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Rh(II)-Catalyzed Skeletal Reorganization of 1,6- and 1,7-Enynes through Electrophilic Activation of Alkynes

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Abstract: The skeletal reorganization of 1,6- and 1,7-enynes leading to 1-vinylcycloalkenes using Rh(II) as a catalyst is reported. Two possible isomers of 1-vinylcycloalkenes, type **I** and type **II**, can be obtained, the ratio of which are highly dependent on the substitution pattern of the enynes used. Formation of type **I** compounds involves a single cleavage of a C−C double bond, the product of which is identical to that of enyne metathesis. In contrast, the formation of type **II** compounds involves the double cleavage of both the C−C double and triple bonds, which has an anomalous bond connection. The presence of both a phenyl group at the alkyne carbon and a methyl group at the internal alkene carbon facilitates the formation of type **II** compounds. The electronic and steric nature of the substituents on the aromatic ring also affects the ratio of type **I** and type **II**. The nature of a tether also has a significant effect on the course of the reaction. Experimental evidence for the intermediacy of a cyclopropyl rhodium carbenoid, a key intermediate in the skeletal reorganization of enynes, is also reported. In addition to the skeletal reorganization of enynes, Rh(II) complexes were found to have a high catalytic activity for some cycloisomerization reactions of alkyne derivatives, including the bicyclization of enynes to bicyclo[4.1.0]heptene derivatives and the cyclization of alkynylfurans to phenol derivatives.

Introduction

The development of new, efficient methods for the construction of ring systems from simple acyclic building blocks represents an important ongoing challenge for synthetic organic chemists. One of the most recently studied methods involve transition metal catalyzed cycloisomerization reactions of enynes and their related processes.[1] From a mechanistic perspective, metallacycles or metal vinylidene complexes have been proposed as a key intermediate in most of the cycloisomerization reactions of enynes reported thus far. The electrophilic activation of alkynes by transition metal halides or their cation complexes, such as Ru(II), Pt(II), Pt(IV), Ir(I), Au(I), Au(III), and even typical elemental halides, such as Ga(III) and In(III), has recently

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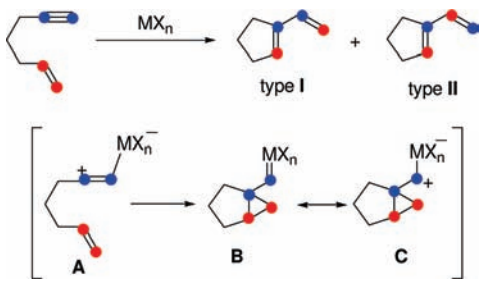
Scheme 1. Skeletal Reorganization of Enynes



been recognized as a key step in various cycloisomerization reactions of alkyne derivatives, such as enynes,[2−7] ynebenzenes,[8] and other alkyne derivatives.[9−11] Cycloisomerization reactions of enynes catalyzed by such electrophilic metal complexes have recently attracted considerable attention because of the great diversity of products that can be produced from them. Among the various cycloisomerization reactions of enynes, skeletal reorganization is most interesting because of the potential synthetic utility as well as the anomalous bond connection provided by this process as shown in Scheme 1. Two possible isomers, type **I** and type **II**, can be produced in the skeletal reorganization of enynes. The formation of type **I** isomers involves the cleavage of the original alkene C−C bonds and the migration of the terminal alkene carbon on the terminus of the alkyne. In contrast, the formation of type **II** isomers involves a double cleavage of both the C−C double and C−C triple bonds. The terminal alkene carbon migrates between the two alkyne carbons. The course of the reaction is highly dependent on the catalyst used and substitution patterns of the substrates. In the skeletal reorganization of enynes,[2−6] electrophilic interactions between metal complexes, MX_n, and an alkyne, as in **A**, are proposed to trigger the catalysis, and a cyclopropyl metal carbene **B** is proposed as a key intermediate in the case of late transition metal halide complexes based on experiments involving the trapping of the metal carbenoid intermediate[9] and on DFT studies (Scheme 1).[12] In fact, we and other groups succeeded in trapping metal carbenoid **B** by cyclopropanation with intra-[9] and intermolecular alkenes[10] and by addition of carbon nucleophiles.[13] Cyclopropyl metal carbenoid **B** was also oxidatively trapped by the treatment with diphenylsulfoxide.[14] A zwitter ionic resonance form **C** of a cyclopropyl gold carbenoid was trapped by intramolecular alkenes.[15]

The possible intermediacy of metal carbenoid complex **B** in the skeletal reorganization of enynes prompted us to use Rh(II) complexes as a catalyst for the skeletal reorganization of enynes. It is well-known that Rh(II) complexes have the ability to stabilize carbenes and to function as catalysts in various reactions involving carbenes as intermediates,[16] and rhodium(II) complexes were recently found to serve as an activator of an alkyne.[17] In addition, we have already reported that a Rh(II) complex was active in polycyclization of dienes-ynes.[9a] We wish to report in full detail how a Rh(II) complex shows high catalytic activity for various types of cycloisomerization reactions of alkyne derivatives, including the skeletal reorganization of

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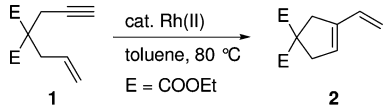
enynes leading to the production of 1-vinylcycloalkenes, the bicyclization of enynes to bicyclo[4.1.0]heptene derivatives, and the cyclization of yne-furans to phenol derivatives. All of these reactions are initiated by the electrophilic activation of alkynes by Rh(II). In addition, experimental evidence for the intermediacy of a cyclopropyl rhodium carbenoid in the skeletal reorganization of enynes is also described.

