Organic Synthesis

Synthesis of Seven-Membered-Ring Ketones by Arylative Ring Expansion of Alkyne-Substituted Cyclobutanones**

*Takanori Matsuda, Masaomi Makino, and Masahiro Murakami**

Medium-sized carbocyclic ring systems are often present as the structural core in natural products of interesting biological activities. Thus, the development of new synthetic methods for medium-sized carbocyclic rings has been one of the prime targets in organic synthesis.[1] Fragmentation of an easily accessible bicyclic system circumvents unfavorable enthalpic and entropic factors associated with direct formation of the medium-sized ring by annulation or cyclization.[2] A number

[*] Dr. T. Matsuda, M. Makino, Prof. Dr. M. Murakami
Department of Synthetic Chemistry and Biological Chemistry
Kyoto University
Katsura, Kyoto 615–8510 (Japan)
Fax: (+81) 75-383-2748
E-mail: murakami@sbchem.kyoto-u.ac.jp

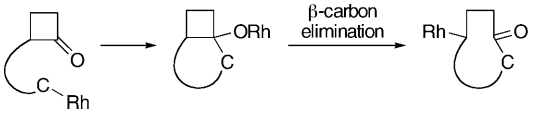
[**] This work was supported by a Grant-in-Aid for Young Scientists (B; No. 15750085) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  DOI: 10.1002/anie.200500799

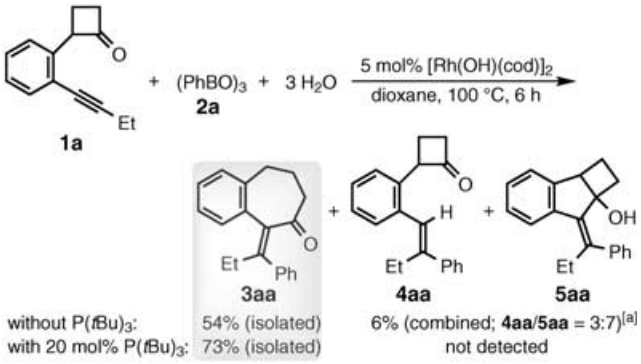
of ring-expansion reactions, which are promoted by acids, radicals, and transition metals, as well as heat, have been developed. Most of them are aided by the release of ring strain as the driving force.

Recently, we found that an arylrhodium adds to a cyclobutanone intermolecularly to afford a ring-opened ketone through β-carbon elimination from the resulting rhodium cyclobutanolate.[3] We then envisaged that intramolecular addition of an organorhodium group to cyclobutanone[4] followed by β-carbon elimination would provide a ring-expansion process [Eq. (1)]. Herein, we describe a new method for construction of seven-membered ring skeletons.



(1)

To establish a route to an organorhodium species necessary for such intramolecular additions, cyclobutanones **1** that bear an alkyne moiety were designed (Scheme 1). 2-(2-But-1-ynylphenyl)cyclobutanone (**1a**) was synthesized in three steps

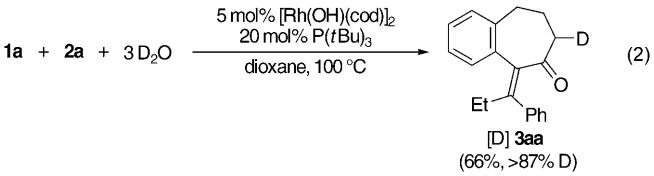


Scheme 1. Rhodium-catalyzed reaction of alkyne-substituted cyclobutanone **1a** with triphenylboroxin (**2a**). [a] Estimated from ^{1}H NMR spectroscopy of the crude reaction mixture.

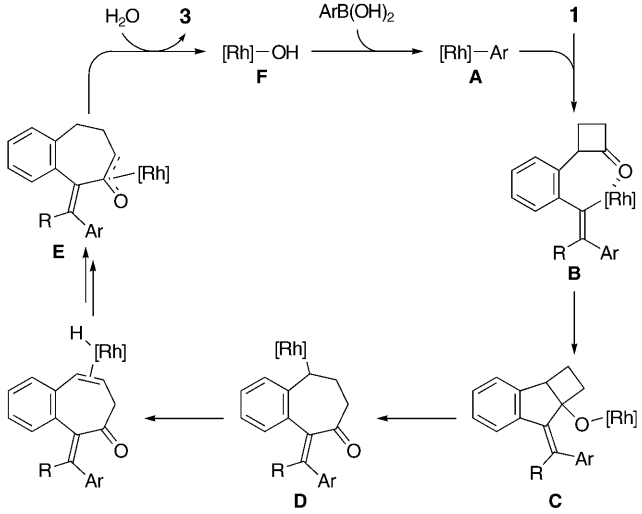
starting from commercially available 2-bromobenzaldehyde.[5] As a rhodium catalyst, we initially employed hydroxo(diolefin)rhodium(I) complexes, which have recently been used successfully in the rhodium-catalyzed reactions of arylboronic acids.[4b,d] Thus, a mixture of **1a**, triphenylboroxin (**2a**, 1.0 equiv), and water (3.0 equiv)[6] was heated in the presence of $[Rh(OH)(cod)]_2$ (10 mol% Rh; cod = cyclo-1,5-octadiene) in 1,4-dioxane at 100 °C. After heating for 6 h, seven-membered-ring ketone **3aa** was isolated in 54% yield along with small amounts of 1,2-adduct **4aa** and cyclobutanol **5aa**. The use of $P(tBu)_3$ as the additional ligand improved the yield of **3aa** to 73% without the formation of **4aa** and **5aa**.

