/ Review

Creation of Novel Cyclization Methods Using *sp*-Hybridized Carbon Units and Syntheses of Bioactive Compounds

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Some recent results on the development of new and reliable procedures for the construction of diverse ring systems based on the chemistry of *sp*-hybridized species, especially allene functionality, are described. This review includes: (i) synthesis of the multi-cyclic skeletons by combination of the π -component of allene with suitable other π -components such as alkyne, alkene, or additional allene under Rh-catalyzed conditions; (ii) synthesis of heterocycles as well as carbocycles by reaction of the *sp*-hybridized center of allene with some nucleophiles in an *endo*-mode manner; and (iii) total syntheses of natural products and related compounds from the *sp*-hybridized starting materials.

Key words *sp*-hybridized carbon; allene; alkyne; cyclization; alkene; bioactive compound

Introduction

We have been investigating the chemistry of alkynes, a typical (*sp-sp*)-hybridized two carbon species, particularly focusing on the Nicholas reaction and Pauson–Khand reaction of alkyne derivatives for over two decades. Those accomplishments were summarized in several previous reviews.^{1–7)} On the other hand, another representative *sp*-hybridized substrate, the allenes (Fig. 1), have an accumulated diene structure consisting of the unique (*sp*²-*sp*-*sp*²)-hybridized three-carbon unit, which not only creates a significantly high reactivity but also provides a wide variety of possible reaction modes. We envisioned that appropriate and selective use of one (distal or proximal) of the two π -components of the allene functionality would open an alternative door for new cyclization methods. Thus we started out the project regarding the development of the new ring-closing reaction by taking advantage of the inherent properties of allenes. In this review, we summarize some successful results that have been accumulated in our laboratory during the last decade. In addition, total syntheses of bioactive compounds and their related ones using the *sp*-hybridized starting materials are described.

1. Carbonylative [2+2+1] Cycloaddition of Allenes

1.1. Carbonylative [2+2+1] Cycloaddition of Allene-Ynes The Pauson–Khand reaction is a carbonylative [2+2+1] cycloaddition of alkyne, alkene, and carbon monoxide (CO) resulting in the formation of cyclopentenone derivatives. The intramolecular version of this reaction is well

Fig. 1. Structure of an Allene

Chart 1. Intramolecular Pauson–Khand Reaction: Attempt to Synthesize a Bicyclo[5.3.0]decenone Derivative (DCE: 1,2-Dichloroethane, TBS: *tert*-Butyldimethylsilyl)

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Chart 2. Construction of the Bicyclo[m.3.0] Skeleton ($m=4, 5$) via the Intramolecular Pauson–Khand-Type Reaction of Allene-Ynes (TMS: Trimethylsilyl, Ts: *para*-Toluenesulfonyl)

known as one of the most reliable and straightforward methods for the construction of bicyclo[3.3.0]octenones **2** ($n=0$) and bicyclo[4.3.0]nonenones **2** ($n=1$) from the corresponding ene-yne **1**. However, it was found that this reaction is not applicable to the efficient preparation of larger-sized bicyclic species such as bicyclo[5.3.0]decenones **2** ($n=2$). We encountered difficulties in synthesizing the bicyclo[5.3.0] derivative **4** from the ene-yne **3**.⁸⁾ Indeed, when the Co₂(CO)₈-complexed alkyne **5**, derived from the reaction of **3** with Co₂(CO)₈, was exposed to isopropyl methyl sulfide, none of target compound **4** could be detected in the reaction mixture, and the unexpected bicyclo[4.3.0]nonenone derivative **6** was produced in a highly stereoselective manner (Chart 1).

We envisioned that the allene functionality having an accumulated diene structure would become an alternative π -component of alkene moiety in the Pauson–Khand-type [2+2+1] carbonylative cycloaddition so as to overcome the insufficiency encountered in preparation of the bicyclo[5.3.0]-

decenone **4**. During our investigations on the carbonylative [2+2+1] cycloaddition of allenes, we mainly used the 3-phenylsulfonyl-substituted allene-yne as substrates due to their ready availability as well as their ability to selectively react at the distal π -bond. Thus 8-trimethylsilyl-3-phenylsulfonyl-octa-1,2-diene-7-yne (**7**) was treated with a catalytic amount of [RhCl(CO)dppp]₂ (dppp: 1,3-bis(diphenylphosphino)propane) in refluxing toluene under CO atmosphere to afford the bicyclo[4.3.0]nonadienone **8** in 97% yield, which must have been formed by exclusively taking part in the distal double bond of allene.^{9–11)} The other possible isomer, the proximal product **9**, could not be detected. This Rh^I-catalyzed [2+2+1] carbonylative cycloaddition of allene-yne **7** could be expanded to various kinds of one-carbon homologated substrates **10** using [RhCl(CO)dppp]₂ and/or [RhCl(CO)₂]₂ leading to the efficient construction of bicyclo[5.3.0]decadienone derivatives **11**. This Rh^I-catalyzed carbonylative reaction^{9–11)} requires neither a geminal dialkyl substituent effect nor a template

