CHEMISTRY
A EUROPEAN JOURNAL

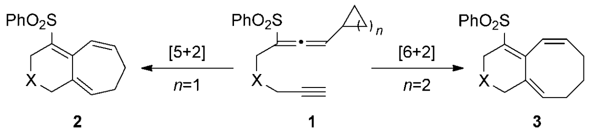
DOI: 10.1002/chem.201101441

Rh^I-Catalyzed [6+2] Cycloaddition of Alkyne–Allenylcyclobutanes: A New Entry for the Synthesis of Bicyclo[6.m.0] Skeletons

Fuyuhiko Inagaki, Katsuya Sugikubo, Yuki Oura, and Chisato Mukai*[a]

The strained cyclobutanone has been shown to serve as a unique four-carbon unit in the transition-metal-catalyzed ring-closing reaction leading to the formation of a variety of ring systems.[1] The rhodium(I)-catalyzed intramolecular [6+2] cycloaddition between 2-vinylyclobutanone and olefin moieties[2] efficiently provided the corresponding bicyclo[6.3.0]undecenones, whereas the desired eight-membered compounds could not be obtained when either the cyclobutanone was replaced by a simple unfunctionalized cyclobutane or the π counterpart was changed from the alkene to alkyne functionality. The nickel(0) catalyst was highly effective for the synthesis of the bicyclo[6.3.0]undecadienones[3] via the intermolecular [4+2+2] cycloaddition of cyclobutanones with the 1,6-diynes. The coordination of the carbonyl functionality of the cyclobutanone with the nickel catalyst is regarded as one of the significant processes in the proposed mechanism. These two transformations might indicate that some suitable functional groups, such as a carbonyl group seems to be essential for the ring cleavage of the strained four-carbon unit[4–6] during the transition-metal-catalyzed cycloaddition.

On the other hand, we recently reported that the rhodium(I)-catalyzed cycloisomerization of alkyne–allenylcyclopropanes **1** ($n=1$) effected the [5+2] ring-forming reaction[7] under rather milder conditions to afford the bicyclic seven-membered compounds **2** ($n=1$, Scheme 1). Based on the easy cleavage of the unfunctionalized cyclopropane ring that was activated by the adjacent allenyl moiety, we next postulated that the replacement of the highly strained allenylcyclopropane by the strained allenylcyclobutane might still give rise to the facile formation of the one-carbon homologated bicyclic eight-membered rings **3** ($n=2$, Scheme 1). We now report the rhodium(I)-catalyzed [6+2] cycloaddition of alkyne–allenylcyclobutanes resulting in the efficient preparation of the bicyclo[6.4.0] and bicyclo[6.3.0] frameworks, in which the functionalized cyclobutanes, such as a cyclobutanone, a hydroxycyclobutane[6,8] or a cyclobutylidene[9] unit, were not mandatory, but the simplest cyclobutane could serve as a suitable four-carbon unit.



Scheme 1. Rh^I-catalyzed cycloisomerization of alkyne–allenylcyclopropanes and alkyne–allenylcyclobutanes.

Our initial evaluation was carried out as follows: a solution of the *N*-tosyl derivative **1a**[10] was heated at 80 °C in 1,2-dichloroethane (DCE, 0.025 M) in the presence of $[RhCl(CO)_2]_2$[11] (10 mol %) for 0.2 h to afford the desired bicyclo[6.4.0]dodecatriene **3a** in 40 % yield and the monocyclic compound **4a** in 52 % yield (Table 1, entry 1). Compound **3a** became the major product (80 %) along with the formation of **4a** (16 %) when **1a** was exposed to $[RhCl(CO)dppp]_2$ in toluene[11] (Table 1, entry 2). Conversion of **1a** into **3a** could also be realized even at room temperature, although the reaction rate was significantly decreased (Table 1, entry 3). Other rhodium carbonyl catalysts gave unsatisfactory results (Table 1, entries 4–7). $[RhCl(dppp)_2]$[12] afforded the best result (84 %, Table 1, entry 10) among the examined monomeric rhodium catalysts without the carbon monoxide ligand (Table 1, entries 8–12). A decrease in loading amount of $[RhCl(dppp)_2]$ from 10 to 5 mol % led to the lower yield of **3a** (68 %) and **4a** (13 %). However, 5 mol % $[RhCl(dppp)_2]$ in dioxane at 80 °C for 0.2 h provided a similar result (**3a** (82 %) and **4a** (15 %)) to that of entry 10 (Table 1). Finally, the highest yield (87 %) of compound **3a** was unexpectedly attained when the reaction was performed in 0.1 M dioxane solution in the presence of 5 mol % $[RhCl(dppp)_2]$ for 0.2 h (see Table 2, entry 1).

