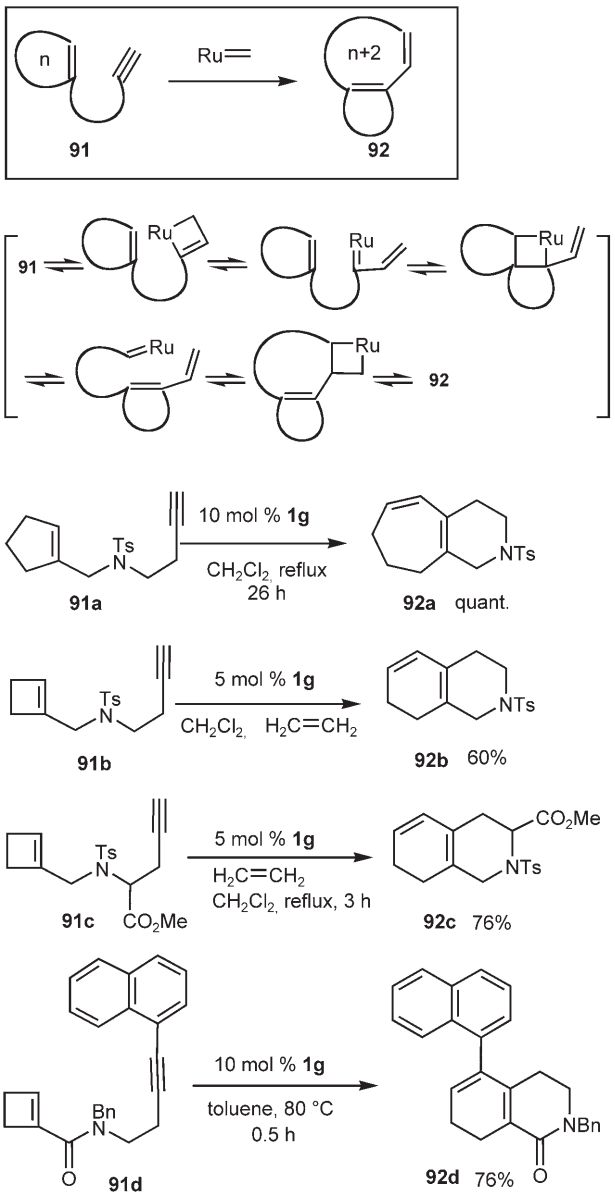
Scheme 24. Synthesis of pipecolinic acid from alkyne, alkene and imine.