The reaction in the presence of D_2O gave [D]**3aa** with deuterium incorporated exclusively at the α position of the carbonyl group, suggesting the formation of η^3-oxaallylrhodium prior to protonolysis, as previously reported [Eq. (2)].[3]

We propose the following mechanism for the transformation, which consists of a consecutive array of two C–C bond-forming and one C–C bond-cleaving steps (Scheme 2).



(2)

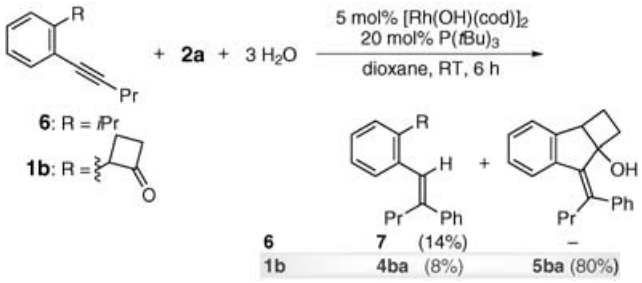


Scheme 2. Proposed mechanism for the formation of **3** from **1**.

Arylrhodium species **A**, generated from hydroxorhodium **F** and arylboronic acid, adds regioselectively across the carbon–carbon triple bond[4b–d,6b,7] of **1** in preference to the carbonyl group to afford vinylrhodium species **B**. Then, 1,2-addition to the adjacent carbonyl group of the cyclobutanone[4] forms rhodium cyclobutanolate **C**. β-Carbon elimination occurs regioselectively with the benzylic carbon atom,[8] and thus the bicyclic [3.2.0] skeleton of **C** is expanded with release of the ring strain to give alkylrhodium **D**. Successive β-hydride elimination/readdition processes take place, leading to the formation of η^3-oxaallylrhodium **E**.[9] Finally, protonolysis of **E** yields **3** and regenerates **F**.

Compound **4aa** is produced when the vinylrhodium species **B** is protonated through a 1,4-shift of rhodium. Protonolysis of the cyclobutanolate **C** affords **5aa**.

To examine the effect of coordination of the carbonyl group of **1**, a control experiment was carried out using 2-isopropyl-1-(pent-1-ynyl)benzene (**6**), whose alkyne structure is sterically similar to that of **1**, which comprises a cyclobutanone moiety (Scheme 3). The reaction of **6** with **2a** was sluggish at room temperature to give 1,2-adduct **7** in 14% yield after 6 h. In contrast, the analogous alkyne **1b** with a cyclobutanone substituent furnished 80% of cyclobutanol **5ba** as well as 8% of **4ba**. These contrasting results obtained with **6** and **1b** clearly indicate that the carbonyl group of **1b** facilitates the initial arylrhodation of the carbon–carbon triple bond by coordination. It also proved that the arylrhodation of **1b** and the following intramolecular carbonyl addition take place at room temperature and that the only ring-opening step by β-carbon elimination requires an



Scheme 3. Effect of coordination of the carbonyl group of **1**.

elevated temperature. It is conceivable that the coordination of the carbonyl group retards the 1,4-shift of rhodium[4c,6b,10] which possibly occurs with the intermediate **B** to produce **4**.

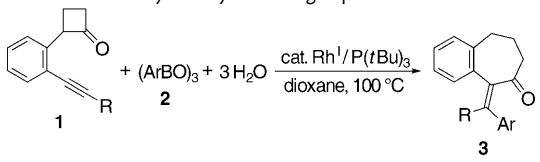
Arylboroxins **2b**–**2d** were subjected to the arylative ring-expansion reaction with cyclobutanone **1a** to give **3ab**–**3ad** in 63–71% yields (Table 1, entries 1–3).[11] Next, substituents at the alkyne termini of **1** were examined. Cyclobutanones **1b**–**1d**, which have other alkyl substituents (R), reacted with **2a** to afford the corresponding seven-membered-ring ketones **3ba**–**3da** (Table 1, entries 4–6).