Biography

Chisato Mukai was born in Toyama in 1953. He received his B.Sc. degree from Kanazawa University in 1976. After earning his Ph.D. at Osaka University in 1981, he joined Faculty of Pharmaceutical Sciences, Kanazawa University as Research Associate. He spent two years (1986–1988) at Stanford University with Professor Paul Wender as a part of his postdoctoral studies. He became Associate Professor in 1989 and Full Professor in 1998. He spent four months at Emory University as a visiting researcher in 2003. He has been the Dean of Faculty of Pharmaceutical Sciences (2007–2011) and Trustee and Vice President of Kanazawa University since 2014. He received the Takaoka Citizen Cultural Award in 1999, the Pharmaceutical Society of Japan Award for Divisional Scientific Promotions in 2002, and the Pharmaceutical Society of Japan Award in 2016. His research interests are directed toward the development of efficient reactions based on transition metals and the stereoselective total syntheses of natural products.

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effect. The ester functionality as well as hydroxyl and siloxy groups can be tolerated,^{9–11)} and both azabicyclic and oxabicyclic frameworks^{12,13)} are constructed as expected. Some examples^{9–13)} are shown in Chart 2.

Our endeavors then turned to the application of this Rh^I-

Chart 3. Construction of the Bicyclo[6.3.0] Skeleton via the Intramolecular Pauson–Khand-Type Reaction of Allene-Ynes **12** and **14**

catalyzed [2+2+1] carbonylative cycloaddition to the construction of one-carbon enlarged bicyclo[6.3.0] skeletons.¹⁴⁾ The simple linear allene-yne **12** (Z=H) and allene-yne **12** (Z=CO₂Me) in refluxing xylene underwent the ring-closing reaction to give the bicyclo[6.3.0] derivatives **13** in 23 and 43% yield, respectively. Higher yields were obtained when allene-ynes **14** (R=H and Ph) were exposed to Rh^I-catalyst to produce the benzene-fused bicyclo[6.3.0]undecadienones **15** (R=H: 90% and R=Ph: 83% yield) (Chart 3). Formation of the one-carbon shortened bicyclo[4.3.0]nonadienones was easily accomplished by this method as expected.¹⁴⁾

When the 1,3,3-trisubstituted allene derivative **16** was exposed to the standard conditions, the desired bicyclo[5.3.0] derivative **17** was obtained in 19% yield. The seven-membered triene **18** was found to be the major product (68%).^{12,13)} This drawback could immediately be solved by increase of pressure of CO. Indeed, on treatment under 10 atm of CO, **16** produced the [2+2+1] cycloaddition product **17** in 79% yield along with the triene **18** in 8% yield. The formation of triene **18** could be rationalized in terms of the intermediacy of the common rhodabicyclic species **A**, which would undergo β -hydride elimination to furnish the triene **18** through reductive elimina-

Chart 4. Intramolecular Pauson–Khand-Type Reaction of Trisubstituted Allene-Ynes

Chart 5. Thermal [2+2] Cycloaddition of Allene-Ynes

tion of the intermediate **A'**. The other successful examples^{12,13)} are depicted in Chart 4. As can be expected by consideration of the reaction mechanism, the triene **18** was exclusively formed in 83% yield when the reaction was carried out under N₂ atmosphere instead of CO. On the other hand, it should be mentioned that the bicyclo[4.2.0] frameworks **20** were easily

synthesized by heating the allene-yne **19** in xylene in the absence of Rh^I-catalyst under N₂ atmosphere. Both bicyclo[5.2.0] and bicyclo[6.2.0] derivatives¹⁵⁾ could also be produced by simple heating in xylene or mesitylene; some of these are shown in Chart 5. The formation of these bicyclo[m.2.0] compounds might be rationalized by the biradical intermediates **B**.