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



Scheme 26. Synthesis of an alanine derivative from a glycine

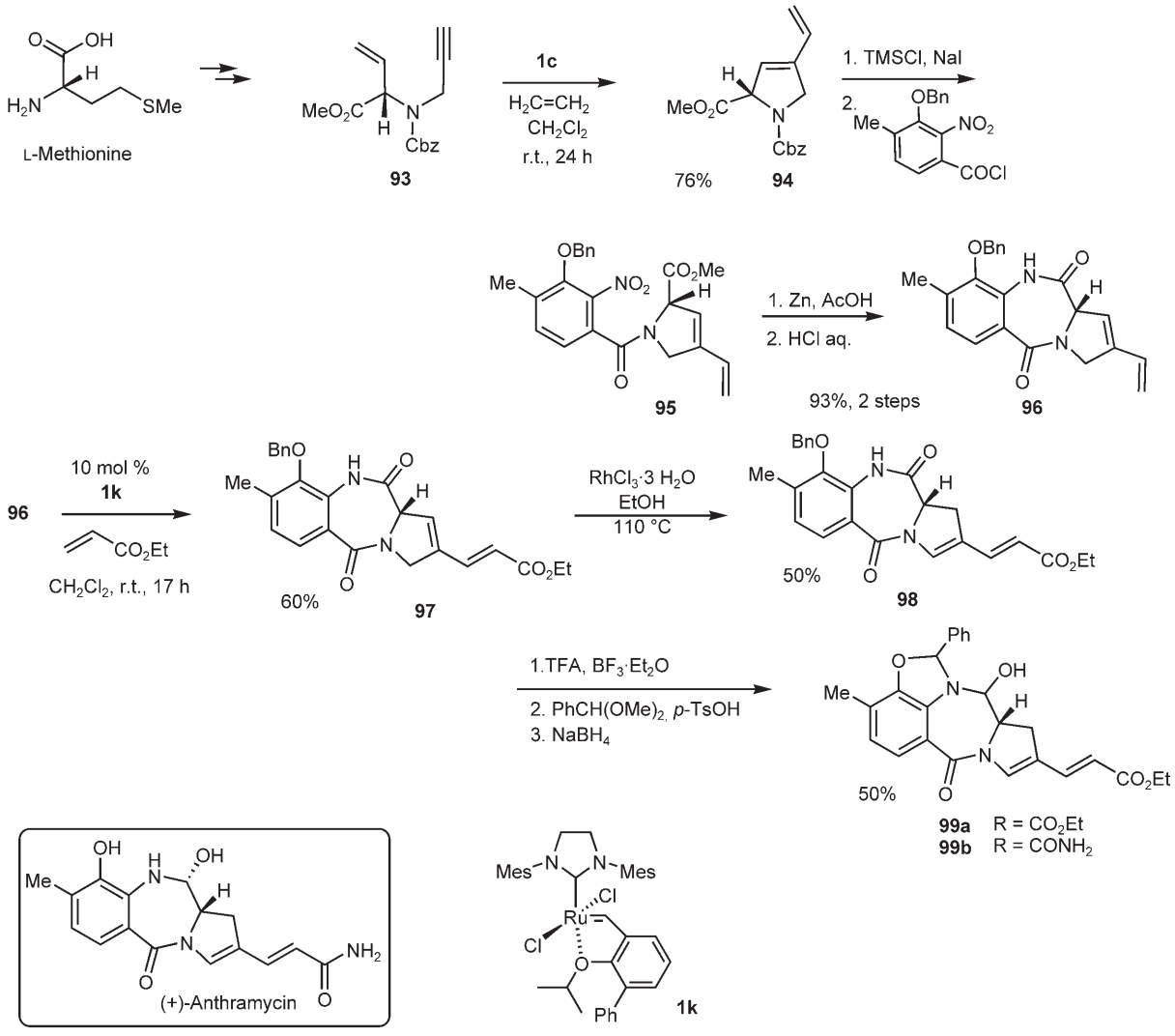


Scheme 27. Synthesis of bicyclic heterocycles using ROM of cyclobutene-yne.

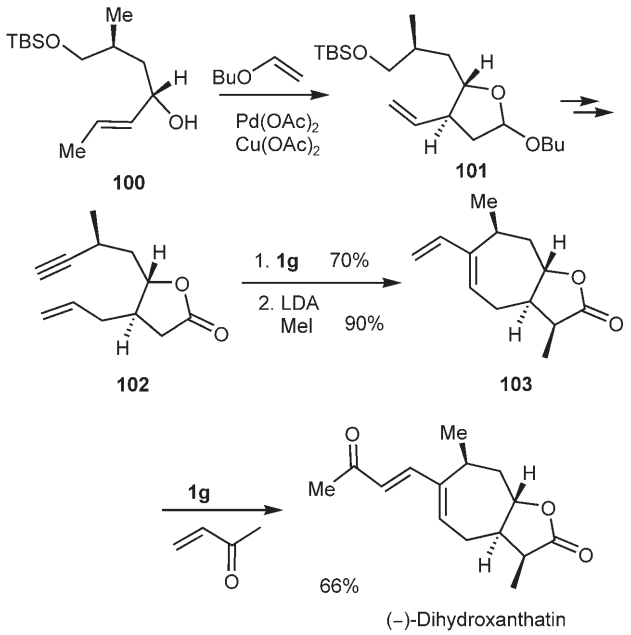
5 Synthesis of Natural Products and Related Compounds using Ring-Opening Metathesis (ROM) and Ring-Closing Metathesis–Cross Metathesis (RCM-CM)

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]

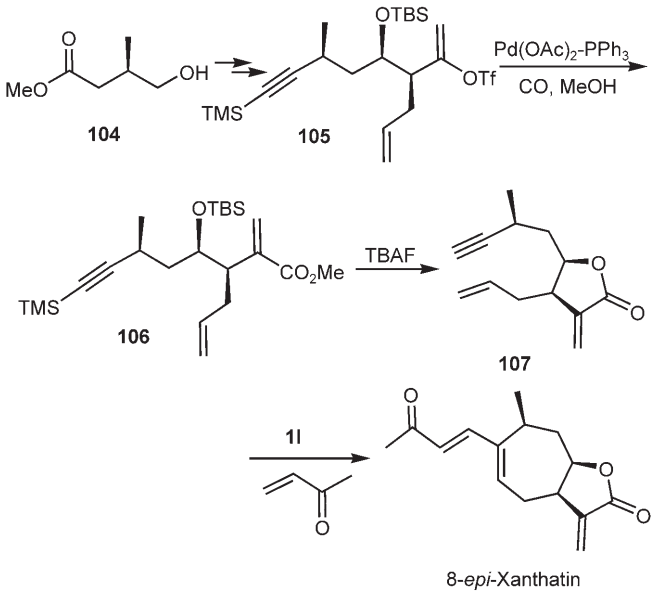
The synthesis of anthramycine derivative **99a** was achieved using RCM and CM (Scheme 28).[53] L-Methionine was converted into enyne **93**, and RCM of **93** using **1c** gave pyrrolidine derivative **94**. Deprotection followed by condensation with a commercially available acid chloride gave **95**. 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 α,β-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 $RhCl_3 \cdot H_2O$ afforded the desired compound **98**, the amide group of which was converted into aminal



