Cyclization Reactions

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Rhodium(I)-Catalyzed Cycloisomerization of Alkene-Substituted Allenylcyclopropanes: Stereoselective Formation of Bicyclo-[4.3.0]nonadienes**

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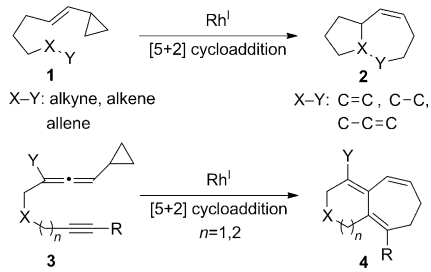
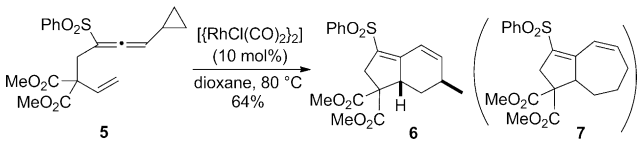
Cyclopropane undergoes facile ring opening assisted by relief of the strain energy (27.5 kcal mol^{-1})[1] and is therefore a variable acyclic C_3 building block[2] in various types of transition-metal-catalyzed reactions. Thus, the rhodium(I)-catalyzed [5+2] cycloaddition of vinyl cyclopropanes **1** with alkynes[3,4] led to the highly efficient formation of bicyclo-[5.3.0]decadienes **2** (in which X–Y is C=C; Scheme 1). This method was successfully applied to [5+2] cycloaddition



Scheme 1. Rhodium(I)-catalyzed [5+2] cycloaddition.

reactions with allenes[5] as well as alkenes[4a,5a,b,6] to produce the corresponding bicyclic compounds containing a seven-membered ring. We recently developed a rhodium(I)-catalyzed [5+2] cycloaddition of allenylcyclopropane–alkyne species **3**[7] to provide a straightforward synthesis of bicyclo-[5.4.0]undecatrienes **4** ($n=1$) and bicyclo[5.5.0]dodecatrienes **4** ($n=2$). We have now investigated the cycloaddition of allenylcyclopropanes with alkenes instead of alkynes and discovered a novel and highly stereoselective domino-type transformation into the corresponding bicyclo[4.3.0]nona-1(9),2-diene derivatives.

[{RhCl(CO)$_2$}$_2$] was a suitable catalyst for the transformation of allenylcyclopropane–alkyne substrates **3** into bicyclo[5.4.0]undecatrienes **4**.[7] Thus, when the simple vinyl derivative **5** was exposed to [{RhCl(CO)$_2$}$_2$] (10 mol%) in dioxane at 80 °C for 3 h, we observed exclusive production of the bicyclo[4.3.0] derivative **6** in 64% yield with a methyl group oriented *cis* to the hydrogen atom at the ring junction (Scheme 2). The bicyclo[5.3.0] compound **7** expected on the

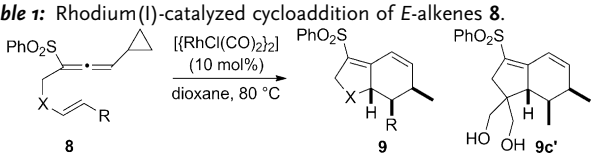


Scheme 2. Rhodium(I)-catalyzed cycloaddition of the vinyl derivative **5**.

basis of the previous results with the alkyne congeners[7] was not obtained. We screened several solvents and Rh^I catalysts, including [{RhCl(CO)dppp}$_2$] (dppp = 1,3-bis(diphenylphosphino)propane), which was another suitable catalyst for the conversion of **3** into **4**, but none of them gave a better result than that observed with [{RhCl(CO)$_2$}$_2$] in dioxane at 80 °C.

We next investigated the ring-closing reaction of the *E*-alkene derivatives **8a–d** (Table 1). The treatment of the *E*-

Table 1: Rhodium(I)-catalyzed cycloaddition of *E*-alkenes **8**.