Chart 6. Rhodium(I)-Catalyzed Pauson–Khand-Type Reaction of Allene-Enes

Chart 7. Construction of the Bicyclo[m.3.0] ($m=5-7$) Skeleton via the Pauson–Khand-Type Reaction of Bisallenes and Diels–Alder Reaction of Trienes **31** with Dienophiles

1.2. [2+2+1] Carbonylative Cycloaddition of Allene-Enes The carbonylative [2+2+1] cycloaddition has been limited almost exclusively to the use of alkyne as one of π -components. The promising results from the carbonylative [2+2+1] cycloaddition of allene-ynes prompted us to investigate Rh^I-catalyzed carbonylative [2+2+1] cycloaddition of allene-ynes.¹⁶⁾ Based on the established conditions for allene-ynes (Charts 2 and 3), allene-ene **21** was treated with Rh^I-catalyst under 5 atm of CO in toluene at 120°C to afford the bicyclo[4.3.0]nonenone derivative **22** in 96% yield as a mixture of *trans*- and *cis*-isomers in a ratio 79:21 *via* isomerization of the initially formed **22'** by participation of the distal double bond of the allene. Alternatively, modified conditions (addition of AgBF₄ under a low CO pressure)¹⁷⁾ also worked well, in particular, when the substrates have 1,1-disubstituted alkene as exemplified by conversion of **23** into **24**. Allene-ynes having an electron-withdrawing group on the allenyl moiety such as **21** tend to produce cyclopentenone derivatives, whereas alkyl-substituted ones such as **23** afford cyclopentanone frameworks. This Rh^I-catalyzed [2+2+1] carbonylative cycloaddition of allene-ynes could be applied to the construction of not only the seven-membered bicyclo[5.3.0]decenone but also the more complex tricyclic derivative (Chart 6).

1.3. [2+2+1] Carbonylative Cycloaddition of Bisallenenes It was clearly shown that changing one of the two π -components (alkyne or alkene) of ene-ynes to an allene group led to significant improvement of yields, particularly in the case of the formation of bicyclo[5.3.0] frameworks. These results would be considered mainly due to use of the allene functionality. However, efficient formation of the corresponding eight-membered structures from allene-ynes

(and -enes) was not consistently attained except for the ones possessing template effects. We envisioned that larger-sized bicyclo[6.3.0]undecadienones might be synthesized in satisfactory yields if the two π -components of bisallene species could participate in the ring-closing process. Thus our next efforts were directed toward Rh^I-catalyzed [2+2+1] carbonylative cycloaddition of bisallenes.^{18–20)} The initial attempt was performed by treatment of bisallenes **25** with a catalytic amount of [RhCl(CO)₂]₂ or [RhCl(CO)dppp]₂ to afford the bicyclo[5.3.0]decadienones **26** in high yields. The larger-sized eight-membered bicyclo[6.3.0]undecadienones **28** were obtained from **27** in satisfactory-to-high yields.^{18–20)} A more complicated tricyclic (6/8/5) compound was prepared by this method.²¹⁾ Furthermore, it would become interesting to see whether construction of the nine-membered bicyclo[7.3.0]dodecadienone skeletons **30**²⁰⁾ would be possible using this method. The bisallene **29** was exposed to Rh^I-catalyst in refluxing xylene to give the desired **30** in a rather low yield (33%) along with the nine-membered monocyclic compound **31** possessing a bis(exo-methylene) group (17%). Exclusive formation of **31** was realized when **29** was exposed to Rh^I-catalyzed conditions under N₂ atmosphere instead of CO to furnish **31** in 96% yield.²⁰⁾ The common intermediate **C** would be considered for the production of both **30** and **31** (Chart 7). The thus formed monocyclic compound **31** subsequently underwent [4+2]-type cycloaddition with suitable dienophiles²²⁾ resulting in the formation of bicyclo[m.4.0] derivatives **32** in high yields (Chart 7).

