Ruthenium(II)-Catalyzed Isomer-Selective Cyclization of 1,6-Dienes Leading to *exo*-Methylenecyclopentanes: Unprecedented Cycloisomerization Mechanism Involving Ruthenacyclopentane(hydrido) Intermediate

Yoshihiko Yamamoto, Yu-ichiro Nakagai, Naoki Ohkoshi, and Kenji Itoh*

Contribution from the Department of Molecular Design and Engineering, and Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Chikusa, Nagoya 464-8603, Japan

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Abstract: In the presence of a catalytic amount of ruthenium(II) complexes, $[RuCl_2(cod)]_n$, $RuCl_2(cod)(MeCN)_2$, $[RuCl_2(nbd)]_n$, $[RuCl_2(CO)_3]_2$, and Cp*Ru(cod)Cl, 1,6-dienes were effectively converted into the corresponding *exo*-methylenecyclopentanes in good to excellent yields with good isomer purity in *i*-PrOH at 90 °C. The alcoholic solvent was essential for the present catalytic cyclization, and the efficiency increased in the following order: *t*-BuOH ≪ EtOH ≤ *i*-PrOH. In contrast, a Ru(0) complex, $(C_6Me_6)Ru(cod)$, catalyzed the cycloisomerization only in 1,2-dichloroethane. The unusual isomer-selectivity occurred when a 1,7-octadiene was subjected to cyclization to give a similar *exo*-methylenecyclopentane isomer as the major product. The identical isomer selectivity was observed for the cyclization of unsymmetrical 1,6-dienes having one terminal- and one internal-alkene termini. On the basis of the results from the studies using the known ruthenium hydrides and deuterium-labeling substrates, the novel mechanism via the Ru(II) ↔ Ru(IV) system involving a ruthenacyclopentane(hydrido) intermediate was proposed, which better explains the particular regiochemistry of the present cyclization than other previous mechanisms.

Introduction

Transition-metal-promoted cyclizations of α,ω-diynes and enynes are useful tools for the syntheses of carbo- and heterocycles.[1] Similar cyclization of α,ω-dienes, however, has received less attention due to their lack of reactivity compared to the above alkynyl bifunctional molecules. To realize such a diene-cyclization, the most extensively studied systems were the intramolecular reductive alkene couplings promoted by low-valent titanium or zirconium reagents.[1c,d] Although these methods provide various functionalized cyclic products after trapping a metallacyclopentane intermediate with electrophiles such as protic acids, halogens, O_2, and CO,[2] their stoichiometric nature with respect to the transition-metal complexes is a serious drawback for further improvement based on the ligand-field design. With this in mind, the titanium- or zirconium-catalyzed cyclomagnesiations and carboaluminations[3] have been developed as transition-metal-atom-economical protocols and have been successfully extended to their asymmetric versions.[4] Along this line, organolanthanide-catalyzed silylative diene-cyclizations have also been developed and applied to the natural product synthesis.[5]

Catalytic cycloisomerizations are another powerful tool for the diene-cyclization.[1b,6] This method is quite simple but highly advantageous because it requires no additional reagents except for an appropriate catalyst. *In addition, its intrinsic atom-economical nature coupled with the transition-metal catalysis*

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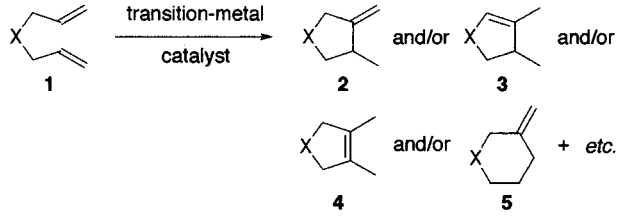
Scheme 1

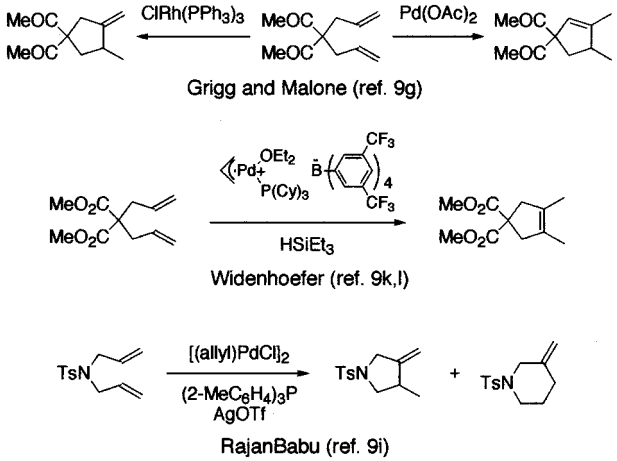


makes this protocol an environmentally benign process. A wide variety of transition metals have been employed toward this end. Titanium catalysts produced by the in situ reduction of Cp_2TiCl_2 or titanium alkoxides, and the Ziegler-type catalyst, Cp'_2ZrCl_2/MAO, have proved to effectively catalyze the cycloisomerization of α,ω-dienes.[7] An interesting example involving the C−C bond activation under scandium catalysis has also been reported by Bercaw et al.[8] In addition to the above early-transition-metal catalyses, late-transition-metal catalyses have received continuous attention because they have general applicability in organic synthesis due to their tolerance to polar functional groups.[9−12] In fact, RajanBabu et al. have recently demonstrated that a cationic nickel catalyst system converted a wide range of 1,6-dienes having an ester, amide, amine, or ether functionality into cyclic products in good to excellent yields.[9j]

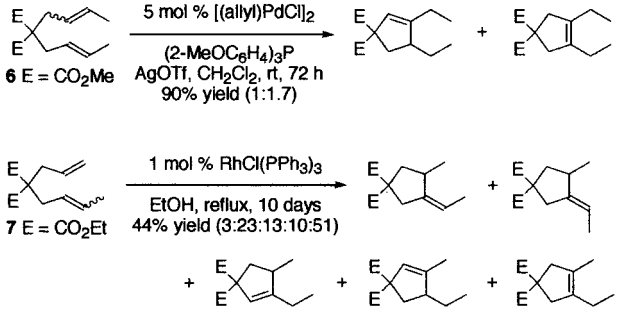
The cyclization of 1,6-dienes **1** has been the most frequently investigated since the first report by Malone et al.[9a] As shown in Scheme 1, it produces a mixture of several cyclic isomers **2**−**5** and acyclic byproducts via a sequence of simple olefin isomerizations, depending on the employed substrate and the catalyst as illustrated in Scheme 2. Among the above products, *exo*-methylenecyclopentanes **2** are fascinating synthetic intermediates because the *exo*-methylene moiety can be readily transformed to other important functionalities such as a ketone via ozonolysis, or a primary alcohol via hydroboration, etc. Rhodium- and nickel-catalysts selectively provide the *exo*-methylene isomers from terminal 1,6-dienes,[9a,d,c,f,g,i] whereas palladium catalysts predominantly furnish the more substituted olefins **3** or **4**.[9e,g,i,j,k] One drawback of the present protocols is that the presence of an internal olefin in a diene substrate diminishes the product selectivity. For example, a 2,7-nonadiene **6** gave a 1:1.7 mixture of cyclopentenes upon treatment with a cationic palladium catalyst (Scheme 3).[9i] Moreover, an unsymmetrical 1,6-octadiene **7** gave a more complex mixture of cyclic products under the rhodium catalysis, indicative of no regioselectivity (Scheme 3).[9g]

Recently, we reported the first ruthenium-catalyzed cycloisomerization of α,ω-dienes.[13,14] In striking contrast to the above examples, the ruthenium catalysis regioselectively converted the unsymmetrical 1,7-octadiene **8** or 1,6-octadiene **9a** into *exo*-methylenecyclopentane **10a** as the major product in good yields in alcoholic solvents (Scheme 4). Herein, we wish to report the detailed results of our study on the Ru-catalyzed cycloisomerization of 1,6-dienes and discuss the origin of the remarkable regioselectivity preferable to the *exo*-methylene isomer.