Scheme 2. Rh(II)-Catalyzed Skeletal Reorganization of Enynes



$Rh_2(OAc)_4$	20 h	no reaction
$Rh_2(O_2CC_7H_{15})_4$	20 h	no reaction
$Rh_2(O_2CCF_3)_4$	1.5 h	80%
$Rh_2(O_2CC_3F_7)_4$	20 h	53%

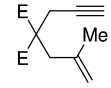
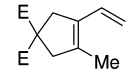
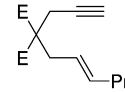
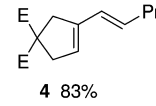
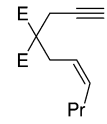
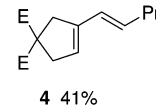
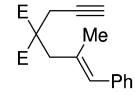
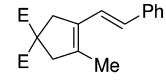
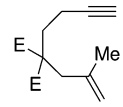
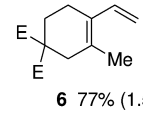
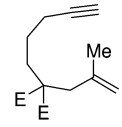
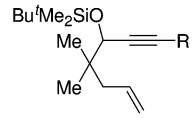
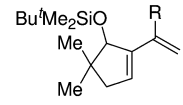
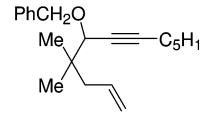
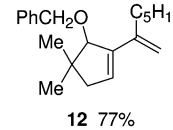
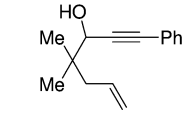
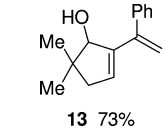
Results and Discussion

The treatment of a simple enyne **1** (0.5 mmol) with a catalytic amount of $Rh_2(OAc)_4$ (0.01 mmol) in toluene (2.5 mL) at 80 °C for 20 h resulted in no reaction (Scheme 2). Changing the solvent to CH_2Cl_2 failed to improve the reaction. However, the use of $Rh_2(O_2CCF_3)_4$ as a catalyst gave the expected 1-vinylcyclopentene **2** in 80% yield after only a reaction time of 1.5 h. This result indicates that a highly electrophilic catalyst is required to activate an alkyne. Although $Rh_2(O_2CC_3F_7)_4$ is more electrophilic than $Rh_2(O_2CCF_3)_4$, its reactivity was lower than that of $Rh_2(O_2CCF_3)_4$. This is probably due to a steric hindrance of a perfluorocarboxylate moiety.

Results for reactions of various enynes in the presence of $Rh_2(O_2CCF_3)_4$ as the catalyst are shown in Table 1. Irrespective of the geometries of the starting enynes with respect to the alkene moiety, only the trans isomer was obtained, as in **4**. This trend is similar to previously reported Ru(I)- and Pt(II)-catalyzed reactions[2a,b] but in sharp contrast to the Ga(III)- and In(III)-catalyzed reaction of enynes, in which the reaction proceeds in a stereospecific manner.[2d,e] The reaction was also applicable to 1,7-enynes leading to the production of 1-vinylcyclohexene **6**. However, the reaction of a 1,8-enyne gave no reaction. It is noteworthy that the substitution of an oxy group at the propargylic position facilitated the reaction. Enynes having a siloxy group at the propargylic position gave the corresponding 1-vinylcyclopentenes **7**−**11** in high yields, irrespective of the nature of the substituent on the alkyne carbon. Thus, enynes with a substituent on the alkyne carbon served as good substrates, in contrast to previously reported examples in which they were not appropriate in most cases, except for a $PtCl_2$-catalyzed reaction.[2b] Although the use of a benzyloxy group at the propargylic position gave the corresponding product **12** in high yield, the acetoxy isomer gave complex mixtures (result not shown in Table 1). It is noteworthy that a hydroxyl group, if present on the starting material, need not be protected as in **13**. The selectivity proved to be general for a number of additional substrates, rendering the present reaction a unique method for preparing substituted 1-vinylcyclopentenes. In all examples of enynes that contain substituents at the alkyne carbon or terminal alkene carbon shown in Table 1, type **I** compounds were selectively obtained.

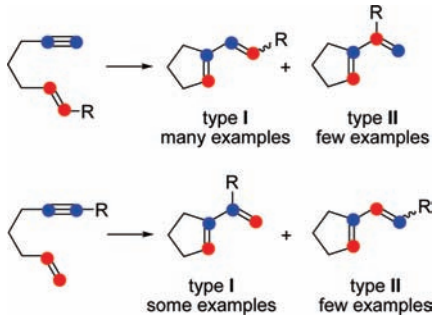
The present skeletal reorganization at first glance appears to be the same transformation as enyne metathesis[1,18] since both lead to formation of 1-vinylcycloalkenes. However, the significant difference between the two reactions is the operative mechanism. Enyne metathesis is initiated by a [2 + 2] cycloaddition of a carbene complex and an alkyne (or alkene). In contrast, the electrophilic interaction between the alkyne and the catalyst initiates the skeletal reorganization of enynes, as shown in Scheme 1. Most importantly, the possible formation

Table 1. $Rh_2(O_2CCF_3)_4$-Catalyzed Skeletal Reorganization of Enynes[a]

enyne	yield (%)[b]
	 **3** 89% (1.5 h)
 (*E*:*Z* = 87:13)	 **4** 83%
 (*E*:*Z* = 8:92)	 **4** 41%
	 **5** 84%
	 **6** 77% (1.5 h)
	no reaction
 R = Me, R = C_5H_{11}, R = Ph, R = Cl, R = COOEt	 **7** 92% (3 h), **8** 87%, **9** 85%, **10** 71% (3 h), **11** 89% (2 days)[c]
	 **12** 77%
	 **13** 73%

[a] Reaction conditions: enyne (0.5 mmol), $Rh_2(O_2CCF_3)_4$ (0.01 mmol), toluene (2.5 mL) at 80 °C for 20 h. [b] Isolated yield. [c] $Rh_2(OAc)_4$ was used as the catalyst.