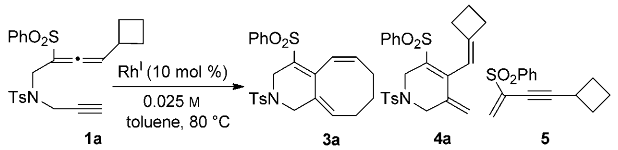
The formation of **3a** and **4a** was tentatively interpreted by the mechanism shown in Scheme 2. The first coordination of **1a** with Rh^I would occur between three components; an allenic distal double bond, an alkyne, and the carbon–carbon single bond of the strained cyclobutane ring to form the intermediate **A**, which should immediately collapse to the rhodabicyclo[4.3.0]nonadiene skeleton **B**.[2,13] The cyclobutane ring of the intermediate **B** is opened by a β-carbon elimination,[1,3] which releases the ring strain to generate the nine-membered intermediate **C**; the reductive elimination of which would result in the formation of **3a**. On the other

---

[a] Dr. F. Inagaki, K. Sugikubo, Y. Oura, Prof. Dr. C. Mukai
Division of Pharmaceutical Sciences
Graduate School of Natural Science and Technology
Kanazawa University, Kakuma-machi
Kanazawa 920-1192 (Japan)
Fax: (+81) 76-234-4410
E-mail: cmukai@kenroku.kanazawa-u.ac.jp

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201101441.

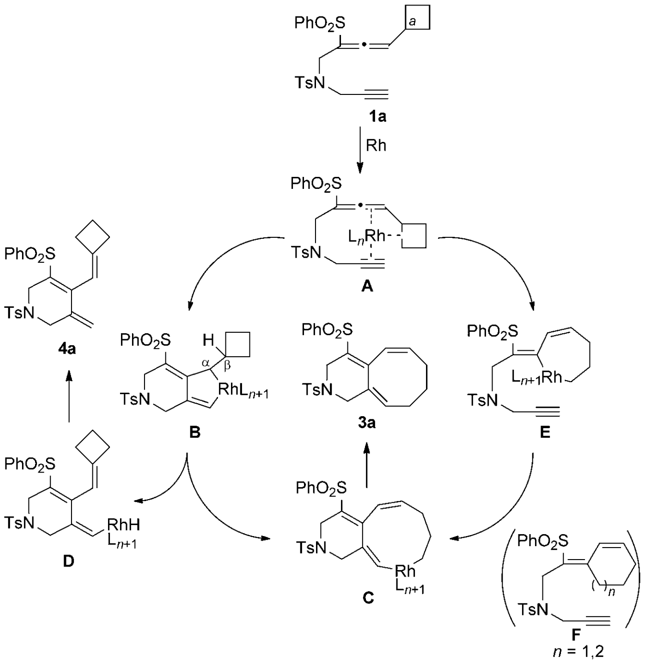
Table 1. Cycloaddition reaction of alkyne–allenylcyclobutane **1a** in the presence of various Rh catalysts.[a]



Entry	Catalyst	t [h]	Product and Yield [%][b]	
1[c]	[RhCl(CO)$_2$]$_2$	0.2	**3a**: 40	**4a**: 52
2	[RhCl(CO)dppp]$_2$	0.2	**3a**: 80	**4a**: 16
3[d]	[RhCl(CO)dppp]$_2$	33	**3a**: 16	
4	[RhCl(CO)dppm]$_2$	0.2	**3a**: 24	**4a**: 66
5	[RhCl(CO)dppe][e]	0.2	**3a**: 64	**4a**: 23
6	[RhCl(CO)dppb]$_2$	1	**3a**: 48	**4a**: 52
7	[RhCl(cod)]$_2$	7	**3a**: 17	**4a**: 81
8	[RhCl(dppm)$_2$]	12	**3a**: 25	**4a**: 55
9	[RhCl(dppe)$_2$]	0.5	**4a**: 48	**5**: 50
10[f,g]	[RhCl(dppp)$_2$]	0.2	**3a**: 84	**4a**: 16
11	[RhCl(dppb)$_2$]	0.5	**3a**: 40	**4a**: 43
12[h]	[RhCl(PPh$_3$)$_3$]	0.2	**3a**: 25	**4a**: 73