Scheme 2. Selected Examples of Cycloisomerization of 1,6-Dienes Catalyzed by Late Transition Metals



Scheme 3. Selected Examples of Cycloisomerization of 2,7-Nonadiene and 1,6-Octadiene



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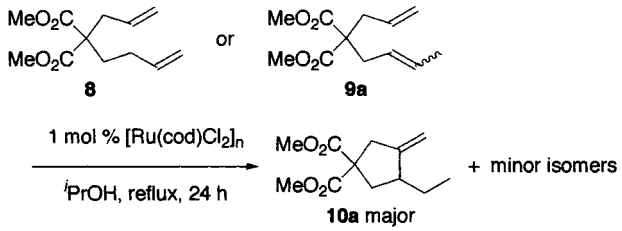
Scheme 4



Results

Recently, we[15] and others[16,17] have expanded the synthetic potential of ruthenium(II) complexes having an η^5-cyclopentadienyl-type ancillary ligand with respect to catalytic C−C bond formations. During the course of our study of the Ru(II)-catalyzed cycloaddition between 1,6-heptadiynes and norbornene,[15f] we have observed that the ring-opening-metathesis-polymerization (ROMP) product of norbornene was formed in the reaction mixture. Similarly, upon treatment of a catalytic amount of Cp*Ru(cod)Cl (Cp* = pentamethylcyclopentadienyl) *in EtOH in air*, norbornene gave the same ROMP polymer. To extend the scope of the ruthenium-catalyzed metathesis, we next applied the present catalyst system to the ring-closing metathesis of dimethyl diallylmalonate (**1a**). In the presence of 10 mol % Cp*Ru(cod)Cl, the diene **1a** was heated at 80 °C in EtOH for 24 h *in air* to afford an *exo*-methylenecyclopentane **2a** in 82% yield instead of the expected metathesis product **11** (Scheme 5). We further explored the scope, limitations, and the mechanism of the novel ruthenium-catalyzed cycloisomerization of 1,6-dienes as follows.

Optimization of Reaction Conditions and Catalysts. At the outset, the catalytic activities of various ruthenium complexes were examined with respect to the cycloisomerization of **1a**. As already mentioned, the treatment of **1a** with 10 mol % Cp*Ru(cod)Cl *in air* in refluxing EtOH afforded **2a** in good yield. The cycloisomerization was also found to proceed with other ruthenium complexes such as $RuCl_3 \cdot 3H_2O$ and $[RuCl_2(cod)]_n$ (cod = 1,5-cyclooctadiene), but $RuCl_2(PPh_3)_3$ and $[Cp^*RuCl_2]_2$ were not effective at all under the same reaction conditions. Surprisingly, the *oligomeric and almost insoluble* $[RuCl_2(cod)]_n$ exhibited the highest catalytic activity. The desired product **2a** was almost quantitatively obtained using 5 mol % $[RuCl_2(cod)]_n$.

Scheme 5

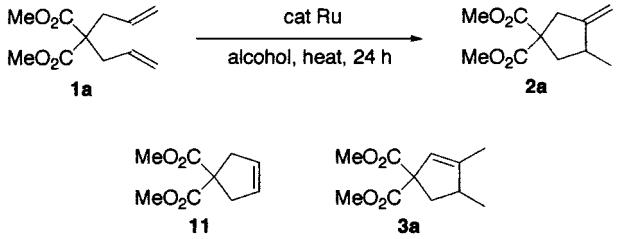


Table 1. Ru-Catalyzed Cycloisomerization of 1,6-Heptadiene **1a**[a]

entry	catalyst (mol %)	isolated yield (%)	purity (%)[b]
1	$[Ru(cod)Cl_2]_n$ (1)	89	95
2	$[Ru(cod)Cl_2]_n$ (0.1)	87	88
3	$[Ru(cod)(NCMe)_2Cl_2$ (0.1)	98	84
4	$[Ru(nbd)Cl_2]_n$ (5)	94	84
5	$[Ru(CO)_2Cl_2]_n$ (5)	89	86
6	Cp*Ru(cod)Cl (5)	94	98

[a] All reactions were carried out in *i*-PrOH under Ar at 90 °C for 24 h. [b] Purity was determined by GC analyses of the isolated product.

The alcoholic solvent plays a decisive role in the ruthenium catalysis. The cyclization did not proceed in aprotic polar and nonpolar solvents such as 1,2-dichloroethane, acetonitrile, and toluene. In addition, the catalytic activity was clearly dependent on the nature of the alcoholic solvent. In a secondary alcohol, *i*-PrOH, **2a** was obtained in 90% yield upon treatment only with 1 mol % of the catalyst at 90 °C for 24 h, whereas *tert*-BuOH, possessing no hydrogen atom α to the hydroxy group, hardly gave **2a** under the same reaction conditions. On the basis of these results, we assumed that the alcoholic solvent is required to generate a ruthenium hydride complex. In fact, benzaldehyde dibenzyl acetal was formed via oxidation of benzyl alcohol, when the reaction was carried out in benzyl alcohol as the solvent. This observation is in good agreement with the above assumption (vide infra).

The catalytic activity was further improved *in the absence of air* as summarized in Table 1. Upon treatment of **1a** with 1 mol % $[RuCl_2(cod)]_n$, the *exo*-methylenecyclopentane **2a** was obtained in 89% yield with 95% purity (entry 1). A diminished amount of the catalyst (0.1 mol %) gave **2a** in a comparable yield of 87% albeit with a slightly lower purity (entry 2). Highly soluble and monomeric $RuCl_2(cod)(MeCN)_2$ gave the best yield of 98% but the product purity was moderate (entry 3). In this case, the formation of an internal alkene **3a** was detected by ^{1}H NMR. This shows that the soluble catalyst has a higher catalytic activity compared to the insoluble ones, however, the *exo*-methylene product **2a** was subsequently isomerized to the more stable **3a**. The catalytic conversion of **2a** into **3a** was confirmed by the treatment of the isolated **2a** with $[RuCl_2(cod)]_n$ for 3 days. Other complexes, $[RuCl_2(nbd)]_n$ (nbd = norbornadiene), $[RuCl_2(CO)_3]_2$, and Cp*Ru(cod)Cl, are less effective than $[RuCl_2(cod)]_n$. Accordingly, 5 mol % of these catalysts were required for the complete conversion of the starting diene **1a** (entries 4−6). On the basis of the above results, $[RuCl_2(cod)]_n$ in *i*-PrOH proved to be the best choice of cycloisomerization catalyst.

Functional Group Compatibility. As mentioned above, the early-transition-metal-catalyzed diene-cyclizations are highly sensitive to polar functionalities such as carbonyl and cyano

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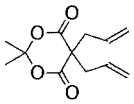
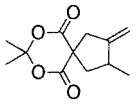
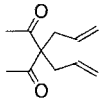
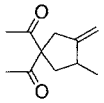
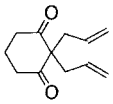
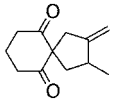
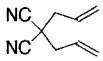
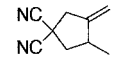
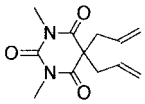
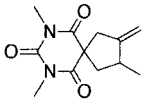
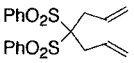
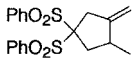
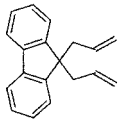
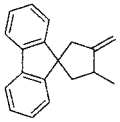
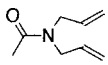
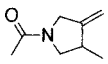
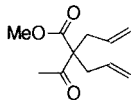
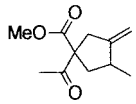
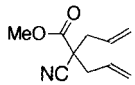
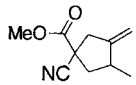
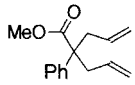
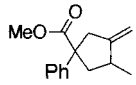
Table 2. Ru-Catalyzed Cycloisomerization of 1,6-Heptadienes **1b**−**i**, **m**−**o**[a]

1,6-heptadiene (cat. amount)	product yield (purity)[b]
 **1b** (1 mol %)	 **2b** 80% (100%)
 **1c** (1 mol %)	 **2c** 78% (93%)
 **1d** (5 mol %)	 **2d** 83% (98%)
 **1e** (5 mol %)	 **2e** 91% (99%)
 **1f** (5 mol %)	 **2f** 91% (98%)[c]
 **1g** (10 mol %)	 **2g** 97% (97%)[c]
 **1h** (5 mol %)	 **2h** 98% (88%)[c]
 **1i** (5 mol %)	 **2i** 62% (83%)
 **1m** (0.5 mol %)	 **2m** 75% (94%)[d]
 **1n** (5 mol %)	 **2n** 93% (97%)[d]
 **1o** (1 mol %)	 **2o** 95% (99%)[d]