Entry	Substrate	R	X	*t* [h]	Product (yield [%])[a]
1	**8a**	Me	$C(CO_2Me)_2$	0.2	**9a** (87)
2	**8b**	Me	$C(CH_2OMe)_2$	0.2	**9b** (88)
3	**8c**	Me	$C(CH_2O)_2CMe_2$	1	**9c** (9), **9c′** (88)
4	**8d**	Et	$C(CO_2Me)_2$	0.2	**9d** (73)

[a] Yield of the isolated product.

propenyl derivative **8a** with [{RhCl(CO)$_2$}$_2$] in dioxane produced **9a** in 87% yield (Table 1, entry 1), and the bis(methoxymethyl) compound **8b** was converted into the bicyclo[4.3.0] compound **9b** in high yield (Table 1, entry 2). In the case of the dimethyldioxacyclohexyl substrate **8c**, two bicyclic compounds were obtained in 97% total yield: the bis(hydroxymethyl) derivative **9c′** was isolated in 88% yield as the major product, and **9c** with an intact cyclic acetal moiety was obtained in 9% yield (Table 1, entry 3). When the

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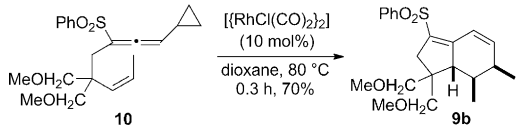
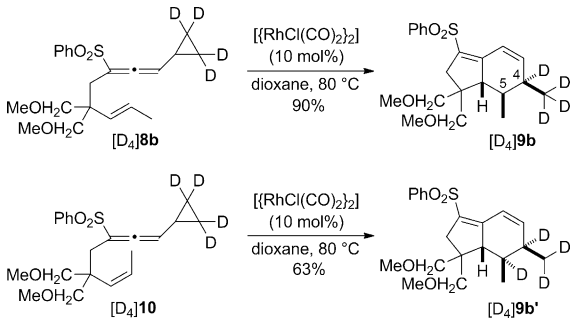
substituent on the alkene moiety was changed from a methyl to an ethyl group, the ring-closing reaction still proceeded in a similar manner to provide the corresponding ethyl derivative **9d** in 73% yield (Table 1, entry 4) with the same configuration as that of **9a–c**. Thus, it was found that substrates with an *E*-alkene substituent consistently produced bicyclo[4.3.0]nona-1(9),2-dienes **9** in a completely stereocontrolled manner in satisfactory yields. We next subjected compound **10**, the *Z*-isomer of **8b**, to the ring-closing reaction conditions to determine whether the reaction occurred in a stereospecific manner. Upon exposure to the standard conditions, compound **10** was transformed exclusively into **9b** in 70% yield (Scheme 3). This result clearly indicated that the conversion of both **8** and **10** into **9** occurred in a nonstereospecific manner, but in a completely stereoselective fashion in high yield.



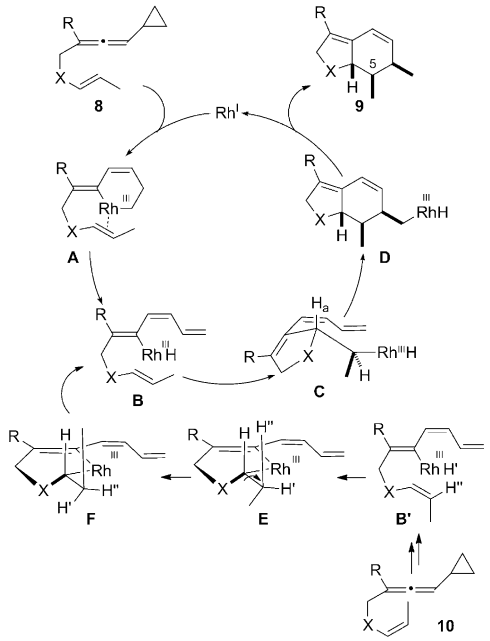
Scheme 3. Rhodium(I)-catalyzed cycloaddition of the *Z* alkene **10**.

We performed two experiments with the tetradeuterated substrates [D$_4$]**8b** and [D$_4$]**10** to obtain some information on the mechanism of the nonstereospecific but stereoselective transformation of **8b** and **10** into **9b**. Treatment of the deuterated *E*-alkene derivative [D$_4$]**8b** with [{RhCl(CO)$_2$}$_2$] under the standard conditions produced the deuterated product [D$_4$]**9b** in 90% yield. It became apparent that the four deuterium atoms were exclusively incorporated at the allylic C4 position and in the C4 methyl group of [D$_4$]**9b** as indicated in Scheme 4. In the case of the deuterated *Z*-alkene derivative [D$_4$]**10**, the product [D$_4$]**9b′** contained two deuterium atoms at the C4 and C5 positions and the other two deuterium atoms in the C4 methyl group.