Scheme 3. Type I vs Type II

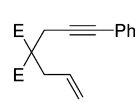
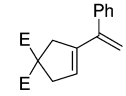
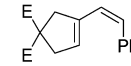
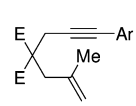
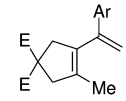
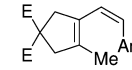
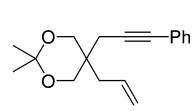
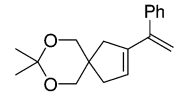
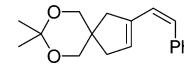
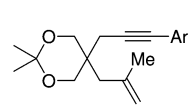
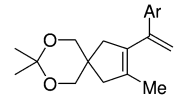
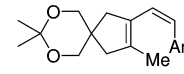
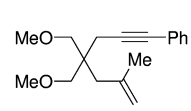
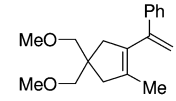
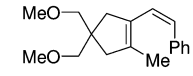
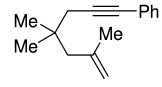
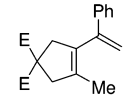
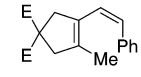


of type **II** compounds is the characteristic feature of this type of skeletal reorganization (Scheme 3). The formation of type **II** compounds involves an unusual bond reconstitution, in which the double cleavage of both C−C double and triple bonds. However, only a limited number of studies have reported the occurrence of type **II** compounds, among which their selective formation is rare.[19] In most cases, type **I** products were selectively obtained. In fact, type **I** products were clearly formed in the Rh(II)-catalyzed skeletal reorganization of enynes, as shown in Table 1.

Because of this, we were prompted to examine various effects, such as the electronic and steric nature of substituents, chain length, and the nature of tether atoms on the ratio of type **I** and type **II** compounds. It was found that the structure of the enynes used has a significant effect on the distribution of type **I** and type **II** products, as shown in Table 2. The reaction of enyne **14**, which contains a phenyl group at the alkyne carbon, gave **15-I** (type **I**) selectively. On the other hand, the substitution of a methyl group at the internal alkene carbon, as in **16a**, led to the formation of a mixture of **17a-I** (type **I**) and **17a-II** (type **II**) in nearly a 1:1 ratio. Surprisingly, the product **17a-II** had a *cis* configuration. We next examined the electronic effects of substituents on the phenyl ring on product distribution. The presence of an electron-withdrawing group, as in **16d** and **16e**, dramatically increased the ratio of type **II** products. Based on these results, it is expected that a type **I** product will be a major isomer in the reaction of an enyne with a 4-methoxypheny group on the phenyl ring, as in **16b**, because of its strong electron-donating nature. However, this was not the case. The reaction of **16b** gave the bicyclo[3.2.0]heptene derivative **18** as a major isomer, along with **17b-II** (Scheme 4), with no type **I** compound being formed. Use of a sterically hindered aryl group, as in **16f**, also selectively gave a type **II** product (Table 2). These results suggest that a malonate tether would favor the formation of type **I** products, as in **14**, but this effect is overcome by the effect of a methyl group at the internal alkene carbon (**14** vs **16a**) and a substituent having an electron-withdrawing effect (**16a** and **16c** vs **16d** and **16e**).

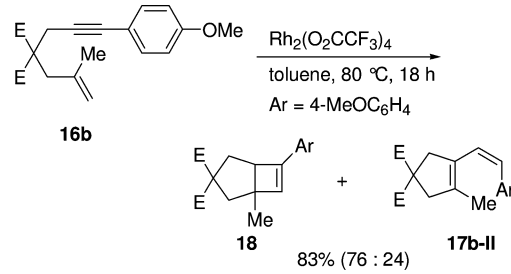
Of more interest is the dramatic effect of a substituent in the tether. Replacement of a malonate tether by a ketal tether facilitated the formation of a type **II** compound (compare **14** with **19**). Analogous to the case of malonates, the presence of a methyl group at an internal alkene carbon, as in **21**, led to the

Table 2. $Rh_2(O_2CCF_3)_4$-Catalyzed Skeletal Reorganization of 1,6-Enynes[a]

enyne	yields (%)[b] type **I**	type **II**
 **14**	 48% (**15-I** : **15-II** = >98 : 2) (24 h)	
		
16a Ar = C_6H_5	89% (**17a-I** : **17a-II** = 52 : 48)	
16b Ar = 4-$MeOC_6H_4$	see Scheme 4	
16c Ar = 4-MeC_6H_4	81% (**17c-I** : **17c-II** = 61 : 39)	
16d Ar = 4-$MeO_2CC_6H_4$	93% (**17d-I** : **17d-II** = 13 : 87)	
16e Ar = 4-$CF_3CC_6H_4$	76% (**17e-I** : **17e-II** = 9 : 91) (4 h)	
16f Ar = 2-MeC_6H_4	94% (**17f-I** : **17f-II** = 2 : >98)	
 **19**	 64% (**20-I** : **20-II** = 64 : 36)	
		
21a Ar = C_6H_5	76% (**22a-I** : **22a-II** = 7 : 93)[c]	
21b Ar = 4-$CF_3C_6H_4$	72% (**22b-I** : **22b-II** = 5 : 95) (3 h)[c]	
21c Ar = 2-Np[d]	76% (**22c-I** : **22c-II** = 2 : >98)[c]	
 **23**	 73% (**24-I** : **24-II** = 2 : >98) (5 h)	
 **25**	 67% (**26-I** : **26-II** = 2 : >98) (3 h)	

[a] Reaction conditions: enyne (0.5 mmol), $Rh_2(O_2CCF_3)_4$ (0.01 mmol), toluene (2.5 mL) at 80 °C for 20 h. [b] Isolated yield. [c] The reaction was carried out at 60 °C. [d] Np = naphthyl.