[a] All reactions were carried out using $[Ru(cod)Cl_2]_n$ in *i*-PrOH at 90 °C for 24 h (48 h for **1g**) under Ar. [b] Purity was determined by the GC analyses of the isolated products. [c] Purity was determined by the HPLC analyses of the isolated products. [d] Diastereomer ratio were determined by ^{1}H NMR as 1:1 (**2m**), 2.8:1 (**2n**), and 1.7:1 (**2o**).

groups, whereas they are of synthetic significance. Late-transition-metal catalysts are expected to overcome such a drawback. Indeed, the cyclization of the functionalized dienes has been achieved by the palladium-catalyzed silylative cyclization[18] and the nickel-catalyzed cycloisomerization.[9i] To examine the functional group compatibility of our new protocol, 1,6-heptadienes having various functional groups at the 4-position **1b**−**i** were subjected to the cycloisomerization under the optimized reaction conditions (Table 2). In a similar manner with **1a**, a cyclic 1,3-diester **1b** gave pure **2b** in 80% yield. Ketones **1c** and **1d**, a nitrile **1e**, an amide **1f**, and a sulfone **1g** also gave cyclized products **2c**−**g** in good to high yields with high purity. In addition, a diallyl fluorene **1h** having no coordinating group underwent cycloisomerization to furnish **2h** in excellent yield. These results are in marked contrast to the

(18) (a) Widenhoefer, R. A.; DeCali, M. A. *J. Am. Chem. Soc.* **1998**, *120*, 3805. (b) Stengone, C. N.; Widenhoefer, R. A. *Tetrahedron Lett.* **1999**, *40*, 1451. (c) Widenhoefer, R. A.; Stengone, C. N. *J. Org. Chem.* **1999**, *64*, 8681. (d) Perch, N. S.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **1999**, *121*, 6960. (e) Perch, N. S.; Pei, T.; Widenhoefer, R. A. *J. Org. Chem.* **2000**, *65*, 3836. (f) Pei, T.; Widenhoefer, R. A. *Org. Lett.* **2000**, *2*, 1469.

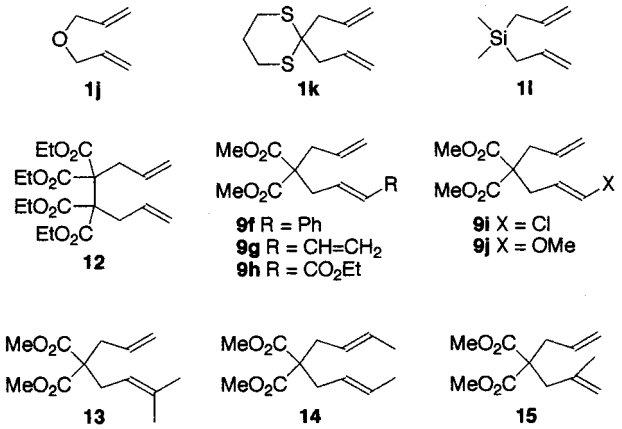


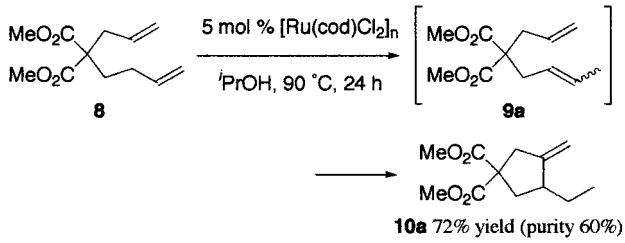
Figure 1. Dienes which failed to undergo Ru-catalyzed cycloisomerization.

palladium-catalyzed silylative cyclization, in which only dienes possessing at least one homoallylic ester, ketone, or ether group underwent cyclization.[18] Our protocol was then applied to heterocycle formations. *N*,*N*-Diallylacetoamide **1i** was converted into a *N*-acetyl pyrrolidine derivative **2i** in 62% yield with 83% purity. The diallyl ether **1j**, however, gave no cyclization product using the present ruthenium catalysis, indicative of the subsituents at the 4-position being essential for the cyclization (Figure 1). The tertiary- or secondary-centers on the tether connecting the two alkene termini might assist the cyclization due to the Thorpe−Ingold effect. This is in good accordance with the observation that the acyclic ester **1a** and ketone **1c** require a smaller amount of the catalyst for the complete conversion than their cyclic analogues **1b** and **1d**, respectively. Exceptionally, dienes **1k** and **1l** failed to cyclize, whereas they have a tertiary center at the 4-position (Figure 1). In the former case, the strong coordination by the sulfur atoms might deactivate the ruthenium catalyst. The failure of the latter might be ascribed to the elongation of the tether by the two Si−C single bonds. If this is true, the Ru-catalyzed diene-cycloisomerization is quite sensitive to the distance between the alkene termini (vide infra).

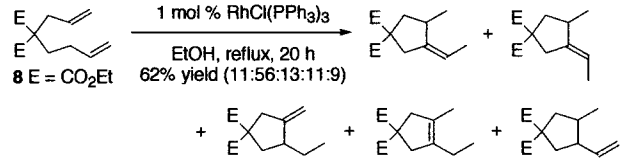
Diastereoselectivity. The stereocontrol in the diene-cyclization remains a challenging subject. Recently, diastereoselective cycloisomerizations have been reported for a few diene substrates using titanium catalysts.[7g,h] On the other hand, the diastereocontrolled diene-cycloisomerization has not yet been achieved using the late-transition-metal catalyses. With this in mind, the diastereocontrol by the ruthenium catalyst was examined with respect to dienes possessing two different substituents at the 4-position. As a result, dienes **1m**−**o** gave the cyclization products **2m**−**o** with only low diastereoselectivities ranging from 1:1 to 2.8:1 albeit in high yields and excellent purity (Table 2). The configuration of these isomers was not established.

Cyclization of 1,7-Dienes. Having elucidated the feasibility of the 1,6-heptadiene cyclization, we then investigated the cycloisomerization of the 1,7-octadienes. The expected six-membered ring product, however, was not obtained from a symmetrical 4,4,5,5-tetra(ethoxycarbonyl)-1,7-octadiene **12** (Figure 1)**.** This result clearly shows that the ruthenium-catalyzed cycloisomerization is sensitive to the distance between the alkene termini as anticipated from the failure of the cyclization of **1l**. On the other hand, an unsymmetrical 4,4-di(methoxycarbonyl)-1,7-octadiene **8** furnished the unexpected five-membered ring product **10a** as the major product (yield 72%, purity 60%: Scheme 6). The rhodium-catalyzed cycloisomerization of a similar 1,7-diene has already been reported; however, the *exo*-

Scheme 6



Scheme 7

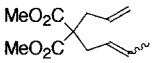
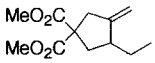
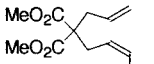
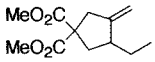
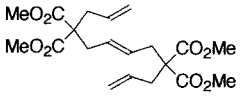
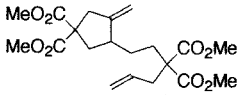
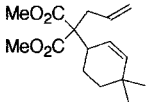
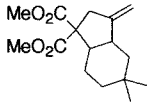
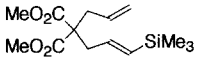
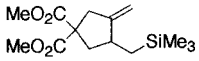


methylenecyclopentane was formed only as the minor part of the five-isomers (Scheme 7).[9g] The 1,7-diene **8** was possibly converted into **10a** via a 1,6-diene intermediate **9a**. If this is true, the following two significant features are involved in the ruthenium catalysis. First, the C−C double bond at the homoallylic position to the malonate unit was selectively isomerized to the internal allylic alkene. In other words, the methoxycarbonyl groups suppress the isomerization of the alkene placed at the allylic position under the ruthenium catalysis. The resistance of the allylic olefin toward the isomerization also plays an important role for the selective formation of the *exo*-methylenecyclopentanes **2** by avoiding the undesired conversion of **2** into the more substituted cyclopentenes **3** and **4**. Second, the thermodynamically unfavorable *exo*-methylenecyclopentane was selectively produced from the unsymmetrical 1,6-diene **9a**. Such a regioselectivity is unprecedented and in sharp contrast to that observed for the rhodium-catalyzed cycloisomerization (Scheme 3).[9g] Focusing our attention on these unique features, we further investigated the regiochemistry in the cyclization of the unsymmetrical 1,6-octadienes.