[a] A solution of **1a** in toluene (0.025 M solution) was heated at 80 °C in the presence of Rh catalyst (10 mol %). [b] Yield of isolated product. [c] Reaction was performed in 1,2-dichloroethane (DCE). [d] Reaction was carried out at room temperature. [e] 20 mol % of Rh catalyst was used. [f] [RhCl(dppp)$_2$] (5 mol %) in toluene gave **3a** (68 %) and **4a** (13 %). [g] When the reaction was carried out in dioxane in the presence of [RhCl(dppp)$_2$] (5 mol %), **3a** (82 %) was obtained together with **4a** (15 %). [h] When the reaction was carried out in the presence of AgOTf, **3a** (30 %) and **4a** (66 %) were obtained. No significant difference between chemical yield of **3a** with and without AgOTf could be observed. Ts = p-toluenesulfonyl; dppp = 1,3-bis(diphenylphosphino)propane; dppm = 1,1-bis(diphenylphosphino)methane; dppe = 1,2-bis(diphenylphosphino)ethane; dppb = 1,2-bis(diphenylphosphino)butane; cod = 1,5-cyclooctadiene.

hand, the β-hydride elimination, instead of the β-carbon elimination of the common intermediate **B**, must produce the intermediate **D**, which should give **4a** through the reductive elimination step. Another plausible mechanism might involve the rhodacycloheptene intermediate **E**, which should be derived from the intermediate **A** through ring-opening of the cyclobutane. The insertion reaction of the sp^2 C–Rh^{III} bond of **E** into the triple bond leading to the intermediate **C**.[14–16] The previously reported Rh^I-catalyzed [5+2] cycloaddition of alkyne–allenylcyclopropane[7] produced cyclopentenylidene derivatives **F** (n = 1) as a byproduct which would strongly rationalize this pathway (**A**→**E**→**C**). However, in the case of **1a**, the corresponding cyclohexenylidene derivative **F** (n = 2) could not be detected. Thus, the reaction path via the intermediate **B** would be more understandable than the one via intermediate **E**.

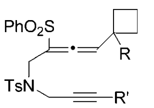
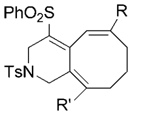
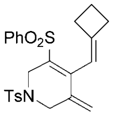
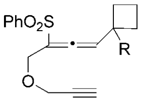
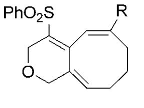
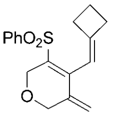
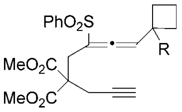
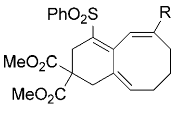
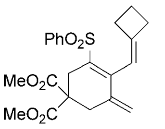
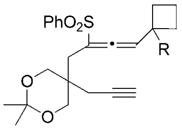
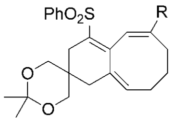
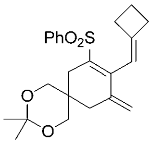
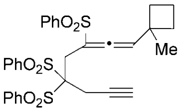
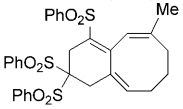
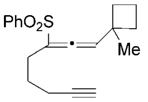
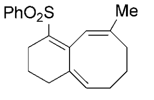
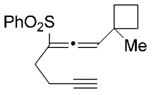
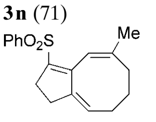
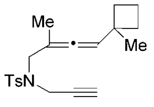
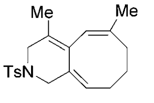


Scheme 2. Plausible mechanism for the formation of **3** and **4**.