Scheme 4. Formation of Four-Membered Product



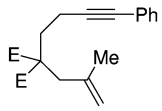
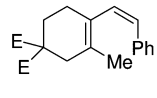
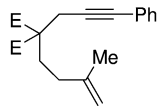
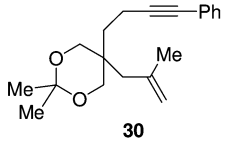
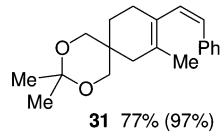
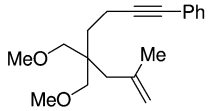
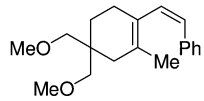
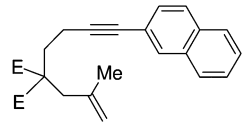
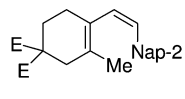
selective formation of type **II** products **22-II**. The presence of a gem-dimethyl group, as in **25**, also gave a type **II** product selectively.

The reaction was also applicable to 1,7-eynes, as shown in Table 3. In most cases, type **II** products were exclusively obtained. The trend for the preferential formation of a (*Z*)-isomer

(18) For recent reviews on the enyne metathesis, see: Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1–18. Villar, H.; Frings, M.; Bolm, C. *Chem. Soc. Rev.* **2007**, *36*, 55–66.

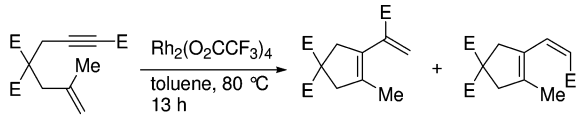
(19) To the best of knowledge, there are four papers in which selective formation of type **II** is described. But, only one specific example was shown in each paper. See refs 2b, 4f, 4g, and 5b.

Table 3. $Rh_2(O_2CCF_3)_4$-Catalyzed Skeletal Reorganization of Phenyl-Substituted 1,7-Enynes[a]

enyne	yield (%)[b]
 **27**	 **28** 76% (>98%)
 **29**	no reaction
 **30**	 **31** 77% (97%)
 **32**	 **33** 81% (98%)
 **34**	 **35** 86% (96%)

[a] Reaction conditions: enyne (0.5 mmol), $Rh_2(O_2CCF_3)_4$ (0.01 mmol), toluene (2.5 mL) at 80 °C for 20 h. [b] Isolated yield. The number in parentheses is selectivity for type **II**.

Scheme 5. Ester-Substituted 1,6-Enyne

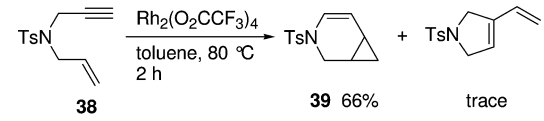


appears to be quite general, similar to the case of 1,6-enynes. The reaction of **27** gave type **II** product **28** exclusively, even though **27** contained a malonate tether and no electron-withdrawing group on the phenyl ring, showing that chain length has a stronger effect than both tether and electronic effects (**16a** vs **27**). Curiously, the reaction of enyne **29** resulted in no conversion, indicating that the position of a malonate in the tether also has a significant effect on the efficiency of the reaction. In all cases shown in Table 3, type **II** products were formed exclusively.

The reaction of an enyne **36** containing an ester group at the alkyne carbon was examined (Scheme 5). In sharp contrast to enynes containing an aryl group at the alkyne carbon, the type **I** product was the major isomer. This result is in contrast with the case of the $PtCl_2$-catalyzed reaction, in which a mixture of type **I** and type **II** products is obtained with type **II** being favored.[2b]

The nature of the tether in enynes has a marked effect on the course of the reaction, even for cases where the chain consists

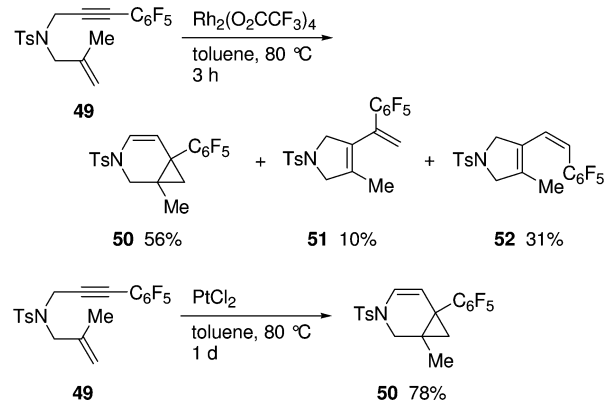
Scheme 6. Rh(II)-Catalyzed Bicyclization of Enyne with a Nitrogen Tether



of all carbons, as shown in Table 2. It was found that the presence of a nitrogen tether had more significant effects on the course of the reaction. The reaction of enynes with a *p*-tosylamide functionality in the tether, such as **38**, gave the bicyclization product **39** as the major isomer, along with a small amount of the skeletal reorganization product (Scheme 6).

This type of transformation was first reported by Blum, who reported that 1,6-enynes containing an oxygen atom in the tether underwent bicyclization in the presence of $PtCl_4$, to give oxabicyclo[4.1.0]heptenes.[20] Later, Früstner[4d,e] and Echavarren[21] found that $PtCl_2$ is a good catalyst for the bicyclization of 1,6-enynes having an oxygen or nitrogen atom in the tether. Ir(I),[22] Au(I),[23] and an (NHC)−Pt complex[24] were also recently reported to catalyze the cycloisomerization of 1,6-enynes that contain a nitrogen functionality in the tether to azabicyclo[4.1.0]-heptenes. Rh(II) is also found to be active in the bicyclization of various enynes with a nitrogen or oxygen atom in the tether, as shown in Table 4. However, use of 1,7-enyne **45** led to the selective formation of type **II** product **46**, although the $PtCl_2$-catalyzed reaction gave a bicyclization product **47**. Similar to the case of a malonate tether, as in **27** and **29**, shown in Table 3, the position of an NTs group also has a significant effect on the reactivity of substrates. Thus, in sharp contrast to **45**, **48** was completely unreactive.