Influence of Alkene Substituent and Regioselectivity. As expected, the *trans*-rich 1,6-octadiene **9a** treated with the 5 mol % catalyst afforded the *exo*-methylenecyclopentane **10a** in 94% yield with 77% purity (Table 3). In the same manner, the *cis*-rich **9a** gave *exo*-methylenecyclopentane **10a** with a similar yield; however, the purity was lower than that with the *trans*-rich **9a**. To establish the generality of this remarkable regioselectivity, other unsymmetrical 1,6-dienes were subjected to the cycloisomerization. The transition-metal-catalyzed cascade cyclizations of polyenynes are powerful methods to construct complex polycyclic compounds only in a single operation.[19] Along this line, titanium- or zirconium-catalyzed cascade carboaluminations[3g,4c] and the yttrium-catalyzed silylative cyclization[5e] of trienes have been reported, but no example of the cascade cycloisomerization of polyenes was found so far. In this context, a 1,6,11-triene **9b** was applied to the present catalytic cycloisomerization, however, only a single-cyclization product **10b** was obtained in good yield. Using our protocol, an interesting fused bicycle **10c** was able to be synthesized from a cyclohexenyl malonate derivative **9c** with good yield and purity. Moreover, the trimethylsilyl group proved to be an excellent directing group favoring the desired *exo*-methylene isomer. Consequently, a homoallylsilane **10d** was obtained from a vinyl silane **9d** with the highest purity (93%). In contrast, unsymmetrical dienes possessing a terminal Csp^2 substituent **9f**−**h**, and a hetero substituent **9i**,**j** gave no cycloisomerization product (Figure 1).

(19) Selected examples, see: (a) Zhang, Y.; Wu, G.; Angel, G.; Negishi, E. *J. Am. Chem. Soc.* **1990**, *112*, 8590. (b) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9421. (c) Zuercher, W. J.; Scholl, M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 4291.

Table 3. Ru-Catalyzed Cycloisomerization of 1,6-Dienes **9a**−**d**[a]

diene (cat. amount)	product (isolated yield / purity)[b]
 **9a**[c] (5 mol %)	 **10a** (94% / 77%)
 **9a** (5 mol %)	 **10a** (95% / 63%)
 **9b** (10 mol %)	 **10b** (90% / 60%)[d]
 **9c** (10 mol %)	 **10c** (90% / 80%)
 **9d** (2.5 mol %)	 **10d** (94% / 93%)

[a] All reactions were carried out using $[Ru(cod)Cl_2]_n$ ($Ru(cod)(MeCN)_2Cl_2$ for **9c**) in *i*-PrOH at 90 °C for 24 h under Ar. [b] Purity was determined by the GC analyses of the isolated products. [c] *cis*/*trans* = 16/84. [d] Purity was determined by the HPLC analysis of the isolated products.

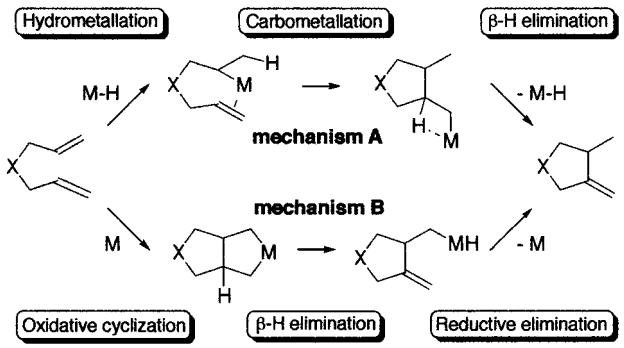


Figure 2. General mechanisms of cycloisomerization leading to *exo*-methylenecyclopentane.

As shown above, the nature of the alkene substituents plays a critical role. The Csp^3- and Si-substituents effectively control the regiochemistry. On the other hand, the Csp^2- and hetero-substituents suppress the cyclization. The substitution pattern of the alkene moiety also has a significant influence on the cyclization. The ruthenium catalyst could not cyclize a diene having a trisubsituted alkene **13**, a diene having two internal alkenes **14**, and a diene having an internal substituent **15** (Figure 1). In these cases, the dienes were recovered intact.

Reaction Mechanism. The two principal mechanisms for the formation of *exo*-methylenecyclopentane from the 1,6-dienes have been postulated as outlined in Figure 2. One involves a metal hydride species as the active catalyst (mechanism A), and the other involves a metallacycle intermediate (mechanism B). The former proceeds via a sequence of hydrometalation/carbometalation followed by β-hydride elimination regenerating the metal hydride. This mechanism is believed to operate in

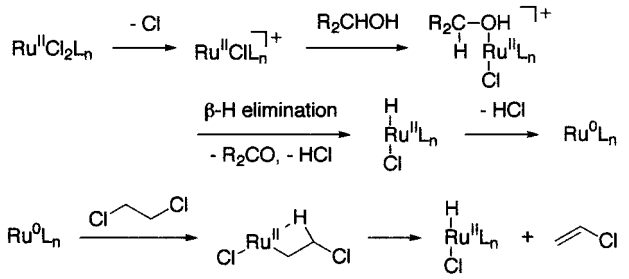
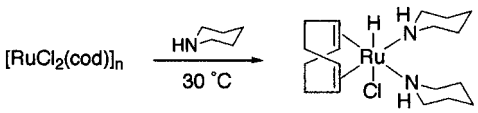


Figure 3. Generations of catalytically active species.

Scheme 8



many of the 1,6-diene cycloisomerizations.[7h,9a,d,i,g] On the other hand, the latter mechanism starts with the formation of the metallabicycle, and subsequent β-hydride elimination and reductive elimination gave the product. This mechanism was postulated for the recently reported titanium aryloxide catalysis.[7g] In our case, alcoholic solvents are essential for the generation of the active catalyst. The Ru(II)Cl_2 fragment can be reduced to Ru(0) via an intermediate complex, HRu(II)Cl (Figure 3). The resultant ruthenium(0) species might be involved in mechanism B (Figure 2). Such a possibility was, however, discarded by the following experiments using a Ru(0) complex, C_6Me_6Ru(cod). Upon treatment with the 0.5 mol % Ru(0) complex in 1,2-dichloroethane at 90 °C for 24 h, the desired product **2a** was obtained in 99% yield with 81% purity. As expected, the alcoholic solvent was not required; however, the reaction did not proceed in other solvents such as chlorobenzene with or without HCl, CH_3CN, or toluene. On the basis of these results, we envisaged that the Ru(0) complex undergoes oxidative addition to the C−Cl bond in 1,2-dichloroethane followed by β-hydride elimination to produce the HRu(II)Cl species, which acts as the net catalyst (Figure 3), although the detection of such a ruthenium hydride species was unsuccessful.

Turning our attention to the mechanism A, we searched for an active ruthenium hydride catalyst. Recently, Mori et al. have shown that RuClH(CO)$(PPh_3)_3$ effects the enyne-cycloisomerization in refluxing toluene.[14a] This hydride complex, however, hardly catalyzed the diene-cycloisomerization. Other complexes, $CpRuH(PPh_3)_2$ and $Cp^*RuH_3(PPh_3)$ also failed to effect the cyclization of **1a**. In addition to these complexes, a hydride complex supported by the 1,5-cyclooctadiene ligand, RuClH(cod)$(piperidine)_2$, was then examined as a phosphine-free hydride complex, because among the complexes having the Ru(II)Cl_2 fragment, only $RuCl_2(PPh_3)_3$ showed no catalytic activity. According to the literature, $[RuCl_2(cod)]_n$ was heated in excess piperidine at 30 °C to afford RuClH(cod)$(piperidine)_2$ as a pale-green solid (Scheme 8).[20] The existence of the hydride ligand was confirmed by the observation of the Ru−H absorption at 2048 cm^{-1} in the IR spectrum. Using this isolated hydride complex (10 mol %), **1a** was successfully converted into **2a** in 92% yield with 79% purity in toluene at 90 °C. In the same manner, the hydride catalyst quantitatively converted the unsymmetrical diene **9a** into the *exo*-methylene isomer **10a** with 67% purity. Therefore, we concluded that the net active catalyst is a coordinatively unsaturated [HRuCl] species, and the strongly coordinating phosphine ligand suppresses the cyclization.