These two deuteration experiments provided fairly informative insight into the mechanism of the stereoselective formation of **9** from both the *E*- and *Z*-alkene derivatives **8** and **10**. Relief of the high strain energy of the cyclopropane ring[1] would accelerate the production of the rhodacyclohexene **A** as the first step (Scheme 5).[7] β-Hydride elimination



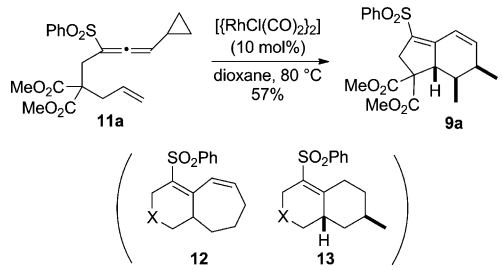
Scheme 4. Rhodium(I)-catalyzed cycloaddition of deuterated substrates [D$_4$]**8b** and [D$_4$]**10**.



Scheme 5. Plausible mechanism for the rhodium(I)-catalyzed cycloaddition of allenylcyclopropane–alkene substrates **8** and **10**.

from **A** would occur with ring opening of the rhodacyclohexene ring to provide the tetraene intermediate **B**, the C(sp^2)–Rh^{III} bond in which might insert into the double bond to form the five-membered-ring-containing triene intermediate **C**. The C(sp^3)–Rh^{III} bond in **C** could in turn insert stereoselectively into the terminal double bond from the opposite face to that occupied by H$_a$ to produce the bicyclo[4.3.0] intermediate **D**. Reductive elimination of Rh^{III} from **D** would finally give the product **9**. In the reaction of the *Z*-alkene isomer **10**, initial formation of the tetraene intermediate **B′** would be expected on the basis of a pathway similar to that for the formation of **B** from **8**. If the next insertion reaction proceeded in line with the process via the intermediates **B**, **C**, and **D**, the intermediate **B′** would be transformed into the C5 epimer of **9**. However, the exclusive production of **9** was observed. Thus, it is reasonable to consider that the Rh^{III}–H bond instead of the C(sp^2)–Rh^{III} bond of **B′** might insert into the double bond to give the six-membered rhodacycle intermediate **E**, which would undergo successive C–C bond rotation and β-hydride elimination to furnish intermediate **B**.

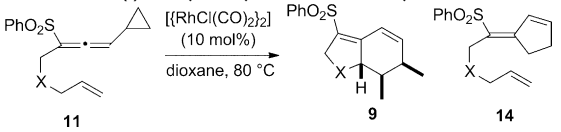
Since the rhodium(I)-catalyzed cycloisomerization of the allenylcyclopropane–alkene substrates **5**, **8**, and **10** unexpectedly produced the bicyclo[4.3.0]nona-1(9),2-dienes **6** and **9**, we next applied this novel transformation to allenylcyclopropane substrates containing an allyl group at the position X. Surprisingly, upon exposure to the standard reaction conditions ([{RhCl(CO)$_2$}$_2$] in dioxane at 80 °C, 3 h), the malonate derivative **11a** was converted in 57% yield into the bicyclo[4.3.0]nona-1(9),2-diene **9a**: the same product as that formed from the *E*-alkene derivative **8a**. Neither compound **12** nor **13**, both of which might have been predicted on the basis of the conversion of **3** ($n=1$) into **4** ($n=1$) (Scheme 1) or **5** into **6** (Scheme 2), was obtained (Scheme 6).



Scheme 6. Rhodium(I)-catalyzed cycloaddition of allyl derivative **11a**.

Other allyl substrates with a *gem*-disubstituent effect[8] were next examined (Table 2). The reaction of the bis(methoxymethyl) derivative **11b** afforded **9b** in 71% yield together with the cyclopentenylidene derivative **14b**[9] in 3%

Table 2: Rhodium(I)-catalyzed cycloaddition of allyl substrates **11**.

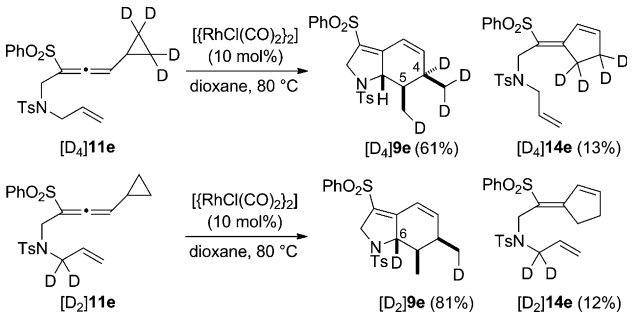


Entry	Substrate	X	*t* [h]	Product (yield [%])[a]	
1	**11b**	$C(CH_2OMe)_2$	3	**9b** (71)	**14b** (3)
2	**11c**	$C(CH_2O)_2CMe_2$	3	**9c** (54)	–
3	**11e**	NTs	3	**9e** (64)	**14e** (12)
4	**11f**	NNs	3	**9f** (45)	**14f** (23)
5	**11g**	O	4	–	**14g** (62)

[a] Yield of the isolated product. Ns = 2-nitrobenzenesulfonyl, Ts = *p*-toluenesulfonyl.