The [2+2+1] carbonylative cycloaddition of allenes developed in our laboratory can be summarized as follows. Rh^I-catalyzed reaction of allene-ynes consistently pro-

Chart 8. Hetero-[2+2+1] Carbonylative Cycloaddition of Carbodiimide-Ynes **33** and Allene-Nitriles **35** and **37** (PMB: *para*-Methoxybenzyl, THP: 2-Tetrahydropyranyl)

duced the bicyclo[5.3.0]decadienones (seven-membered compounds) in satisfactory-to-high yields, whereas the classical Pauson–Khand reaction of ene-yne generally afforded the bicyclo[5.3.0] frameworks in unsatisfactory yields. We also showed that allene-enes produced the bicyclo[5.3.0] frameworks in good yields. However, allene-yne and allene-enes were not suitable substrates for preparation of bicyclo[6.3.0]-undecadienones (eight-membered compounds) except for specific cases where substrates have a template effect such as a benzene ring. This limitation can be completely overcome by introduction of an additional allene group to the substrates. Thus bicyclo[6.3.0]undecadienones could be obtained in high yields when bisallenes were exposed to Rh^I-catalyzed standard conditions. It should be emphasized that even nine-membered bicyclo[7.3.0]dodecadienone was also prepared, although the yield was unsatisfactory.

1.4. Hetero-[2+2+1] Carbonylative Cycloaddition The carbodiimide group is N(sp²)-C(sp)-N(sp²) functionality and regarded as an isoelectronic alternative to the allenyl moiety in the [2+2+1] carbonylative cycloaddition of allene-yne. After screening several catalytic conditions,^{23,24} we found that the pyrrolo[2,3-*b*]indol-2-one skeleton **34** could be prepared when carbodiimide-yne derivatives **33** were treated with a catalytic amount of Co₂(CO)₈ (30 mol%) and tetramethylthiourea (TMTU) (30 mol%) in toluene. Several successful examples are depicted in Chart 8. Thus it became clear that the carbodiimide functionality could serve as an alternative to the allene group in [2+2+1] carbonylative cycloaddition. On the other hand, the nitrile group, which is formally regarded as an aza-congener of an alkyne group, is frequently used as the reactive aza- π -component in the [2+2+2] cycloaddition reaction leading to pyridine derivatives. In sharp contrast to those results, the nitrile group cannot be used in the [2+2+1] carbonylative cycloaddition as π -component. We expected that a combination of nitrile with allene might work well to yield the corresponding five-membered lactams. Thus treatment of allene-nitriles **35**²⁵ with 10 mol% [RhCl(CO)dppp]₂ in toluene under CO atmosphere afforded benzo[*f*]oxyindoles **36**. This reaction could be applied to the non-benzene ring-containing aliphatic compounds **37** to produce the azabicyclo[3.3.0] derivatives **38**²⁵ (Chart 8). The larger-sized azabicyclo[*m*.3.0] derivatives (*m*=4, 5) could be constructed by this method, although their yields were low. We tentatively understood that these reactions would proceed *via* the *in situ* formed allene-ketenimine species **39** on the basis of several experiments (Chart 8).

2. Cycloaddition of Bisallenes

Benzene-1,2-bisallene and ene-bisallene species could be

prepared from the corresponding bis(propargyl alcohol)s and expected to undergo 6 π -electrocyclic reaction leading to formation of 2,3-naphthoquinodimethane and *o*-quinodimethane intermediates. On the basis of this prediction, we investigated the following reactions.

2.1. Allene–Benzene–Allenes On treatment with dialkyl(chloro)phosphanes in tetrahydrofuran (THF) under mild conditions (from –78°C to room temperature), the benzene-bridged bis(propargyl alcohol)s **40**^{26,27} underwent sequential dual formation of (propargyl ester) and its [2,3]-sigmatropic rearrangement to form the bisallene **41**, which immediately collapsed to the 2,3-naphthocyclobutene derivative **42** *via* the predicted 6 π -electrocyclic reaction and cyclobutene ring formation. Several examples are shown in Chart 9.

2.2. Allene–Ene–Allenes Based on the results in 2.1,^{26,27} we envisioned that efficient generation of *o*-quinodimethanes **44** could be realized if ene-bis(propargyl alcohol) derivatives **43** were employed as starting materials. The 1,3-diene moiety of the *in situ*-formed *o*-quinodimethanes **44** would be intramolecularly or intermolecularly captured by suitable dienophiles to afford **45**. Indeed, the ene-bis(propargyl alcohol) derivative **46**, for example, was treated with phenylsulfenyl chloride in the presence of dimethyl fumarate to provide the tetralin derivative **47** in 73% overall yield (including treatment with *meta*-chloroperoxybenzoic acid [*m*-CPBA] to simplify structure determination).^{28–30} The *o*-quinodimethane intermediate (*e.g.*, **44**) reacted with a variety of dienophiles irrespective of the properties of the olefinic counterpart,^{28–30} although it was obvious that electron-deficient olefins showed much higher reactivity than electron-rich ones. The intramolecular version of the above [4+2] cycloaddition of the ene-bis(propargyl alcohol) derivatives efficiently afforded tricyclic compounds as exemplified by transformation of **48** into **49** (Chart 10). It is noteworthy that this tandem procedure was applicable to the synthesis of steroid skeleton **50**.^{28–30}