(20) Potvin, C.; Manoli, J. M.; Pannetier, G.; Chevalier, R. *J. Organomet. Chem.* **1978**, *146*, 57.

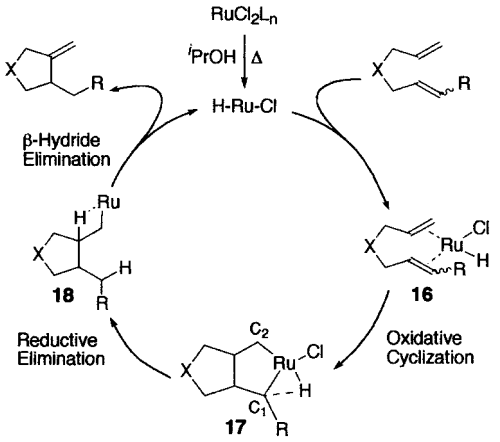
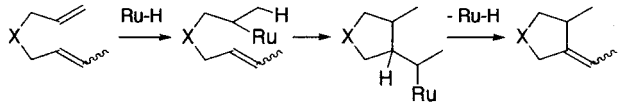
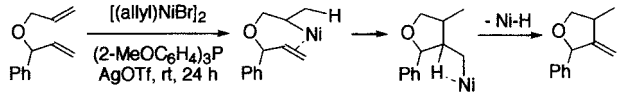


Figure 4. Plausible mechanism for the Ru-catalyzed formation of *exo*-methylenecyclopentane.

Scheme 9



Scheme 10

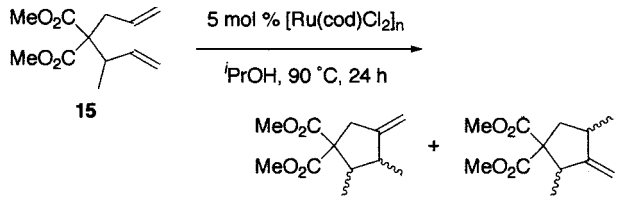


Although the active species was confirmed as the ruthenium(II) hydride, the sequential hydroruthenation/carboruthenation/β-hydride elimination mechanism cannot explain the selective formation of the *exo*-methylenecyclopentanes. Because the hydrometalation is expected to take place at the less hindered alkene, consequently, the reverse regioselectivity must result in the formation of the more stable internal *exo*-alkene as depicted in Scheme 9. In fact, the Rh-catalyzed cycloisomerization of **8** via **7** gave ethylidenecyclopentanes as the major olefin isomer (Scheme 7).

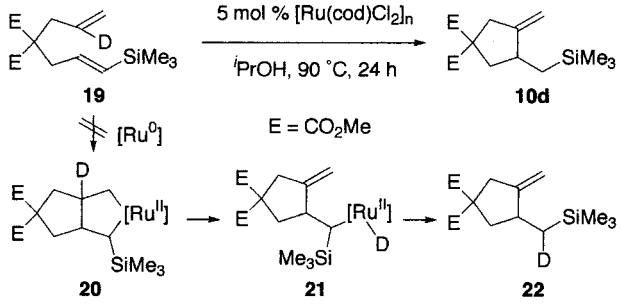
Moreover, the cationic nickel hydride has been reported to regioselectively convert an unsymmetrical diallyl ether into a tetrahydrofuran derivative (Scheme 10).[9i] This example suggested that the hydrometalation took place by avoiding the steric repulsion due to the allylic substituent. On the other hand, a diene having an allylic methyl substituent **15** was treated with the ruthenium catalyst to give regioisomers with a 1:1 ratio in our system. The related silylative cyclization initiated by the silylpalladation exhibited a similar regioselectivity with the rhodium- and nickel-hydride catalysts.[18]

These discrepancies in regiochemistry between the ruthenium-hydride catalysis and the other conventional metal hydride catalysts made us propose a novel mechanism as outlined in Figure 4. The ruthenium(II) complexes, $RuCl_2L_n$, were heated in the hydride-donor solvent *i*-PrOH to produce the [H−Ru−Cl] species supported by only labile ligands such as the solvent or COD. Therefore, this species must behave as a "naked" chlororuthenium(II) hydride, which can readily accommodate the two olefin units of the substrates simultaneously to form a hydride−diene complex **16**. As a result, the complex possessing a more labile ligand showed higher catalytic activity as summarized in Table 1. In turn, a strong coordinating ligand, PPh_3, inhibited the cyclization. In the next stage, the oxidative cyclization of **16** [Ru(II) → Ru(IV)] gave a ruthenacyclopentane(hydrido) complex **17**, in which the more substituted C_1−Ru bond is longer and weaker than the less substituted C_2−Ru bond

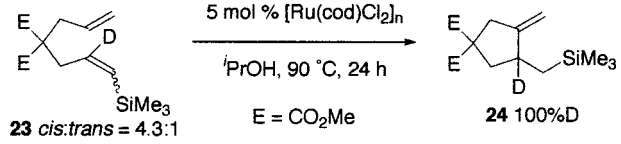
Scheme 11



Scheme 12



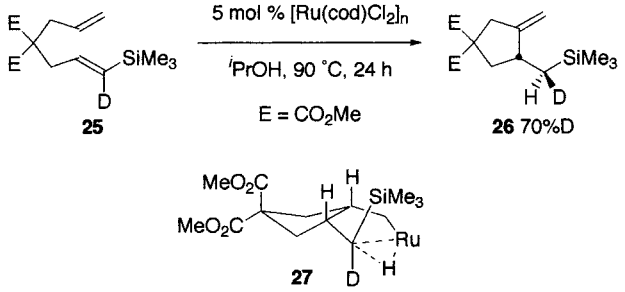
Scheme 13



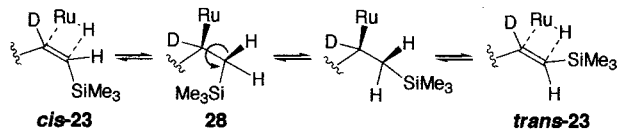
due to the steric repulsion between the substituent R and the ruthenium fragment. Consequently, the reductive elimination takes place on the more substituted side to produce **18**. This can also explain the reason why the regiochemistry was not controlled by the internal allylic substituent as shown in Scheme 11. Finally, the β-hydride elimination of [H−Ru−Cl] from **18** forms the *exo*-methylenecyclopentane.

To obtain further insight into the mechanism, deuterium-labeling studies were carried out using deuterated dienes **19**, **23**, and **25**. The diene **19** was treated with 5 mol % $[RuCl_2(cod)]_n$ in *i*-PrOH at 90 °C for 24 h to afford **10d** possessing no deuterium atom (Scheme 12). This result supports the fact that the Ru(0)-mediated oxidative cyclization mechanism via **20** and **21** does not operate in the present cyclization because the ruthenium-mediated intramolecular D-atom transfer (**19** → **22**) was not observed. This is in accordance with the ruthenium(0) complex, $C_6Me_6Ru(cod)$, that did not catalyze the cyclization of **1a** in the absence of 1,2-dichloroethane. In the same manner, the cyclization of dienes **23** (*cis*:*trans* = 4.3:1) and **25** were performed. As a result, the deuterated product **24** was obtained from **23**, indicative of no deuterium migration and no D−H exchange (Scheme 13). The incorporation of the hydrogen atom from the Ru−H species was obviously established by the conversion of **25** into **26** (Scheme 14). The cyclopentane **26** was obtained as a single diastereomer, whereas its stereochemistry was tentatively assigned based on the proposed mechanism, in which the H atom was diastereospecifically transferred from the ruthenium center to the silylmethyne carbon via a transition state **27**. It should be noted that the *cis*-rich mixture of **23** (*cis*:*trans* = 4.3:1) was treated with 10 mol % $RuClH(PPh_3)_2$ to form the *trans*-rich mixture of **23** (*cis*:*trans* = 1:10), although the formation of trace **24** was only detected by GC analysis. Accordingly, the hydroruthenation of the vinylsilane generated the alkylruthenium intermediate **28** (Scheme 15), which, however, hardly participated in the subsequent carboruthenation of the other alkene terminus leading to **24**. The partial loss of the D content of **26** was also caused by this sequence of hydroruthenation/β-hydride elimination steps depicted in Scheme 15. These facts suggest that the hydroruthenation of the Ru−H species cannot trigger the cycloisomerization. The novel cycloisomerization mechanism involving the ruthenacyclopentane(hydrido) intermediate is still speculative; however, it reasonably explains these observations and, in particular, the regiochemistry of the cycloisomerization.