If the starting material **1a** possesses a substituent at the allenic position a (Scheme 2), an unfavorable β-hydride elimination of the intermediate B might be completely retarded. As a matter of fact, the methyl derivative **1b** was exposed to the optimized conditions ([RhCl(dppp)$_2$] (5 mol %), and dioxane (0.1 M) solution at 80 °C) to produce the desired eight-membered product **3b** in 98 % yield (Table 2, entry 2). The butyl derivative **3c** (76 %) was also obtained as the sole product, although the reaction time was rather longer (Table 2, entry 3). The benzyloxymethyl and ethoxycarbonyl derivatives **1d** and **1e** exclusively gave **3d** and **3e** in 85 and 67 % yields, respectively (Table 2, entries 4 and 5). This ring-closing reaction was found to be applicable to the internal alkyne species and **3f** was obtained in 91 % yield (Table 2, entry 6). The oxygen congeners **1g** and **1h** revealed behaviors similar to those of **1a** and **1b** (Table 2, entries 7 and 8). It was shown that the carbon homologues **1i** and **1k**, without a substituent at the allenic position a, tend to produce significant amounts of the β-hydride elimination products **4i** and **4k** (37 and 21 % yields, respectively, Table 2, entries 9 and 11) compared with those the nitrogen and oxygen species **1a** and **1g**.[17] The introduction of a methyl group at the allenic position a (**1j** and, **1l**, and **1m**) again led to the efficient production of the eight-membered products **3j**, **3l**, and **3m** in high yields as expected (Table 2, entries 10, 12, and 13). It is noteworthy that the simple carbon analogue **1n**, which does not possess the geminal disubstituted effect[18] on the carbon tether, such as **1j**, **l**, or **m**, produced the corresponding bicyclo[6.4.0]dodecatriene **3n** in an acceptable yield[19] (Table 2, entry 14).

The one-carbon shortened substrate **6** was also efficiently transformed into the bicyclo[6.3.0]undecatriene derivative **7**[20] in a high yield (> 99 %) under the standard conditions (Table 2, entry 15). Thus, it became clear that alkyne–allenylcyclobutanes possessing a substituent at the allenic position consistently produced the bicyclo[6.4.0]dodecatrienes and bicyclo[6.3.0]undecatriene in high yields. Finally, the phenylsulfonyl group on the allenyl moiety was shown not to be mandatory for this efficient ring-closing reaction. Indeed, compound **8** gave the bicyclic derivative **9** in a high yield (> 99 %) under dioxane heated at reflux for 0.5 h (Table 2, entry 16).

Table 2. Rh^{I}-catalyzed [6+2] cycloaddition reaction of alkyne–allenylcyclobutanes.[a]

Entry	Substrate	Product (yield [%])[b]		t [h]
				
1	**1a**: R = R′ = H	**3a**: R = R′ = H (87)	**4a** (13)	0.2
2	**1b**: R = Me, R′ = H	**3b**: R = Me, R′ = H (98)		0.2
3	**1c**: R = *n*Bu, R′ = H	**3c**: R = *n*Bu, R′ = H (76)		7
4	**1d**: R = CH$_2$OBn, R′ = H	**3d**: R = CH$_2$OBn, R′ = H (85)		5
5	**1e**: R = CO$_2$Et, R′ = H	**3e**: R = CO$_2$Et, R′ = H (67)		4
6[c]	**1f**: R = Me, R′ = *n*Bu	**3f**: R = Me, R′ = *n*Bu (91)		3
				
7	**1g**: R = H	**3g**: R = H (82)	**4g** (10)	0.2
8	**1h**: R = Me	**3h**: R = Me (86)		2
				
9	**1i**: R = H	**3i**: R = H (62)	**4i** (37)	1
10	**1j**: R = Me	**3j**: R = Me (95)		0.5
				
11	**1k**: R = H	**3k**: R = H (46)	**4k** (21)	0.5
12	**1l**: R = Me	**3l**: R = Me (>99)		2
				
13[c]	**1m**	**3m** (92)		3
				
14	**1n**	**3n** (71)		4
				
15	**6**	**7** (>99)		1
				
16[c]	**8**	**9** (>99)		0.5

[a] A solution of **1** in dioxane (0.1 M) was heated at 80 °C in the presence of [RhCl(dppp)$_2$] (5 mol %). [b] Yield of isolated product. [c] The reaction was heated to reflux.