3. Cyclization of Allenes with Counterparts Other than π -Components

3.1. Cyclization of 1-Phenylsulfonyl-1-(ω -hydroxyalkyl)-allenes and Their Related Substrates The phenylsulfonylallenes **51** (*n*=1) having a hydroxyethyl group underwent *endo*-mode ring-closing reaction^{31–33} to produce exclusively the corresponding dihydrofurans **52** (*n*=1) in 78% yield when treated with *t*-BuOK. The six- to eight-membered oxacycles **52** (*n*=2,3,4)^{31–34} could also be prepared in high yields under standard conditions. Introduction of (*Z*)-double bond on the alkyl tether of **53** enabled to construct even the nine-membered tetrahydrooxonin **54** in 66% yield.³⁴ Diethyl phospho-

Chart 9. [2+2] Cycloaddition of Allene–Benzene–Allenes **41**

Chart 10. Sequential Electrocyclization/[4+2] Cycloaddition of Allene-Ene-Allenes

Chart 11. Construction of Oxacycles Based on *endo*-Mode Cyclization of Allenes **51** and **53** Chart 12. Construction of Azacycles Based on *endo*-Mode Cyclization of Allenes **55** and **58**

nate functionality could be employed instead of phenylsulfonyl group³⁴) as an electron-withdrawing group in this reaction (Chart 11).

A similar *endo*-mode ring-closing reaction occurred when the terminal nucleophile of **51** was changed from hydroxyl group to nitrogen ones. In the case of the azide derivatives **55**,³⁵) the five- and six-membered azacyclic compounds **56** and **57** were obtained under reductive conditions; however, the seven-membered one could not be formed. On the other hand, on treatment with base, the amide derivatives **58** provided six- and seven-membered enamides **59**³⁵) (Chart 12).

This *endo*-mode ring-closing reaction was applicable to carbon analogues.^{36,37)} Indeed, the substrates **60** having an active methine moiety at the ω -position of alkyl tether produced the five- to seven-membered carbocycles **61**. Production of **61** could be tentatively interpreted by the intermediacy of the initially formed carbocycles **62**, which would easily release one of two electron-withdrawing groups. This plausible mechanism was in part supported by several additional experiments.³⁷⁾ Several examples are shown in Chart 13.

3.2. Indole Syntheses Based on Cyclization of Allenylanilines

A new procedure for the construction of the 2,3-disubstituted-indole nucleus from allenylaniline derivatives was developed based on allene chemistry. Treatment of 2-iodoanilines **63** with allenylstannanes **64** ($R' = \text{alkyl}$) under Stille coupling conditions ($\text{Pd}_2(\text{dba})_3$ [dba: dibenzylideneacetone], tri-2-furylphosphine [TFP], and tetrabutylammonium chloride) directly afforded 2,3-disubstituted indoles **66**.^{38–40)} The formation of **66** could be rationalized by initial Pd-catalyzed coupling reaction, followed by *endo*-mode ring-closing reaction of the resulting allenylaniline derivatives **65**. Indeed, **65** could be isolated under milder conditions and transformed into **66**.^{38–40)} We postulated that introduction of a suitable leaving group into R' of the allenylaniline derivatives **65** would accelerate S_N2' -type displacement by amino functionality at the *sp*-hybridized center leading to *in situ* formation of indole-2,3-quinodimethane such as **67**, which would be subsequently captured by suitable dienophiles. Thus allenylaniline **65** ($R = \text{H}$, $R' = \text{CH}_2\text{OCO}_2\text{Et}$),^{41,42)} which was prepared by the Stille coupling reaction between **63** and **64**, was treated with a catalytic amount of K_2CO_3 in toluene to give the carbazole derivatives **68**. We thereby developed a new method for generation of indole-2,3-quinodimethane (Chart 14).