Scheme 14



Scheme 15



Conclusions

We have provided a new and versatile protocol for the synthesis of functionalized *exo*-methylenecyclopentanes and a related nitrogen heterocycle via the first ruthenium-catalyzed isomer-selective cycloisomerization of 1,6-dienes and a 1,7-diene. The present method has considerable advantages compared to the known methods as follows: (1) The most effective catalyst $[RuCl_2(cod)]_n$ is readily available[21] and extremely stable in air, moisture, and light so that it can be stored for a long period and handled without special precautions. (2) No additives such as acids, alkylating agents, or other supporting ligands are required for the activation of the catalyst. (3) Environmentally less harmful alcohols can be used as the solvent without purification. (4) Synthetically useful *exo*-methylene products are selectively obtained. (5) The catalyst system is tolerant of a wide variety of functional groups including an ester, ketone, nitrile, amide, and sulfone. The most significant feature of the ruthenium catalysis is the regioselective formation of the *exo*-methylene isomers even from unsymmetrical 1,6-dienes having one terminal- and one internal-alkene termini. Such an unusual regiochemistry can be explained by the novel mechanism involving a ruthenacyclopentane(hydrido) intermediate instead of the conventional hydrometalation/carbometalation/β-hydride elimination mechanism. The involvement of the ruthenium hydride species was confirmed by the reaction using the known complex, $RuClH(cod)(piperidine)_2$, which gave the *exo*-methylenecyclopentane with identical selectivity as did the other catalyst precursors. Further deuterium-labeling studies revealed that the hydroruthenation cannot trigger the cycloisomerization.

Experimental Section

General. ^1H and ^{13}C NMR spectra were obtained for samples in $CDCl_3$ solution. Flash chromatography was performed with a silica gel column (Merck Silica gel 60) eluted with mixed solvents [hexane/ethyl acetate]. Elemental analyses were performed by the Microanalytical Center of Kyoto University. Melting points were obtained in sealed

(21) Albers, M. O.; Ashworth, T. V.; Oosthuizen, H. E.; Singleton, E. *Inorg. Synth.* **1987**, *26*, 68.

capillary tubes and are uncorrected. The isomer purities of **3a**−**f** and **8** were determined by ^{1}H NMR or GC analysis, respectively, after isolation. Gas chromatographic analyses were performed on a GLScience GC353 equipped with a GLScience Neutra Bond-1 capillary column (30 m length × 0.25 mm i.d.) with helium as carrier gas. An FID detector connected to an Jasco RC-125 integrator was used for the detection of peaks. 1,2-Dichloroethane was distilled from CaH_2, and degassed. $RuCl_3 \cdot xH_2O$ was purchased from N.E. Chemcat Corporation.

Starting Materials. $[RuCl_2(cod)]_n$,[21] Cp*Ru(cod)Cl,[22] $[RuCl_2(nbd)]_n$,[23] $Ru(cod)(MeCN)_2Cl_2$,[22] $[RuCl_2(CO)_3]_2$,[24] $RuCl_2(PPh_3)_3$,[25] $[Cp^*RuCl_2]_2$,[22] $(C_6Me_6)Ru(cod)$,[26] $RuClH(CO)(PPh_3)_3$,[27] $CpRuH(PPh_3)_2$,[28] and $Cp^*RuH_3(PPh_3)$[29] were obtained according to the literature procedures. Symmetrical dienes were prepared by the standard procedure. Other unsymmetrical dienes were obtained form dimethyl allylmalonate and an appropriate alkenyl halide or alkenyl mesylate.

Analytical data for 1f: mp 49−50 °C (eluent hexane:AcOEt = 3:1); IR (KBr) 1677 (CO) cm^{-1}; ^{1}H NMR (300 MHz) δ 2.71 (4 H, d, J = 7.5 Hz), 3.28 (6 H, s),5.02−5.14 (4 H, m), 5.51 (2 H, ddt, J = 17.1, 10.2, 7.8 Hz); ^{13}C NMR (125 MHz) δ 28.28 (2C), 43.08 (2 C), 57.19, 120.56 (2 C), 130.73 (2 C), 151.01, 170.79 (2 C); MS (FAB) *m*/*z* (rel intensity) 237 (MH^+, 100), 195 (49), 169 (41); Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.16; H, 6.89; N, 11.64.

Analytical data for 9b: oil (eluent hexane:AcOEt = 20:1); IR (neat) 1732 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz) δ 2.56−2.62 (8 H, m), 3.71 (12 H, s), 5.07−5.15 (4 H, m), 5.34 (2 H, m), 5.61 (2 H, m); ^{13}C NMR (125 MHz) δ 35.61 (2 C), 36.76 (2 C), 52.29 (4 C), 57.44 (2 C), 119.00 (2 C), 128.31 (2 C), 132.02 (2 C), 170.70 (2 C), 170.74 (2 C); MS (FAB) *m*/*z* (rel intensity) 397 (MH^+, 100), 333 (20), 273 (20), 225 (209, 165 (47); Anal. Calcd for $C_{20}H_{28}O_8$: C, 60.59; H, 7.12. Found: C, 60.54; H, 7.17.

Analytical data for 9c: oil (eluent hexane:AcOEt = 20:1); IR (neat) 1733 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz) δ 0.90 (3 H, s), 0.96 (3 H, s), 1.35−1.73 (4 H, m), 2.69 (2 H, m), 2.79 (1 H, m), 3.68 (3 H, s), 3.71 (3 H, s), 5.02−5.12 (2 H, m), 5.44 (1 H, ddd, J = 10.5, 2.4, 1.5 Hz), 5.52 (1 H, ddd, J = 10.5, 1.8, 1.5 Hz), 5.76 (1 H, ddt, J = 17.1, 10.2, 7.2 Hz); ^{13}C NMR (125 MHz) δ 21.17, 28.30, 30.80, 31.42, 36.74, 37.46, 39.63, 51.74, 52.01, 61.56, 118.27, 124.96, 133.09, 138.66, 170.55, 170.86; MS (FAB) *m*/*z* (rel intensity) 281 (MH^+, 100), 211 (47), 207 (49); Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.56; H, 8.60.

Analytical data for 9d: oil (eluent hexane:AcOEt = 20:1); IR (neat) 1734 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz) δ 0.033 (9 H, s), 2.63 (2 H, ddd, J = 7.5, 1.2, 0.9 Hz), 2.68 (2 H, d, J = 6.0 Hz), 3.70 (6 H, s), 5.05−5.12 (2 H, m), 5.58−5.89 (3 H, m); ^{13}C NMR (125 MHz) δ; −1.30, 37.13, 39.91, 52.24, 57.71, 118.93, 132.18, 135.79, 139.67, 170.92; MS (FAB) *m*/*z* (rel intensity) 285 (MH^+, 100), 269 (20), 253 (23); Anal. Calcd for $C_{14}H_{24}O_4Si$: C, 59.12; H, 8.51. Found: C, 59.21; H, 8.42.

Typical Procedure for Ru(II)-Catalyzed Cycloisomerization of 1,6-Heptadienes. To a solution of diene **1a** (212 mg, 1.0 mmol) in degassed *i*-PrOH (4 mL) was added $[RuCl_2(cod)]_n$ (2.8 mg, 1 mol %). The reaction mixture was stirred at 90 °C for 24 h under Ar. The solvent was removed, and the residue was purified by silica gel flash column chromatography (eluent hexane:AcOEt = 20:1) to give *exo*-methylenecyclopentane **2a** (195 mg, 92%) as colorless oil. The reactions of **2a** using other ruthenium complexes, and the cyclizations of other dienes were also carried out similarly. Conditions and yields were summarized in Tables 1−3. Cyclopentanes **2a**,[9i] **2c**,[9g] **2h**,[7g,h] **2i**[9b] are known compounds.