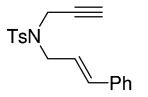
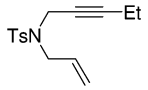
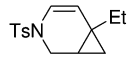
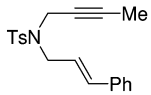
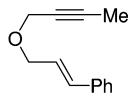
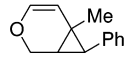
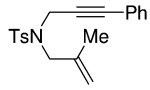
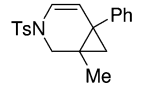
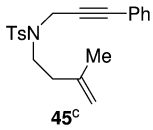
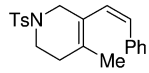
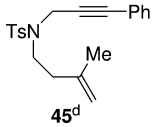
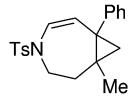
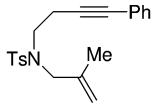
Scheme 7. Cycloisomerization of Pentafluorophenyl-Substituted Enyne



An interesting result was observed when pentafluorophenyl-substituted enyne **49** was used a substrate (Scheme 7). The reaction of **49** gave all three possible products, the bicyclization product **50**, **51** (type **I**), and **52** (type **II**). When $PtCl_2$ was used as a catalyst in place of $Rh_2(O_2CCF_3)_4$, the bicyclization product

(20) Blum, J.; Beer-Kraft, H.; Badrieh, Y. *J. Org. Chem.* **1995**, *60*, 5567–5569.
(21) Nevado, C.; Ferrer, C.; Echavarren, A. M. *Org. Lett.* **2004**, *6*, 3191–000.
(22) Shibata, T.; Kobayashi, Y.; Maekawa, S.; Toshida, N.; Takagi, K. *Tetrahedron* **2005**, *61*, 9018–9024.
(23) Lee, S. I.; Kim, S. M.; Choi, M. R.; Kim, S. Y.; Chung, Y. K. *J. Org. Chem.* **2006**, *71*, 9366–9372.
(24) Brissy, D.; Skander, M.; Jullien, H.; Retailleau, P.; Marinett, A. *Org. Lett.* **2009**, *11*, 2137–2139.

Table 4. Rh(II)-Catalyzed Bicyclization of Enynes with a Heteroatom in the Tether[a]

enyne	yield (%)[b]
	 **40** 50%
	 **41** 58%
	 **42** 93%
	 **43** 67% (1 h)
	 **44** 86% (5 h)
 **45**[c]	 **46** 53%
 **45**[d]	 **47** 21%
 **48**	no reaction

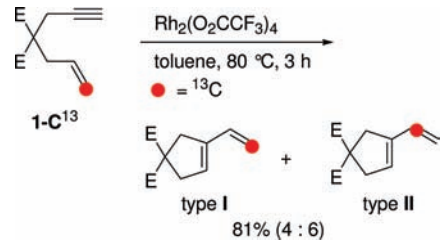
[a] Reaction conditions: enyne (0.5 mmol), $Rh_2(O_2CCF_3)_4$ (0.01 mmol), toluene (2.5 mL) at 80 °C for 20 h. [b] Isolated yield. [c] The reaction was carried out by using $Rh_2(O_2CCF_3)_4$ (0.15 mmol) at 100 °C. [d] $PtCl_2$ (0.01 mmol) was used as a catalyst.

50 was formed in 78% yield as a single product. This serves to demonstrate the complexity of enyne reactions.

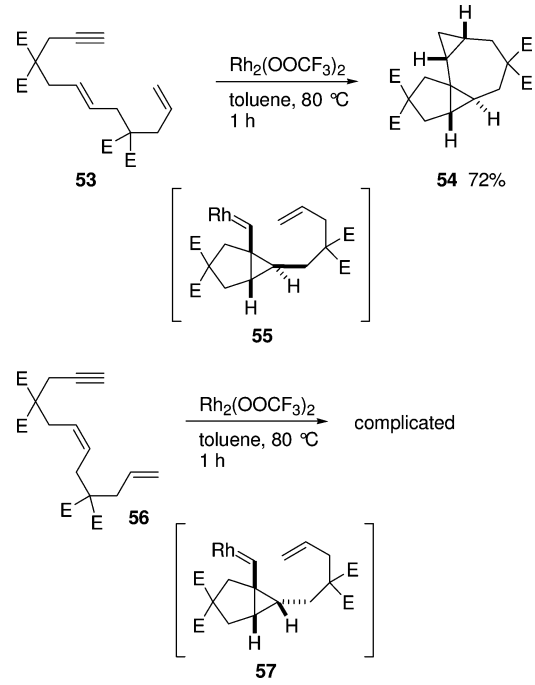
A ^{13}C-labeling experiment using the simple enyne **1-C**^{13} was performed to determine which type of product is formed in the case of a simple enyne.[4f] It would be helpful to have precise information on the ratio of type **I** to type **II** compounds produced, to better understand the reaction mechanism for the skeletal reorganization of enynes. The reaction of **1-C**^{13} in the presence of $Rh_2(O_2CCF_3)_4$ in toluene at 80 °C gave a mixture of type **I** and **II** isomers with type **II** being slightly favored, showing that the anomalous bond connection is a slightly favored route, even in the case of a simple enyne (Scheme 8).[25]

(25) Nakai, H.; Chatani, N. *Chem. Lett.* **2007**, *36*, 1494–1495.