3.3. Cyclization of 1-Phenylsulfonyl-1-(ω -iodoalkyl)allenes and Their Related Substrates

The terminal hydrogen of allene group is acidic when a suitable electron-withdrawing group is in residence at the 3-position. We envisioned that intramolecular trapping of allenyl anions generated by base treatment of the substrates **69**, prepared from **51** in Chart 11, might produce the corresponding cyclic compounds **70** having alkyne appendage. On the basis of our simple analysis,^{43,44)} we examined the ring-closing reaction of **69** as depicted in Chart 15. The iodo or tosylate derivatives **69** were exposed to tetra-

Chart 13. Construction of Carbocycles Based on *endo*-Mode Cyclization of Allenes **60** Chart 14. Synthesis of Indole and Carbazole Derivatives from Allenylanilines **65** (Boc: *tert*-Butoxycarbonyl) Chart 15. Ring-Closing Reaction of Allenic Anions Generated from Sulfonylallenes **69**

butylammonium fluoride (TBAF) or sodium hydride (NaH) in *N,N*-dimethylformamide (DMF) at 0 °C to furnish the three- to seven-membered carbocycles **70** in high yields. Predictably, the electron-withdrawing group on the allenyl moiety was essential in this transformation and no reaction occurred when a phenylsulfonyl group on this moiety was exchanged to alkyl groups.^{43,44)}

4. Rh-Catalyzed Cycloaddition and Cycloisomerization of Allenylcycloalkanes

4.1. [5+2] Cycloaddition of Allenylcyclopropane–Alkynes Highly strained cyclopropane derivatives have served as useful and powerful C₃-building blocks for the construction of various ring systems. In sharp contrast to the extensive investigation of the Rh^I-catalyzed [5+2] cycloaddition of vinylcyclopropanes with π -counterparts, very few examples of the ring-closing reaction of allenylcyclopropanes have been reported. We investigated the intramolecular cycloaddition of allenylcyclopropane–alkyne derivatives **71**.⁴⁵⁾ Treatment of **71** with Rh^I-catalyst effected not only the ring opening of cyclopropane but also cycloisomerization to produce bicyclo[5.4.0]-undecatrienes **72**. In some cases, small amounts of the cyclo-pentenylidene derivatives **73** were isolated. The formation of both **72** and **73** could be rationalized by the common rhodacyclohexenylidene intermediate **74**, which should arise by aid of

Chart 16. Rhodium(I)-Catalyzed [5+2] Cycloaddition of Allenylcyclopropane–Alkynes **71**

the release of the high strain energy (27.5 kcal/mol) of cyclopropane. The intermediate **74** would in turn collapse to **72** via successive insertion of alkyne group into the C–Rh bond and reductive elimination. Alternatively, direct reductive elimination of **74** must result in the production of **73**. The seven/seven-membered bicyclo[5.5.0]dodecatrienes **75** could also be prepared by this ring-closing reaction⁴⁵⁾ (Chart 16).

4.2. Cycloaddition of Allenylcyclopropane–Alkenes

The easy conversion of **71** into **72** made us imagine easy preparation of the dihydro derivatives of **72** using an alkene counterpart instead of alkyne group. Therefore we next investigated cycloaddition of allenylcyclopropanes with alkenes.⁴⁶⁾ Allenylcyclopropane–alkene **76** was exposed to 10 mol% of [RhCl(CO)₂]₂ in dioxane at 80 °C to produce bicyclo[4.3.0]-nonadiene **77** in 57% yield in an exclusively stereoselective manner. The bicyclo[5.4.0] skeleton **78**, being expected on the basis of conversion of **71** into **72**, could not be detected. We postulated that isomerization of an allyl substituent to a propenyl group would occur before (or after) forming the rhoda-

Chart 17. Rhodium(I)-Catalyzed Cycloaddition of Allenylcyclopropane-Alkenes

Chart 18. Rhodium(I)-Catalyzed Cycloaddition of Allenylcyclopropane-Alkenes **81** (Ns: *ortho*-Nitrobenzenesulfonyl)

cyclohexenylidene intermediate (e.g., **74** in Chart 16). To demonstrate our hypothesis, the internal alkene **79** (R=Me) was exposed to standard conditions to afford **77** in higher yield (87%). The corresponding (*Z*)-isomer **79'** also furnished **77** in 70% yield. Those two experiments using propenyl derivatives obviously disclosed that this transformation is highly stereoselective, but not stereospecific. The ethyl congener **79** (R=Et) gave **80** in 73% yield. In order to understand the mechanism for production of **77** from **76**, **79**, and **79'**, we performed several experiments using deuterated substrates and found that this transformation involves domino-type reaction and should provide new insights into allene chemistry⁴⁶⁾ (Chart 17).