Typical Procedure for Ru(0)-Catalyzed Cycloisomerization of 1,6-Heptadiene 1a. To a solution of diene **1a** (212 mg, 1.0 mmol) in degassed 1,2-dichloroethane (4 mL) was added $(\eta^6\text{-}C_6Me_6)Ru(cod)$ (1.9 mg, 0.5 mol %). The reaction mixture was stirred at 90 °C for 24 h under N_2. The solvent was removed, and the residue was purified by silica gel flash column chromatography (eluent hexane:AcOEt = 20:1) to give **2a** (210 mg, 99%) as colorless oil.

Analytical data for 2b: oil (eluent hexane:AcOEt = 20:1); IR ($CHCl_3$) 1739 (CO) cm^{-1}; ^{1}H NMR (300 MHz) δ 1.18 (3 H, d, J = 6.6 Hz), 1.75 (3 H, s), 1.77 (3 H, s), 2.04 (1 H, dd, J = 12.5, 11.7 Hz), 2.50 (1 H, dd, J = 12.5, 8.1 Hz), 3.00 (1 H, m), 3.09 (2 H, dd, J = 3.6, 2.1 Hz), 4.90 (1 H, m), 4.97 (1 H, m); ^{13}C NMR (125 MHz) δ 16.94, 28.72, 28.91, 38.15, 44.83, 46.65, 51.30, 104.82, 105.79, 152.29, 170.57, 171.16; MS (FAB) *m*/*z* (rel intensity) 225 (MH^+, 19), 209 (100), 196 (18); Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.22; H, 7.24.

Analytical data for 2d: mp 49−50 °C (eluent hexane:AcOEt = 30:1); IR ($CHCl_3$) 1696 (CO) cm^{-1}; ^{1}H NMR (300 MHz) δ 1.07 (3 H, d, J = 6.6 Hz), 1.68 (1 H, dd, J = 12.6, 11.4 Hz), 1.85−2.10 (2 H, m), 2.33 (1 H, dd, J = 12.6, 7.8 Hz), 2.53 (1 H, m), 2.60−2.80 (4 H, m), 2.89 (2 H, dd, J = 3.6, 2.1 Hz), 4.77 (1 H, m), 4.89 (1 H, m); ^{13}C NMR (125 MHz) δ 17.17, 17.92, 37.27, 37.34, 37.50, 38.24, 42.18, 70.51, 104.95, 153.20, 207.36, 207.86; MS (FAB) *m*/*z* (rel intensity) 192 (M^+, 63), 174 (42), 164 (100); Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.96; H, 8.40.

Analytical data for 2e: oil (eluent hexane:AcOEt = 20:1); IR ($CHCl_3$) 2251 (CN) cm^{-1}; ^{1}H NMR (300 MHz) δ 1.24 (3 H, d, J = 6.6 Hz), 2.00 (1 H, dd, J = 12.6, 10.5 Hz), 2.73 (1 H, ddd, J = 12.6, 7.5, 1.8 Hz), 2.84 (1 H, m), 3.09 (1 H, dq, J = 16.5, 2.4 Hz), 3.22 (1 H, br d, J = 16.5 Hz), 5.06 (1 H, m), 5.14 (1 H, m); ^{13}C NMR (125 MHz) δ 18.01, 31.91, 36.58, 44.73, 45.67, 109.75 (2 C), 115.89, 116.08, 147.35; MS (FAB) *m*/*z* (rel intensity) 146 (M^+, 21), 131 (50), 118 (21), 104 (100); Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N, 19.16. Found: C, 74.08; H, 7.16; N, 18.74.

Analytical data for 2f: mp 49−50 °C (eluent hexane:AcOEt = 4:1); IR ($CHCl_3$) 1682 (CO) cm^{-1}; ^{1}H NMR (300 MHz) δ 1.15 (3 H, d, J = 6.6 Hz), 1.91 (1 H, dd, J = 12.4, 11.1 Hz), 2.35 (1 H, dd, J = 12.4, 7.8 Hz), 2.91 (1 H, m), 2.97 (1 H, m), 3.06 (1 H, dq, J = 16.2, 1.8 Hz), 3.31 (6 H, s), 4.88 (1 H, m), 4.95 (1 H, m); ^{13}C NMR (125 MHz) δ 17.01, 28.77, 28.98, 37.82, 42.53, 46.62, 54.80, 70.51, 105.30, 151.12, 152.84, 171.92, 172.20; MS (FAB) *m*/*z* (rel intensity) 237 (MH^+, 100), 221 (17); Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.17; H, 6.76; N, 11.76.

Analytical data for 2g: mp 138−139 °C (eluent hexane:AcOEt = 3:1); IR ($CHCl_3$) 1329, 1147 (SO_2) cm^{-1}; ^{1}H NMR (300 MHz) δ 1.08 (3 H, d, J = 6.0 Hz), 2.22 (1 H, dd, J = 17.5, 13.5 Hz), 2.74 (1 H, m), 2.75 (1 H, dd, J = 17.5, 8.2 Hz), 3.26 (2 H, br s), 4.72 (1 H, m), 4.79 (1 H, m), 7.55−7.63 (4 H, m), 7.72 (2 H, m), 7.99−8.10 (4 H, m); ^{13}C NMR (125 MHz) δ 17.31, 37.59, 38.40, 39.28, 90.84, 106.24, 128.51 (2 C), 128.56 (2 C), 130.96 (2 C), 131.02 (2 C), 134.35, 134.46, 135.97, 136.30, 150.05; MS (FAB) *m*/*z* (rel intensity) 377 (MH^+, 93), 235 (100); Anal. Calcd for $C_{19}H_{20}O_4S_2$: C, 60.61; H, 5.35. Found: C, 60.60; H, 5.36.

Analytical data for 2m: oil (eluent hexane:AcOEt = 20:1); IR (neat) 1743 (CO_2Me), 1716 (COMϵ) cm^{-1}; ^{1}H NMR (300 MHz) δ 1.09 and 1.10 (each 3/2 H, d, J = 6.6 Hz), 1.59−1.80 (1 H, m), 2.16 and 2.18 (each 3/2 H, s), 2.35−2.65 (3 H, m), 2.83−3.04 (2 H, m), 3.73 and 3.74 (each 3/2 H, s), 4.79 (1 H, m), 4.90 (1 H, m); ^{13}C NMR (125 MHz) δ 17.67 and 17.84, 25.90 and 26.42, 36.98 and 37.33, 38.83 and 38.94, 40.64 and 41.01, 52.51 and 52.60, 64.06 and 64.77, 105.24 and 105.30, 152.86 and 152.90, 172.67 and 172.89, 202.79 and 203.07; MS (FAB) *m*/*z* (rel intensity) 197 (MH^+, 100), 165 (49); Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.55; H, 8.43.

Analytical data for 2n: oil (eluent hexane:AcOEt = 10:1); IR ($CHCl_3$) 2243 (CN), 1747 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz) δ 1.18 (3 H, d, J = 6.6 Hz), 1.87 (1 H, dd, J = 12.6, 12.3 Hz), 2.50 (1 H, dd, J = 12.6, 7.2 Hz), 2.84 (1 H, m), 3.03 (2 H, m), 3.84 (3 H, s), 4.95 (1 H, m), 5.02 (1 H, m) [minor isomer δ 1.18 (3 H, d, J = 6.6 Hz), 1.93 (1 H, dd, J = 12.2, 8.8 Hz), 2.61 (1 H, m), 2.84 (1 H, m), 2.96 (1 H,

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dq, J = 16.8, 2.1 Hz), 3.14 (1 H, m), 3.83 (3 H, s), 4.92 (1 H, m), 5.02 (1 H, m)]; ^{13}C NMR (125 MHz) δ 17.46, 37.33, 42.89, 44.48, 46.13, 53.53, 107.42, 119.88, 149.91, 168.84 [minor isomer δ 18.32, 36.54, 43.11, 44.34, 46.13, 53.55, 107.20, 120.15, 150.70, 169.05]; MS (FAB) *m*/*z* (rel intensity) 180 (M^+, 100), 175 (79); Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.16; H, 7.31; N, 7.82.