Scheme 8. ^{13}C-Labeling Experiment



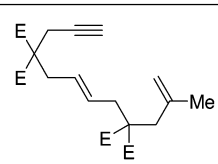
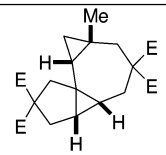
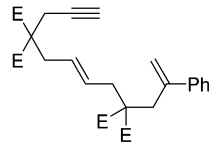
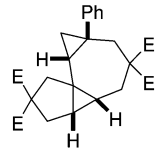
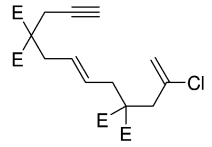
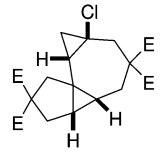
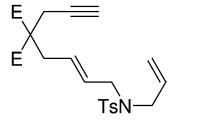
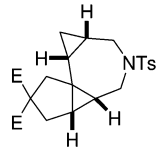
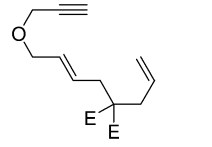
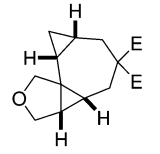
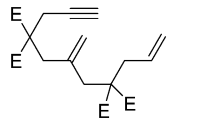
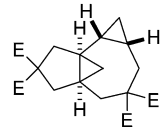
Scheme 9. $Rh_2(O_2CCF_3)_4$-Catalyzed Polycyclization of Diene-ynes



A detailed reaction mechanism will be proposed later, but the intermediacy of a cyclopropyl metal carbenoid is proposed in the skeletal reorganization of enynes. To collect experimental evidence for the intermediacy of a cyclopropyl metal carbenoid in the Rh(II)-catalyzed skeletal reorganization of enynes, an attempt to trap the cyclopropyl metal carbenoid by an intramolecular alkene using **53** was made (Scheme 9).[9a] We were pleased to succeed in trapping the cyclopropyl metal carbenoid by an intramolecular alkene to stereoselectively give the tetracyclic compound **54** in good yield. However, the cis-isomer **56** did not give the corresponding tetracyclic compound, but a complex mixture was obtained. These contrasting results can be rationalized by considering the stereochemistry of the proposed cyclopropyl metal carbenoid intermediates **55** and **57**. The carbenoid moiety in **55** is sufficiently close to react with the intramolecular alkene, since the carbenoid and the alkene, which may react, are located in the cis form in the cyclopropane ring in **55**. On the other hand, the carbenoid moiety in **57** is located too far from the alkene to undergo cyclopropanation since the carbenoid and alkene have a trans relationship.

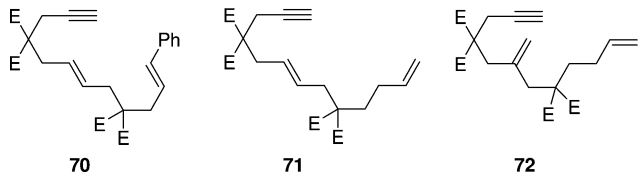
The results for the reaction of diene-ynes are shown in Table 5. The presence of a methyl, phenyl, and chloro substituent at the internal alkene carbon, as in **58**, **60**, and **62**, has little effect on the efficiency of polycyclization. Diene-ynes **64** and **66**, with a heteroatom in the tether, also underwent polycyclization to give **65** and **67**. The reaction of 6-methylene-undec-1-en-10-yne derivatives **68**, in which a second alkene moiety is attached

Table 5. $Rh_2(O_2CCF_3)_4$-Catalyzed Polycyclization of Diene-ynes[a]

diene-yne	products[b]
 **58**	 **59** 90%
 **60**	 **61** 69%
 **62**	 **63** 60%
 **64**	 **65** 45% (2 h)
 **66**	 **67** 34% (1 day)
 **68**	 **69** 51%

[a] Reaction conditions: enyne (0.5 mmol), $Rh_2(O_2CCF_3)_4$ (0.01 mmol), toluene (2.5 mL) at 80 °C for 1 h. [b] Isolated yield. [c] For 2 h. [d] For 1 day.

Scheme 10. Usual Skeletal Reorganization Occurs



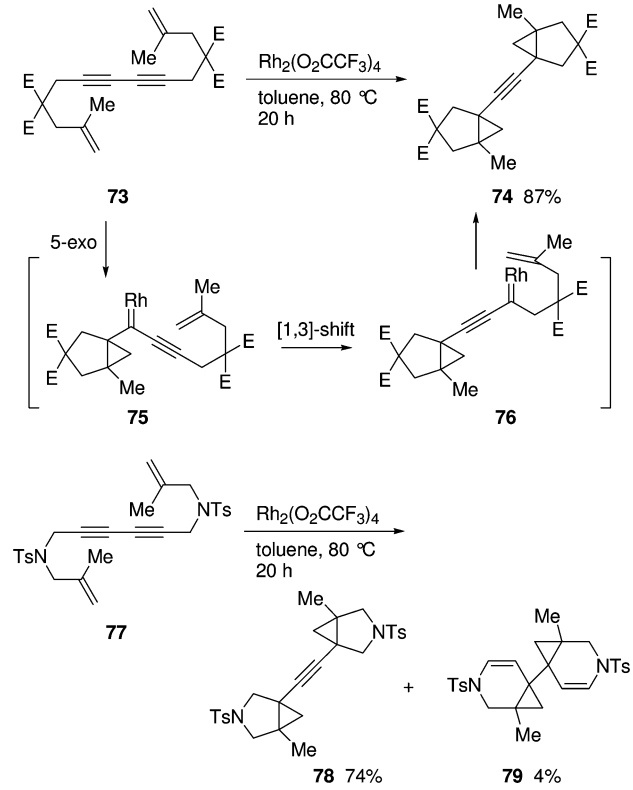
70 **71** **72**

at the internal alkene carbon, also underwent polycyclization to give the tetracyclic compounds **69**.