In summary, we have developed a [RhCl(dppp)$_2$]-catalyzed intramolecular [6+2] cycloisomerization reaction between alkyne and allenylcyclobutane functionalities under mild conditions leading to the efficient formation of the corresponding bicyclo[6.4.0]dodecatriene frameworks, in which the unfunctionalized simple cyclobutane ring served as a four-carbon component. Furthermore, this method was also successfully applied to the construction of the bicyclo[6.3.0]undecatriene ring system.

Acknowledgements

This work was supported in part by a Grant-in Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, for which we are thankful.

Keywords: allenes · bicyclic compounds · cycloaddition · cyclobutanes · rhodium

---

[1] For leading references, see: a) M. Murakami, K. Amii, K. Shigeto, Y. Ito, *J. Am. Chem. Soc.* **1996**, *118*, 8285–8290; b) M. Murakami, K. Takahashi, H. Amii, Y. Ito, *J. Am. Chem. Soc.* **1997**, *119*, 9307–9308; c) M. Murakami, T. Itahashi, H. Amii, K. Takahashi, Y. Ito, *J. Am. Chem. Soc.* **1998**, *120*, 9949–9950; d) M. Murakami, T. Tsuruta, Y. Ito, *Angew. Chem.* **2000**, *112*, 2600–2602; *Angew. Chem. Int. Ed.* **2000**, *39*, 2484–2486; e) M. Murakami, T. Itahashi, Y. Ito, *J. Am. Chem. Soc.* **2002**, *124*, 13976–13977; f) M. Murakami, S. Ashida, T. Matsuda, *J. Am. Chem. Soc.* **2005**, *127*, 6932–6933; g) T. Matsuda, M. Makino, M. Murakami, *Angew. Chem.* **2005**, *117*, 4684–4687; *Angew. Chem. Int. Ed.* **2005**, *44*, 4608–4611; h) T. Matsuda, M. Shigeno, Y. Maruyama, M. Murakami, *Chem. Lett.* **2007**, *36*, 744–745.

[2] P. A. Wender, A. G. Corrrea, Y. Sato, R. Sun, *J. Am. Chem. Soc.* **2000**, *122*, 7815–7816.

[3] M. Murakami, S. Ashida, T. Matsuda, *J. Am. Chem. Soc.* **2006**, *128*, 2166–2167.

[4] The Rh^{I}-catalyzed cycloisomerization of the cyclobutenone-fused cyclobutanes was reported, see: M. A. Huffman, L. S. Liebeskind, *J. Am. Chem. Soc.* **1993**, *115*, 4895–4896.

[5] For a recent review see, M. Murakami, T. Matsuda, *Chem. Commun.* **2011**, *47*, 1100–1105.

[6] In 2006, Wender and co-workers reported the Rh^{I}-catalyzed [6+1] cycloaddition of 1-siloxy-1-allenylcyclobutane and CO. Judging from the proposed reaction mechanism, cyclobutane seemed to cleave without assistance of siloxy group. It is, however, still uncertain if the siloxy group is mandatory (or not) for the cleavage of cyclobutane ring. See: P. A. Wender, N. M. Deschamps, R. Sun, *Angew. Chem.* **2006**, *118*, 4061–4064; *Angew. Chem. Int. Ed.* **2006**, *45*, 3957–3960.

[7] F. Inagaki, K. Sugikubo, Y. Miyashita, C. Mukai, *Angew. Chem.* **2010**, *122*, 2252–2256; *Angew. Chem. Int. Ed.* **2010**, *49*, 2206–2210.

[8] a) H. Nemoto, M. Yoshida, K. Fukumoto, *J. Org. Chem.* **1997**, *62*, 6450–6451; b) R. C. Larock, Ch. K. Reddy, *Org. Lett.* **2000**, *2*, 3325–3327; c) M. Yoshida, K. Sugimoto, M. Ihara, *Tetrahedron Lett.* **2001**, *42*, 3877–3880; d) M. Yoshida, K. Sugimoto, M. Ihara, *Tetrahedron* **2002**, *58*, 7839–7846; e) T. Seiser, N. Cramer, *Angew. Chem.* **2008**, *120*, 9435–9438; *Angew. Chem. Int. Ed.* **2008**, *47*, 9294–9297; f) T. Seiser, N. Cramer, *Chem. Eur. J.* **2010**, *16*, 3383–3391; g) T. Seiser, N. Cramer, *J. Am. Chem. Soc.* **2010**, *132*, 5340–5341.