Scheme 28. Synthesis of anthramycin derivative.



Scheme 29. Synthesis of (−)-dihydroxanthatin.



Scheme 30. Synthesis of 8-*epi*-xanthatin.

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

Morken succeeded in the synthesis of (−)-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 (−)-dihydroxanthatin (Scheme 29).

Martin succeeded in the first total synthesis of the novel sesquiterpene 8-*epi*-xanthatin.[56] Commertially available ester **104** was converted into vinyl triflate **105**. Palladium-catalyzed carbonylation followed by desilylation gave lactone **107**. The total synthesis of 8-*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 cycloalkene-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

[1] a) *Handbook of Metathesis*, (Ed.: R. H. Grubbs), Wiley-VCH, Weinheim, **2003**; b) *Topics in Organometallic Chemistry*, Vol 1, (Ed.: A. Fürstner), Springer-Verlag, Berlin, Heidelberg, **1998**; c) T. M. Trunk, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18; d) A. Fürstner, *Angew. Chem. Int. Ed.* **2000**, *39*, 3012; e) J.-L. Herisson, Y. Chauvin, *Macromol. Chem.* **1971**, *141*. 161.

[2] R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare, M. O'Regan, *J. Am. Chem. Soc.* **1990**, *112*, 3875.

[3] a) S.-B. T. Nguyen, L. K. Johnson, R. H. Grubbs, *J. Am. Chem. Soc.* **1992**, *114*, 3974; b) P. Schwab, M. B. France, J. W. Ziller, R. H. Grubbs, *Angew. Chem. Int. Ed. Engl.* **1995**, *34,* 2039.

[4] a) G. C. Fu, R. H. Grubbs, *J. Am. Chem. Soc.* **1992**, *114*, 5426; b) G. C. Fu, R. H. Grubbs, *J. Am. Chem. Soc.* **1992**, *114*, 7324; c) G. C. Fu, R. H. Grubbs, *J. Am. Chem. Soc.* **1993**, *115*, 3800; d) G. C. Fu, S.-B. T.

Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1993**, *115*, 9856.
[5] a) T. Weskamp, W. C. Schattenmann, M. Spiegler, W. A. Herrmann, *Angew. Chem. Int. Ed.* 1998, **37**, 2490; b) T. Weskamp, W. C. Schattenmann, M. Spiegler, W. A. Herrmann, *Angew. Chem. Int. Ed.* 1999, **38**, 262; c) T. Weskamp, F. J. Kohl, W. Hieringer, D. Gleich, W. A. Herrmann, *Angew. Chem. Int. Ed.* **1999**, *38*, 2416.
[6] a) J. Huang, E. D. Stevens, S. P. Nolan, J. L. Peterson, *J. Am. Chem. Soc.* **1999**, *121*, 2674; b) J. Huang, H.-J. Schanz, E. D. Stevens, S. P. Nolan, J. L. Peterson, *Organometallics* **1999**, *18*, 5375.
[7] a) M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953; b) M. Scholl, T. M. Trnka, J. P. Morgan, R. H. Grubbs, *Tetrahedron Lett.* **1999**, *40*, 2247.
[8] A. K. Chaterjee, J. P. Morgan, M. Scholl, R. H. Grubbs, *J. Am. Chem. Soc.* **2000**, *122*, 3783.
[9] a) T.-L. Choi, C. W. Lee, A. K. Chatterjee, R. H. Grubbs, *J. Am. Chem. Soc.* **2001**, *123*, 10417; b) T.-L. Choi, A. K. Chatterjee, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2002**, *41*, 3171; c) S. J. Connon, S. Blechert , *Angew. Chem. Int. Ed.* **2003**, *42*, 1900.
[10] a) T. J. Katz, T. M. Sivavec, *J. Am. Chem. Soc.* **1985**, *109*, 737; b) T. M. Sivavec, T. J. Katz, M. Y. Chiang, G. X - Q. Yang, *Organometallics* **1989**, *8*, 1620; c) T. J. Katz, G. X.-Q. Yang, *Tetrahedron Lett.* **1991**, *32*, 5895.
[11] a) S. Watanuki, N. Ochifuji, M. Mori, *Organometallics* **1995**, *14*, 5062; b) S. Watanuki, N. Ochifuji, M. Mori, *Organometallics* **1994**, *13,* 4129;c) M. Mori, S. Watanuki, *J. Chem. Soc., Chem. Commun.* **1992**, 1082; c) S. Watanuki , M. Mori, *Heterocycles* **1993**, *35,* 679.
[12] a) M. Mori, *Top. Organomet. Chem.* **1998**, *1*, 133; b) C. S. Poulsen, R. Madsen, *Synthesis* **2003**, 1; c) M. Mori, in: *Handbook of Metathesis*, (Ed.: R. H. Grubbs), Wiley-VCH, Weinheim, **2003**, Vol. II, p 176; d) S. T. Diver, A. Giessert, J. *Chem. Rev.* **2004**, *104*, 1317.
[13] a) A. Kinoshita, M. Mori, *Synlett* **1994**, 1020; b) A. Kinoshita, N. Sakakibara, M. Mori, *Tetrahedron* **1999**, *55*, 8155; c) M. Mori, T. Kitamura, N. Sakakibara, Y. Sato, *Org. Lett.* **2000**, *2*, 543; d) M. Mori, T. Kitamura, Y. Sato, *Synthesis* **2001**, 654.
[14] M. Mori, N. Sakakibara, A. Kinoshita, *J. Org. Chem.* **1998**, *63*, 6082.
[15] a) S.-H. Kim, N. Bowden, R. H. Grubbs, *J. Am. Chem. Soc.* **1994**, *116*, 10801; b) S.-H. Kim, W. J. Zuercher, N. B. Bowden, R. H. Grubbs, *J. Org. Chem.* **1996**, *61*, 1073.
[16] a) A. Kinoshita, N. Sakakibara, M. Mori, *J. Am. Chem. Soc.* **1997**, *119*, 12388; b) A. Kinoshita, N. Sakakibara, M. Mori, *Tetrahedron* **1999**, *55*, 8155.
[17] a) M. Mori, K. Tonogaki, A. Kinoshita, *Org. Synth.* **2004**, *81*, 1; b) K. Tonogaki , M. Mori, *Tetraheron Lett.* **2002**, *43*, 2235; c) J. A. Smulik, S. T. Diver, *Org. Chem.* **2000***,* *65*, 1788; d) J. A. Smulik, S. T. Diver, *Org. Lett.* **2000**, *2*, 2271; e) J. A. Smulik, A. J. Giessert, S. T. Diver, *Tetrahedron Lett.* **2002**, *43*, 209.
[18] R. Stragies, M. Schuster, S. Blechert, *Angew. Chem. Int. Ed.* **1997**, *36*, 2518.
[19] A. K. Kulkarni, S. T. Diver, *Org. Lett.* **2003**, *5*, 3463.
[20] a) J. S. Kingbury, J. P. A. Harrity, P. J. Bonitatebus, Jr., A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121,* 791; b) S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122,* 8168.
[21] F. Royer, C. Vilain, L. Elkaim, L. Grimaud, *Org. Lett.* **2003**, *5*, 2007.
[22] a) T. Kitamura, M. Mori, *Org. Lett.* **2001**, *3*, 1161; b) T. Kitamura, Y. Kuzuba, Y. Sato, H. Wakamatsu, R. Fujita, M. Mori, *Tetrahedon*, **2004**, *60*, 7375.
[23] a) S. Randl, N. Lucas, S. J. Connon, S. Blechert, *Adv. Synth. Catal.* **2002**, *344*, 631; b) A. Rckert, D. Eisele, S. Blechert, *Tetrahedron Lett.* **2001**, *42*, 5245.
[24] B. M. Trost, G. J. Tanoury, *J. Am. Chem. Soc.* **1988**, *110*, 1636.
[25] B. M. Trost, V. K. Chang, *Synthesis* **1993**, 824.
[26] a) N. Chatani, T. Morimoto, T. Muto, S. Murai, *J. Am. Chem. Soc.* **1994**, *116*, 6049; b) N. Chatani, K. Kataoka, S. Murai, *J. Am. Chem. Soc.* **1998**, *120*, 9104.
[27] N. Chatani, H. I noue, H. Kotsuma, S. Murai, *J. Am. Chem. Soc.* **2002**, *124*, 10294.
[28] K. C. Nicholau, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4490.
[29] a) A. Kinoshita, M. Mori, *J. Org. Chem.* **1996**, *61*, 8356; b) A. Kinoshita, M. Mori, *Heterocycles* **1997**, *46*, 287.
[30] a) A. G. M. Barrett, S. P. D. Baugh, D. C. Braddock, K. Flack, V. C. Gibson, P. A. Procopiou, A. J. P. White, D. J. Williams, *J. Org. Chem.* **1998**, *63*, 7893; b) R. Duboc, C. Henaut, M. Savignac, J.-P. Genet, N. Bhatnagar, *Tetrahedron Lett.* **2001**, *42*, 2461.
[31] K. Hammer, K. Undeheim, *Tetrahedron* **1997**, *53*, 10603.
[32] S. Kohta, N. Sreenivasachary, *Eur. J. Org. Chem.* **2001**, 3375.
[33] T. R. Hoye, S. M. Donaldson, T. J. Vos, *Org. Lett.* **1999**, *1*, 277.
[34] M. E. Layton, C. A. Morales, M. D. Shair, *J. Am. Chem. Soc.* **2002**, *124*, 773.
[35] a) J. B. Brenneman, S. F. Martin, *Org. Lett.* **2004**, *6*, 1329; b) J. B. Brenneman, R. M. Machauer, S. F. Martin, *Tetrahedron* **2004**, *60*, 7301; c) M. Mori, T. Tomita, Y. Kita, T. Kitamura, *Tetrahedron Lett.* **2004**, *45*, 4397; d) T. Tomita, Y. Kita, T. Kitamura, Y. Sato, M. Mori, *Tetrahedron* **2006**, *62*, 10518.
[36] V. K. Aggarwal, J. Astle, M. Rogers-Evans, *Org. Lett.* **2004**, *6*, 1469.
[37] A. Fürstner, H. Szillat, B. Gabor, R. Mynott, *J. Am. Chem. Soc.* **1998**, *120*, 8305.
[38] B. M. Trost, G. A. Doherty, *J. Am. Chem. Soc.* **2000**, *122*, 3801.
[39] W. J. Zuercher, M. Scholl, R. H. Grubbs, *J. Org. Chem.* **1998**, *63*, 4291.
[40] E. M. Codesido, L. Castedo, J. R. Granja, *Org. Lett.* **2001**, *3*, 1483.
[41] K. Shimizu, M. Takimoto, M. Mori, *Org. Lett.* **2003**, *5*, 2323.
[42] H. Fukumoto, T. Esumi, J. Ishihara, S. Hatakeyama, *Tetrahedron Lett.* **2003**, *44*, 8047.
[43] a) T. Honda, H. Namiki, K. Kaneda, H. Mizutani, *Org. Lett.* **2004**, *6*, 87; b) T. Honda, H. Namiki, M. Watanabe, H. Mizutani, *Tetrahedron Lett.* **2004**, *45*, 5211.
[44] T. M. Trunka, R. H. Grubbs, K. Grela, S. Harutyunyan, A. Michrewska, *Angew. Chem. Int. Ed.* **2002**, *41*, 4039.