Compounds such as **70**, **71**, and **72** did not give the corresponding polycyclic compound, but the usual skeletal reorganization products were formed (Scheme 10). The distance between the carbenoid and alkene moiety in the proposed cyclopropyl carbenoid is an important aspect of the reaction (**53** vs **71** and **68** vs **72**).

Lee recently reported on the $PtCl_2$-catalyzed double ring-closing reaction of tetradeca-1,13-diene-6,8-diyne derivatives.[26]

Scheme 11. Additional Evidences for the Intermediacy of Cyclopropyl Carbenoid

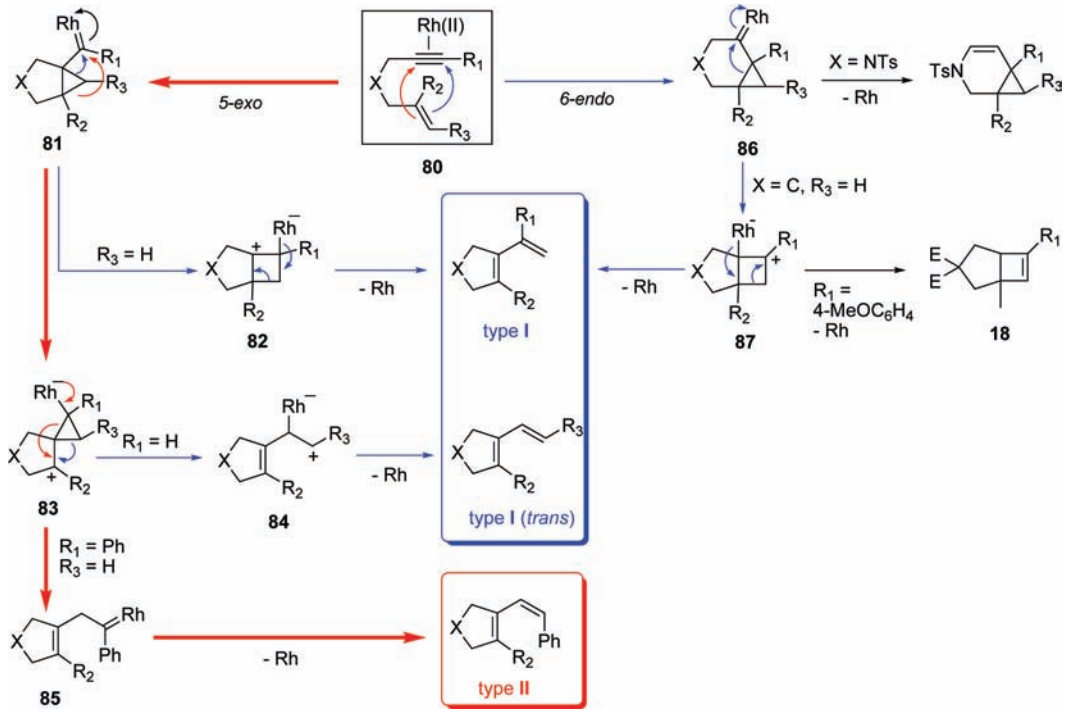


We also found that $Rh_2(O_2CCF_3)_4$ shows high catalytic activity for a similar transformation, as shown in Scheme 11. The reaction of **73** gave **74** in high yield, similar to the case of Lee's system. This involves the 5-exo cyclization of an enyne moiety leading to the production of a cyclopropyl carbenoid **75** followed by a metalotropic [1,3]-shift[27] leading to a second cyclopropyl carbenoid **76**, which undergoes cyclopropanation to give **74**. In sharp contrast to Lee's work, in which 6-endo cyclization occurred selectively when a substrate with nitrogen functionalities in the tether was used as a substrate, even **77** selectively underwent 5-exo cyclization in the presence of a rhodium catalyst to give **78**, and only trace amounts of 6-endo cyclization product **79** was formed.[28]

A proposed reaction mechanism is shown in Scheme 12. The mechanism is essentially the same as that previously proposed for the Pt(II)- and Au(I)-catalyzed reactions.[4f,12] type **I** products are formed via the mechanism depicted by blue arrows. Type **II** products are formed via the mechanism depicted by red solid arrows. The electrophilic interaction of the alkyne in **80** with Rh(II) generates a cyclopropyl rhodium carbenoid **81**, the intermediacy of which has already been proposed, based on the trapping experiments of the corresponding cyclopropyl metal carbenoids by intramolecular and intermolecular alkenes[9,10] and on DFT caluculations.[12] The carbenoid **81** undergoes rearrangement to give the cyclobutene intermediate **82** or a spiro intermediate **83**. Depending on the substitution pattern, the spiro intermediate **83** undergoes fragmentation to give either the

(26) Cho, E. J.; Kim, M.; Lee, D. *Org. Lett.* **2006**, *8*, 5413–5416.
(27) For a review on metalotropic [1,3]-shift, see: Lee, D.; Kim, M. *Org. Biomol. Chem.* **2007**, *5*, 3418–3427.
(28) The reaction of **77** under the same reaction conditions reported by Lee ($PtCl_2$ under 1 atm of CO) gave a 13:87 ratio of **78** and **79** in total 91% yield, in favor of the 6-endo product **79**.

Scheme 12. Proposed Reaction Mechanism of Skeletal Reorganization



carbocation **84** or another carbenoid **85**. The elimination of Rh(II) from **84** and **85** gives two alternative products, type **I** and type **II**, respectively. Hence, a type **I** product is formed from **82** or **84**, and a type **II** product from **85**. When $R_3 = H$, the type **I** product is formed from **82** by ring-opening, because the primary carbocation **84** is too unstable to generate. When substrates have a substitution of R_3 on the alkene carbon, **84** becomes a secondary carbocation, which is stabilized by the presence of the R_3 group, resulting in the exclusive formation of a trans-isomer, as in **4**, irrespective of the stereochemistry of the starting enynes, as shown in Table 1.