[9] D. Crépin, J. Dawick, C. Aïssa, *Angew. Chem.* **2010**, *122*, 630–633; *Angew. Chem. Int. Ed.* **2010**, *49*, 620–623.

[10] In all cases except for entry 16 in Table 2, alkyne–allenylcyclobutanes with a phenylsulfonyl group on the allenyl moiety were employed through this study due to the following grounds; 1) they could be easily prepared from the corresponding propargyl alcohols (L. Horner, V. Binder, *Justus Liebigs Ann. Chem.* **1972**, *757*, 33–68) and 2) they are fairly stable and easily handled; 3) the phenylsulfonyl group was already shown to transform into other functionalities; a) C. Nájera, M. Yus, *Tetrahedron* **1999**, *55*, 10547–10658; b) N. S. Simpkins, *Sulphones in Organic Synthesis*, Pergamon, Oxford, **1993**.

[11] The two sets of conditions: $[RhCl(CO)_2]_2$/DCE and $[RhCl(CO)dppp]_2$/toluene have been found to be effective for the transformation of the alkyne–allenylcyclopropanes **1** ($n=1$) into the bicyclic seven-membered compounds **2** ($n=1$), see Ref. [7].

[12] a) B. R. James, D. Mahajan, *Can. J. Chem.* **1979**, *57*, 180–187; b) G. La Monica, C. Monti, S. Cenini, *J. Mol. Catal.* **1983**, *18*, 93–98.

[13] M. M. Montero-Campillo, J. Rodríguez-Otero, E. M. Cabaleiro-Lago, *Tetrahedron* **2008**, *64*, 6215–6220.

[14] This type of reaction mechanism for the ring opening of vinylcyclopropanes is supported by DFT calculations; a) Z.-X. Yu, P. A. Wender, K. N. Houk, *J. Am. Chem. Soc.* **2004**, *126*, 9154–9155; b) Z.-X. Yu, P. H.-Y. Cheong, P. Liu, C. Y. Legault, P. A. Wender, K. N. Houk, *J. Am. Chem. Soc.* **2008**, *130*, 2378–2379; c) P. Liu, H.-Y. Cheong, Z.-X. Yu, P. A. Wender, K. N. Houk, *Angew. Chem.* **2008**, *120*, 4003–4005; *Angew. Chem. Int. Ed.* **2008**, *47*, 3939–3941; d) P. Liu, L. E. Siros, P. H.-Y. Cheong, Z.-X. Yu, I. V. Hartung, H. Rieck, P. A. Wender, K. N. Houk, *J. Am. Chem. Soc.* **2010**, *132*, 10127–10135.

[15] This type of reaction mechanism for the ring opening of allenylcyclobutanes was already reported by Wender et al; see Ref. [6].

[16] As a control experiment, a solution of **1a** in dioxane was heated at 80 °C for 30 min without any rhodium catalyst resulting in the recovery of **1a** in 98 %. This result rules out the thermal reaction mechanism such as the one via the biradical intermediate. See: M. R. Siebert, J. M. Osbourn, K. M. Brummond, D. J. Tantillo, *J. Am. Chem. Soc.* **2010**, *132*, 11952–11966.

[17] There is no rational explanation to account for the difference in the reactivity between the closely related substrates **1a**, **1g** and **1i**, **1k**.

[18] M. E. Jung, G. Piizzi, *Chem. Rev.* **2005**, *105*, 1735–1766.

[19] The demethylated derivative of **3n** afforded a mixture of the corresponding bicyclo[6.4.0] derivative and cyclohexene derivative in the ratio of 3 to 1.

[20] The demethylated derivative of **6** afforded a mixture of the corresponding bicyclo[6.3.0] derivative and cyclopentene derivative in the ratio of 1 to 1.

Received: May 11, 2011