[45] F.-D. Boyer, I. Hanna, L. Ricard, *Org. Lett.* **2004**, *6*, 1817.
[46] A. Gonzalez, G. Dominguez, J. P. Castells, *Tetrahedron Lett.* **2005**, *46*, 7267.
[47] M. Mori, K. Tonogaki, N. Nishiguchi, *J. Org. Chem.* **2002**, *67*, 224.
[48] S. S. Schurer, S. Blechert, *Tetrahedron Lett.* **1999**, *40*, 1877.
[49] S. Mix, S. Blechert, *Org. Lett.* **2005**, *7*, 2015.
[50] S. Kotha, S. Halder, E. Brahmachary, *Tetrahedron* **2002**, *58*, 9203.
[51] M. Mori, Y. Kuzuba, T. Kitamura, Y. Sato, *Org. Lett.* **2002**, *4*, 3855.
[52] M. Mori, H. Wakamatsu, K. Tonogaki, R. Fujita, T. Kitamura, Y. Sato, *J. Org. Chem.* **2005**, *70*, 1066.
[53] T. Kitamura, Y. Sato, M. Mori, *Tetrahedron* **2004**, *60*, 9649.
[54] H. Wakamatsu, S. Blechert, *Angew. Chem. Int. Ed.* **2002**, *41*, 2403.
[55] M. A. Evans, J. P. Morken, *Org. Lett.* **2005**, *7*, 3371.
[56] D. A. Kummer, J. B. Brenneman, S. F. Martin, *Org. Lett.* **2005**, *7*, 4621.