Analytical data for 2o: oil (eluent hexane:AcOEt = 10:1); IR ($CHCl_3$) 1732 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz) δ 1.14 (3 H, d, J = 6.9 Hz), 1.61 (1 H, dd, J = 12.3, 11.7 Hz), 2.57 (1 H, m), 2.69 (1 H, dq, J = 16.2, 2.7 Hz), 2.99 (1 H, ddd, J = 12.3, 7.0, 2.4 Hz), 3.54 (1 H, dq, J = 16.2, 1.8 Hz), 3.61 (3 H, s), 4.84 (1 H, m), 5.00 (1 H, m), 7.23−7.39 (5 H, m) [minor isomer δ 1.10 (3 H, d, J = 6.6 Hz), 2.18 (1 H, dd, J = 11.7, 9.0 Hz), 2.39 (1 H, dd, J = 7.7, 1.5 Hz), 2.44 (1 H, m), 3.01 (1 H, m), 3.14 (1 H, dq, J = 16.5, 2.1 Hz), 3.62 (3 H, s), 4.84 (1 H, m), 5.00 (1 H, m), 7.23−7.39 (5 H, m)]; ^{13}C NMR (125 MHz) δ 18.87, 37.22, 43.20, 44.56, 52.50, 56.56, 105.45, 126.54, 126.81, 128.19, 142.72, 154.25, 175.54 [minor isomer δ 19.12, 36.07, 42.88, 44.56, 52.25, 55.63, 105.68, 126.31, 126.73, 128.26, 142.04, 154.14, 175.86]; MS (FAB) *m*/*z* (rel intensity) 231 (MH^+, 100); Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.18; H, 8.15.

Analytical data for 10a: oil (eluent hexane:AcOEt = 20:1); IR (neat) 1738 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz) δ 0.93 (3 H, t, J = 7.2 Hz), 1.20−1.38 (1 H, m), 1.60−1.76 (1 H, m), 1.79 (1 H, dd, J = 12.6, 10.2 Hz), 2.44 (1 H, m), 2.59 (1 H, ddd, J = 12.6, 7.8, 1.2 Hz), 2.91 (1 H, dq, J = 16.5, 2.4 Hz), 3.02 (1 H, dq, J = 16.5, 1.2 Hz), 3.72 (3 H, s), 3.73 (3 H, s), 4.82 (1 H, m), 4.93 (1 H, m); ^{13}C NMR (125 MHz) δ 11.70, 26.64, 39.43, 40.99, 43.80, 52.60, 52.65, 58.27, 106.05, 151.78, 172.24 (2 C); MS (FAB) *m*/*z* (rel intensity) (MH^+,); Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.49; H, 8.23.

Analytical data for 10b: oil (eluent hexane:AcOEt = 20:1); IR (neat) 1733 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz) δ 1.17 (1 H, m), 1.48 (1 H, m), 1.76 (1 H, m), 1.91 (1 H, m), 2.49 (1 H, m), 2.61 (1 H, m), 2.90 (1 H, dq, J = 17.0, 2.4 Hz), 3.02 (1 H, br d, J = 17.0 Hz), 3.71 (6 H, s), 3.72 (3 H, s), 3.73 (3 H, s), 4.80 (1 H, m), 4.94 (1 H, m), 5.04−5.16 (2 H, m), 5.62 (1 H, m); ^{13}C NMR (125 MHz) δ 27.84, 30.08, 36.96, 39.56, 40.80, 42.16, 52.36 (2 C), 52.71, 52.77, 57.46, 58.17, 106.51, 119.03, 132.23, 151.10, 171.49, 171.53, 172.03, 172.10; MS (FAB) *m*/*z* (rel intensity) 397 (MH^+, 100), 305 (75), 245 (49); Anal. Calcd for $C_{20}H_{28}O_8$: C, 60.59; H, 7.12. Found: C, 60.49; H, 7.22.

Analytical data for 10c: oil (eluent hexane:AcOEt = 20:1); IR (neat) 1733 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz) δ 0.88 (3 H, s), 0.96 (3 H, s), 1.20−1.91 (7 H, m), 2.27 (1 H, m), 2.64 (1 H, dq, J = 17.7, 1.8 Hz), 3.25 (1 H, m), 3.72 (3 H, s), 3.73 (3 H, s), 4.71 (1 H, m), 4.78 (1 H, m); ^{13}C NMR (125 MHz) δ 24.46, 25.31, 31.01, 32.92, 39.48, 40.41, 42.06, 42.18, 51.89, 52.10, 52.35, 59.90, 103.18, 150.65, 171.42, 172.12; MS (FAB) *m*/*z* (rel intensity) 281 (MH^+, 74), 211 (95), 161 (100); Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.52; H, 8.77.

Analytical data for 10d: oil (eluent hexane:AcOEt = 20:1); IR (neat) 1734 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz) δ 0.039 (9 H, s), 0.50 (1 H, dd, J = 14.5, 10.8 Hz), 1.00 (1 H, dd, J = 14.5, 3.3 Hz), 1.68 (1 H, dd, J = 12.0, 10.8 Hz), 2.52 (1 H, m), 2.62 (1 H, ddd, J = 12.6, 7.2, 1.2 Hz), 2.96 (1 H, dq, J = 16.8, 2.4 Hz), 3.04 (1 H, m), 3.72 (3 H, s), 3.74 (3 H, s), 4.83 (1 H, m), 4.89 (1 H, m); ^{13}C NMR (125 MHz) δ −0.73, 20.76, 39.22, 40.10, 42.14, 52.69, 52.71, 58.07, 105.11, 154.35, 172.07, 172.17; MS (FAB) *m*/*z* (rel intensity) 285 (MH^+, 79), 269 (100); Anal. Calcd for $C_{14}H_{24}O_4Si$: C, 59.12; H, 8.51. Found: C, 58.99; H, 8.64.

Analytical Data for Deuterium-Labeled Compounds. 19: oil (eluent hexane:AcOEt = 20:1); IR (neat) 1734 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz) δ 0.031 (9 H, s), 2.62 (2 H, s), 2.68 (2 H, d, J = 6.0 Hz), 3.70 (6 H, s), 5.10 (2 H, br s), 5.70−5.88 (2 H, m).

23: oil (eluent hexane:AcOEt = 20:1); IR (neat) 1734 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz) δ 0.012 and 0.031 (9 H, s), 2.61−2.73 (1 H, m), 2.68 (1 H, d, J = 6.0 Hz), 3.70 (6 H, s), 5.10 (2 H, br s), 5.70−5.88 (2 H, m).

24: oil (eluent hexane:AcOEt = 20:1); IR (neat) 1734 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz) δ 0.039 (9 H, s), 0.49 (1 H, d, J = 14.7 Hz), 0.99 (1 H, d, J = 14.7 Hz), 1.67 (1 H, d, J = 12.4 Hz), 2.61 (1 H, d, J = 12.4 Hz), 2.96 (1 H, dt, J = 17.1, 2.1 Hz), 3.04 (1 H, dq, J = 17.1, 1.2 Hz), 3.72 (3 H, s), 3.73 (3 H, s), 4.83 (1 H, t, J = 2.1 Hz), 4.90 (1 H, t, J = 2.1 Hz).

25: oil (eluent hexane:AcOEt = 20:1); IR (neat) 1734 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz) δ 0.031 (9 H, s), 2.63 (1 H, dt, J = 7.5, 1.2 Hz), 2.68 (1 H, d, J = 6.9 Hz), 3.70 (6 H, s), 5.07 (1 H, m), 5.12 (1 H, m), 5.65 (1 H, m), 5.81 (1 H, m).

26: oil (eluent hexane:AcOEt = 20:1); IR (neat) 1734 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz) δ 0.037 (9 H, s), 0.97 (1 H, d, J = 3.3 Hz), 1.68 (1 H, dd, J = 12.3, 10.8 Hz), 2.50 (1 H, m), 2.61 (1 H dd, J = 12.0, 7.2 Hz), 2.96 (1 H, dq, J = 17.1, 1.8 Hz), 3.04 (1 H, m), 3.72 (3 H, s), 3.74 (3 H, s), 4.82 (1 H, m), 4.89 (1 H, m).

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