Complex **85** undergoes a 1,2-H shift to give cis-configured type **II** products.[29] Depending on the nature of R_2, the ratio of type **I** and **II** changed when $R_1 = Ph$. Thus, in the case whre $R_1 = Ph$, $R_2 = H$, and $R_3 = H$, a type **I** product is exclusively formed through **82**. In sharp contrast, the selective formation of a type **II** product is observed when $R_2 = Me$. This can be rationalized by the fact that the methyl group (R_2) stabilizes the tertiary cation in **83**, leading to the selective generation of **85**.[30]

When X = NTs, bicyclization occurred, to give the 2-aza-bicyclo[4.1.0]heptene derivative, as shown in Scheme 6 and Table 4. The involvement of a carbenoid complex **86**, generated from **80** via the 6-endo pathway, is inferred based on the formation of a 2-aza-bicyclo[4.1.0]heptene derivative. Another alternative route to type **I** products involves the ring opening of the cyclobutyl cation intermediate **87**, which is formed from **86**. The formation of **18** suggests the generation of **87**, which is stabilized by an electron-donating group, such as 4-$MeOC_6H_4$. It should be noted that, even with nitrogen or oxygen tethered enyne derivatives (**66** in Table 5 and **77** in Scheme 11), the reaction can proceed favorably by the 5-exo pathway as an initial step.

The carbenoids **81** and **86** are limited structural representations of the rapid equilibrium between **81** and **86**. The course of the reaction is determined by the relative rate of conversion from **81** or **86** or the stability of intermediates generated from **81** or **86**. This would explain the observation that enynes with a nitrogen or oxygen atom in the tether react via either the 5-exo and 6-endo pathways, depending on the structure of substrates.

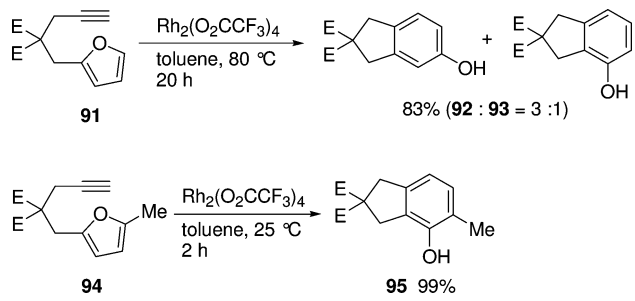
As shown in Table 2, the nature of substituents in the tether has a significant effect on the course of the reaction. The substrates having a ketal functionality in the tether, as in **19** and **21a**, has a tendency to form type **II** products in comparison with the substrates with a malonate tether, as in **14** and **15a**.

The presence of an oxy group at the properglyic position also favors the exclusive formation of type **I** products irrespective of the nature of the substituent at the alkyne carbon, as shown in Table 1. These effects of substituent groups in the tether on the product distribution are not currently clear. Irrespective of the nature of the tether or the substituents on the aromatic ring, 1,7-enynes selectively gave type **II** products, because of the unfavorable 7-endo pathway.

To examine the utility of Rh(II) for use in diverse transformations, some other cycloisomerization reactions, which would involve the electrophilic activation of alkynes as the key step, were also investigated. We were pleased to find that the reaction of alkynylfurans **91** proceeds via cyclization to give a regioisomeric mixture of phenol derivatives **92** and **93** in good yields (Scheme 13). Hashmi has extensively studied this type of reaction using Au(III) as the catalyst,[31] and Echavarren discovered that $PtCl_2$ can also be used to catalyze the same transformation and reveal mechanistic details of the reaction by observation of side products that are produced and by theoretical calculations.[32] Similar to the above cases, the presence of a methyl group at the 5-position, as in **94**, resulted in the selective

(29) Taber, D. F.; Joshi, P. V. *J. Org. Chem.* **2004**, *69*, 4276.
(30) When $R_3 = H$, the path to **83** from **84** does not occur because **84** is a primary cation.

Scheme 13. Cycloisomerization of Alkynylfurans



formation of phenol derivative **95**. In addition, the reaction of **94** was completed within 2 h, even at a temperature of 25 °C.

Conclusions

The findings reported herein demonstrate that Rh(II) complexes are also active in the skeletal reorganization of 1,6- and 1,7-enynes to 1-vinylcycloalkenes. A characteristic feature of the Rh(II)-catalyzed skeletal reorganization of enynes is the wide applicability of enynes having a substituent, such as an alkyl, aryl, chloro, and ester substituent at the alkyne carbon. Most importantly, two possible isomers of 1-vinylcycloalkenes, type **I** and type **II** products, can be obtained, the ratio of which are highly dependent on the substitution pattern of the enynes. The use of enynes having an aryl group at the alkyne carbon and a methyl group at the alkene internal carbon resulted in the exclusive formation of type **II**. The presence of an electron-withdrawing group on the phenyl ring facilitates the formation of type **II** products. The nature of the tether also has a significant effect on the course of the reaction. In addition, Rh(II) is also active in some cycloisomerization reactions of alkyne derivatives, which are known to proceed in the presence of Pt(II), Au(I), or Au(III) as catalysts.

Experimental Section

A few representative examples are listed here. Experimental procedures and spectroscopic data for new compounds can be found in the Supporting Information.

Typical Procedure for Rh(II)-Catalyzed Skeletal Reorganization. A 10-mL two-necked flask equipped with a reflux condenser connected to a N_2 line was flame-dried under a flow of N_2 and cooled to room temperature. Enyne (0.5 mmol) and Rh(II) (0.01 mmol) were added, and toluene (2.5 mL) was added via a syringe. The vessel was heated in an oil bath at 80 °C. The reaction was monitored by GC, and after it was completed, the vessel was cooled. The volatile components were removed *in vacuo*, and the residue was subjected to column chromatography on silica gel to give a product.

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Supporting Information Available: Experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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