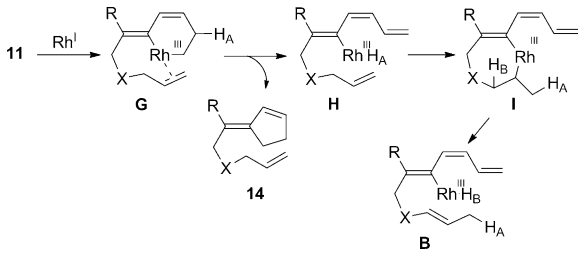
yield (Table 2, entry 1), and the dimethyldioxacyclohexyl derivative **11c** was converted into the corresponding bicyclic compound **9c** in 54% yield (entry 2). Upon exposure to the standard conditions, the nitrogen-containing substrates **11e** and **11f** were transformed into **9e** and **9f** in 64 and 45% yield, respectively, along with cyclopentenylidene derivatives **14** as by-products (Table 2, entries 3 and 4). X-ray crystallographic analysis of **9e** established its structure; thus, the bicyclo[4.3.0]nona-1(9),2-diene skeleton of compounds **6** and **9** was unambiguously confirmed. The reaction of the oxygen congener **11g** did not produce the desired product at all; instead, **14g** was obtained in 62% yield as the sole isolable product (Table 2, entry 5).

We assumed that the isomerization of the allyl group to the internal *E* double bond must occur at some point in the process, and that the resulting vinylic intermediate would then participate in the ring-closing step through the pathway indicated in Scheme 5. To obtain some information on the mechanism, we exposed the tetradeuterated substrate [D_4]**11e** to the standard reaction conditions. This reaction gave [D_4]**9e**, in which one deuterium atom was located at the C4 position and the other three deuterium atoms were distributed over the two methyl groups as shown in Scheme 7, in 61% yield. On the other hand, the dideuterated substrate [D_2]**11e** was converted into [D_2]**9e** in 81% yield, and the two deuterium atoms were found at the C6 position and in the methyl group at C4.



Scheme 7. Rhodium(I)-catalyzed cycloaddition of deuterated substrates [D_4]**11e** and [D_2]**11e**.

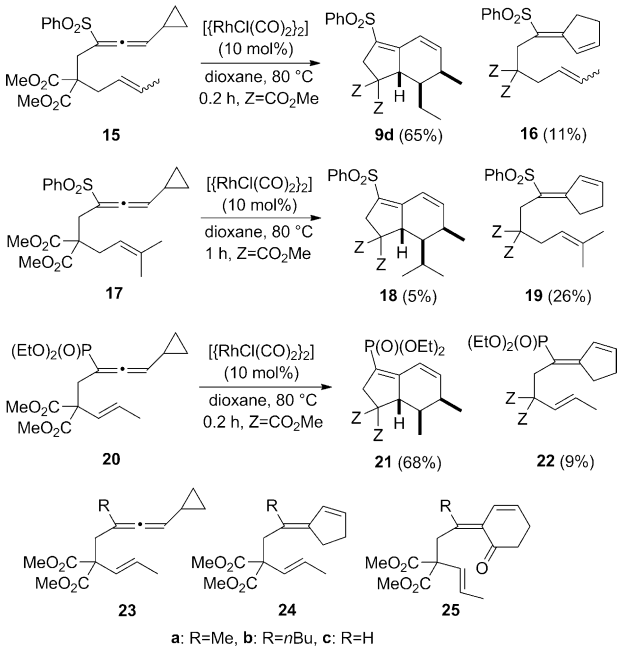
On the basis of these experiments, the isomerization of the allyl moiety of substrates **11** to an internal *E* double bond might be rationalized as follows (Scheme 8): The six-membered rhodacycle **G** would first be formed in a similar way to the formation of intermediate **A** in Scheme 5. The proposal of



Scheme 8. Plausible mechanism for the isomerization of the allyl moiety of **11** to an *E*-alkene in the presence of a Rh^I catalyst.

this step can be justified reasonably by the formation of the deuterated cyclopentenylidene derivatives [D_4]**14e** (13%) and [D_2]**14e** (12%). β-Hydride (H_A) elimination from **G** would produce intermediate **H**, the Rh^{III}–H_A bond of which might then insert into the double bond to form the seven-membered rhodacycle **I**. β-Hydride (H_B) elimination from **I** would then produce intermediate **B**, which was one of the key intermediates in the catalytic cycle depicted in Scheme 5.