4.3. Cycloaddition of Allenylcyclopropane-Alkenes

The observation that exchange of the reactive alkyne part of **71** by an alkene group (i.e., **76** or **79**) drastically changed the reaction pathway prompted us to investigate Rh^I-catalyzed cycloaddition of allenylcyclopropane-allenes.⁴⁷⁾ On exposure to 10 mol% $[\text{RhCl}(\text{CO})\text{dppp}]_2$ in toluene at 80°C , the allenylcyclopropane-allenes **81** were transformed into the bicyclo[5.3.0]decatrienes **82** accompanied by evolution of ethylene. The cyclopentenylidene derivatives **83** were obtained as a major product in most cases. Although the chemical yields of the 1,5,6,7-tetrahydroazulene **82** are far from satisfactory, this transformation is unique and again quite different from those of allenylcyclopropane-alkyne and -alkene derivatives. Thus cyclopropyl group on the allenyl moiety served as C₁-unit in this ring-closing reaction, which might be regarded as a new formal [5+2-2]-type cycloisomerization⁴⁷⁾ (Chart 18).

The results obtained in the cycloaddition of allenylcyclopropanes under Rh^I-catalyzed conditions can be simply summarized as follows. The allenylcyclopropane reacted with an additional π -component in the presence of Rh^I-catalyst to provide three types of products depending on the property of an additional π -counterpart. Namely, allenylcyclopropane-alkynes produced the bicyclo[5.4.0]undecatrienes *via* the [5+2]

Chart 19. Rhodium(I)-Catalyzed [6+2] Cycloaddition of Allenylcyclobutane-Alkynes **84**

cycloaddition process. The bicyclo[4.3.0]nonadiene skeletons became the major products when allenylcyclopropane-alkenes were exposed to Rh^I-catalyzed conditions. The reaction pathway of this transformation is more complicated, but highly stereoselective and non-stereospecific. In the case of allenylcyclopropane-allenes, the formal [5+2-2]-type cycloisomerization occurred with liberation of ethylene.

4.4. [6+2] Cycloaddition of Allenylcyclobutane-Alkynes

Functionalized cyclobutanes such as cyclobutanones and hydroxy- and alkylidenecyclobutanes are widely used as acyclic C₄-building blocks, whereas the simplest cyclobutane without any other functional groups on its ring is rarely employed. The easy cleavage of the unfunctionalized cyclopropane ring that was activated by the adjacent allenyl moiety (described in 4.1) prompted us to examine Rh^I-catalyzed intramolecular [6+2] cycloaddition reaction between alkyne and the one-carbon homologated allenylcyclobutane leading to the formation of bicyclo[6.4.0] frameworks.⁴⁸⁾ Conversion of allenylcyclobutane-alkyne **84** into bicyclo[6.4.0]dodecatrienes **85** could be realized by treatment with 5 mol% of $\text{RhCl}(\text{dppp})_2$ in dioxane at 80°C . The formation of **85** was tentatively interpreted by the pathway *via* the rhodabicyclo[4.3.0]nonadiene intermediate **87**. The cyclobutane ring of **87** is opened by a β -carbon elimination, which releases the ring strain energy (26.3 kcal/mol) to generate the nine-membered intermediate **88**, the reductive elimination of which would result in the formation of **85**. When the starting material **84** possesses no substituent at the allenic position (R¹=H), β -hydride elimination proceeds to produce **86** as a minor pathway. In this ring-

closing reaction, functionalized cyclobutanes were not mandatory, but the simplest cyclobutane could serve as a suitable four-carbon unit⁴⁸⁾ (Chart 19).

4.5. [7+2] Cycloaddition of Allenylcyclopentane–Alkynes Since the strain energies of the normal-sized cycloalkanes, namely cyclopentane and cyclohexane, are considered too low (6.3 and approximately 0 kcal/mol, respectively), use of these rings as acyclic C₅- or C₆-building blocks has not been reported. Encouraged by the successful development of the C_{sp³}–C_{sp³} bond activation of the simplest unactivated cyclobutane described in 4.4, we next investigated the application of this methodology to the analogous cyclopentane derivatives.⁴⁹⁾ After screening various conditions, we found that treatment of allenylcyclopentane–alkynes **89** with Wilkinson catalyst produced the bicyclo[7.4.0] compound **90** via the unprecedented C_{sp³}–C_{sp³} bond cleavage of the unactivated cyclopentane. The formation of **90** is tentatively rationalized in terms of the intermediacy of the rhodabicyclo[4.3.0]nonadiene intermediate **92**, which would be derived from the Rh^I-catalyzed cycloaddition between allene and alkyne moieties of **89**. The intermediate **92** might subsequently collapse to the bicyclo[7.4.0]tridecatriene derivatives **90** via β -carbon elimination (C_{sp³}–C_{sp³} bond activation) in good yields. Changing the Rh^I-catalyst to RhCl(dppp)₂ brought the different reaction mode to produce the spiro[2.4]heptane derivatives **91**. The formation of the spiro[2.4]heptane derivatives **91** could be explained by C γ –H elimination (C_{sp³}–H bond activation) of the common intermediate **92**⁴⁹⁾ (Chart 20).