We next examined the ring-closing reaction of the 2-butenyl derivative **15** to see whether the isomerization of the disubstituted alkene to another disubstituted alkene would occur (Scheme 9). When a solution of **15** as a mixture of *E*- and *Z*-isomers[10] was exposed to [{RhCl(CO)$_2$}$_2$] (10 mol%), product **9d** was obtained in 65% yield as a single isomer along with **16** (11%)[11] with *E* geometry in the cyclopentenylidiene moiety.[12] Interestingly, the 3-methyl-2-butenyl congener **17** was also converted into the bicyclic compound **18** in fairly low yield along with **19** (26%); the formation of **18** must have occurred through isomerization of the trisubstituted alkene to the less stable disubstituted alkene. The ethyl phosphonate derivative **20** behaved similarly to the corresponding phenylsulfonyl derivative **8a** to provide the bicyclic compound **21** in 68% yield together with **22** in 9% yield. However, both the methyl-substituted allene **23a** and the butyl-substituted allene **23b** failed to produce the corresponding bicyclo[4.3.0] derivatives.[13] The unsubstituted allenylcyclopropane **23c** was also shown not to be a suitable substrate for this



Scheme 9. Rhodium(I)-catalyzed cycloaddition of other allenylcyclopropane–alkene substrates.

reaction.[14] These results may indicate that electron-withdrawing groups, such as phenylsulfonyl and ethyl phosphonate groups, are essential for the construction of the bicyclo[4.3.0]nona-1(9),2-diene skeleton by this method, although a clear explanation is not possible at this time.

In summary, the treatment of allenylcyclopropane–alkene substrates with a catalytic amount of $[\{RhCl(CO)_2\}_2]$ produced unexpected *cis*-4,5-dimethylbicyclo[4.3.0]nona-1(9),2-dienes with three contiguous stereogenic centers in a highly stereocontrolled manner. The reaction was found not to be stereospecific, but to be highly stereoselective. This novel transformation is clearly different from the previously described rhodium-catalyzed reaction of the corresponding allenylcyclopropane–alkyne derivatives, in which a [5+2] cycloaddition occurred exclusively to form bicyclo[5.4.0]undecatrienes. The plausible mechanism proposed for the production of the *cis*-4,5-dimethylbicyclo[4.3.0]nona-1(9),2-dienes involves domino-type reactions and should provide new insight into allene chemistry. We are currently investigating the scope and limitations of this method as well as an asymmetric version of the transformation.

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[10] A 7:1 mixture of *E*- and *Z*-isomers was used.

[11] Compound **16** was obtained as a 7:1 mixture of *E* and *Z* isomers with respect to the 2-butenyl moiety.

[12] The cyclopentenylidenes obtained from the reaction of allenylcyclopropane–alkyne substrates **3** consistently had a *Z* configuration with respect to the *exo* double bond of the cyclopentene ring. Compounds **14**, **19**, and **22** have the *Z* geometry, in line with our previous results. However, compound **16** has the opposite, *E*, geometry. We do not yet have a reasonable explanation for these experimental results.

[13] The reaction of the methyl derivative **23a** afforded the undesired products **24a** and **25a** in 49 and 35% yield, respectively, whereas the butyl derivative **23b** was converted into **24b** in 60% yield as the sole product. The formation of **25a** could be interpreted as involving the participation of carbon monoxide on the $[\{RhCl(CO)_2\}_2]$ catalyst; see: a) M. Murakami, K. Itami, M. Ubukata, I. Tsuji, Y. Ito, *J. Org. Chem.* **1998**, *63*, 4–5; b) D. Shu, X. Li, M. Zhang, P. J. Robichaux, W. Tang, *Angew. Chem.* **2011**, *123*, 1382–1385; *Angew. Chem. Int. Ed.* **2011**, *50*, 1346–1349; c) D. Shu, X. Li, M. Zhang, P. J. Robichaux, I. A. Guzei, W. Tang, *J. Org. Chem.* **2012**, *77*, 6463–6472.

[14] The reaction of compound **23c** produced only **25c**[13] in 26% yield.