5. Rh-Catalyzed Cycloisomerization of Benzylallene–Alkynes

In 4.4 and 4.5 we described how the unprecedented C_{sp³}–C_{sp³} bond activation of less-reactive cycloalkanes (simple cyclobutanes and cyclopentanes) could be achieved by Rh^I-catalyzed cycloadditions of **84** and **89**. On the basis of the plausible mechanisms proposed for these reactions, we thought that the allene–alkyne unit works as a highly reactive π -component toward the Rh^I-catalyst to form the common rhodabicyclic intermediate, which can activate a C–C and/or C–H bond near the Rh center. Next, we succeeded in develop-

ing another type of C–H activation of benzylallene–alkynes using this concept.⁵⁰⁾ Treatment of **93** with Rh^I-catalyst effected novel cycloisomerization to produce tricyclo[9.4.0.0^{3,8}]pentadecapentaene derivatives **94** through C_{sp²}–H bond activation. Based on deuteration and competition experiments, a reaction mechanism was proposed, which might involve a vinylidenecarbene–Rh intermediate **95**⁵⁰⁾ (Chart 21).

6. Stereospecific and Stereoselective Rh-Catalyzed [2+2+2] Cycloaddition of Allene–En–Ynes

Transition metal-catalyzed [2+2+2] cycloaddition of allene components could be a useful methodology for constructing complex skeletons; however, this has been less fully explored than the analogous reactions of alkynes or alkenes. Consideration of the rhodabicyclic intermediate of Section 4 led us to envisage that the allene–alkyne derivatives **96** possessing an additional π component would react with Rh^I-catalyst to form the intermediates **98**. Insertion of the remaining π -component into the C–Rh bond followed by reductive elimination would then afford the three-membered ring products **97**.⁵¹⁾ Treatment of **96** with [RhCl(CO)₂]₂ effected the intramolecular [2+2+2]-type ring-closing reaction to produce various tetracyclic derivatives **97** containing a cyclopropane ring. The substrates with acyclic alkenes could also be used resulting in the formation of the tricyclic derivatives. Experiments using the *trans*-alkene **99** and *cis*-alkene **100** derivatives clearly indicated that this intramolecular [2+2+2] cycloaddition is highly stereoselective as well as stereospecific⁵¹⁾ (Chart 22).

7. Total Synthesis of Natural Products and Their Related Compounds

We successfully accomplished total syntheses of more than twenty natural products and their related compounds by taking advantage of the inherent properties of the *sp*-hybridized substrates. These structures are shown in Chart 23.

Conclusion

This review briefly summarized our recent results on the development of new and reliable procedures for construction of diverse ring systems based on the chemistry of *sp*-hybrid-

Chart 20. Rhodium(I)-Catalyzed [7+2] Cycloaddition and Cyclopropanation of Allenylcyclopentane–Alkynes **89** (MOM: Methoxymethyl)

Chart 21. Rhodium(I)-Catalyzed Cycloisomerization of Benzylallene–Alkynes **93**

Chart 22. Rhodium(I)-Catalyzed [2+2+2] Cycloaddition of Allene–Enyne

Chart 23. Natural Products and Their Related Compounds Synthesized from *sp*-Hybridized Substrates

ized species, especially allene functionality. Combination of the π -component of allene with other suitable π -components such as alkyne, alkene, or additional allene under Rh-catalyzed conditions enabled us to build up multi-cyclic skeletons

that might, in general, be harder to obtain by standard procedures. On the other hand, the *sp*-hybridized center of allene tends to be attacked by some nucleophiles in an *endo*-mode manner resulting in the formation of heterocycles as well as

carbocycles. Eventually, total syntheses of natural products and their related compounds were completed using the *sp*-hybridized starting materials.

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