In the reaction of **1e**, which contains a methyl ether linkage, 1,2-adduct **8ea** arising from arylrhodation with the opposite regiochemistry was formed as a byproduct (Scheme 4). Coordination of the ether oxygen center at the propargylic position might cause the regioisomeric 1,2-addition to produce **8ea**. With phenyl-substituted substrate **1f**, a mixture of **3** and **8** in a ratio of almost 1:1 was formed as a result of the barely biased alkyne structure.

Further studies on the scope and limitation of the arylative ring-expansion reaction (Table 2) were carried out. Both fluoro and methoxy substituents at the aryl ring of **1** were tolerated (Table 2, entries 1 and 2). Even a thiophene-derived substrate afforded the corresponding ketone **3ia** in 72% yield (Table 2, entry 3). We failed to obtain the seven-membered-ring ketones from cyclobutanone **1j**, which has an additional methyl substituent at the 2-position; instead, the corresponding cyclobutanol **5ja** was isolated (Table 2, entry 4). It is likely that migration of the rhodium from the oxygen atom to the tertiary carbon atom is difficult for steric reasons.[12] The reaction of **1k**, which contains a tether that is longer by one carbon atom, worked far less efficiently to result in the formation of the eight-membered-ring ketone **3ka** in only 17% yield (Table 2, entry 5).

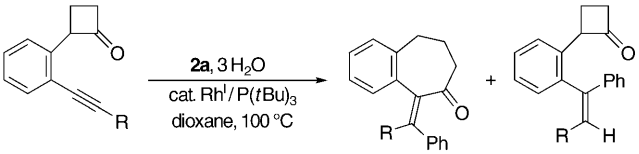
In summary, a new rhodium-catalyzed ring-expansion reaction was developed in which seven-membered-ring ketones **3** were produced from alkyne-substituted cyclobutanones **1** and arylboroxins **2** through ring opening by β-carbon elimination.

Table 1: Rhodium-catalyzed arylative ring expansion of **1** with **2**.[a]



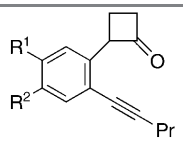
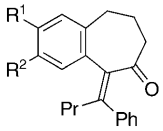
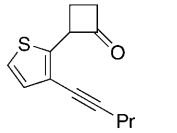
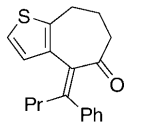
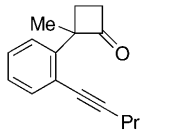
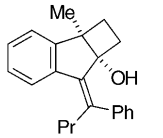
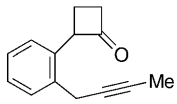
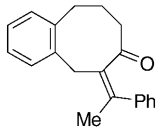
Entry	1	R	2	Ar	3	[%][b]
1	**1a**	Et	**2b**	4-MeC_6H_4	**3ab**	71
2	**1a**	Et	**2c**	4-$MeOC_6H_4$	**3ac**	70
3	**1a**	Et	**2d**	4-FC_6H_4	**3ad**	63
4	**1b**	Pr	**2a**	Ph	**3ba**	74
5	**1c**	*i*Bu	**2a**	Ph	**3ca**	76
6	**1d**	$(CH_2)_2OTBS$[c]	**2a**	Ph	**3da**	50

[a] All reactions were carried out using **1** (0.20 mmol), **2** (0.20 mmol), H_2O (0.60 mmol), $[Rh(OH)(cod)]_2$ (0.010 mmol, 10 mol% Rh), and $P(tBu)_3$ (0.04 mmol, 20 mol%) in 1,4-dioxane (1.0 mL) at 100 °C for 6 h. [b] Isolated yield. [c] TBS = *tert*-butyldimethylsilyl.



Scheme 4. Rhodium-catalyzed arylative ring expansion of **1e** and **1f**. [a] Estimated by ^1H NMR spectroscopy of the crude reaction mixture.

Table 2: Scope and limitation of the Rh-catalyzed arylative ring-expansion reaction.[a]

Entry	Cyclobutanone **1**		Product **3** or **5**		Yield [%][b]
1		$R^1 = R^2 = OMe$ **1g**		**3ga**	67
2		$R^1 = F$, $R^2 = H$ **1h**		**3ha**	58
3		**1i**		**3ia**	72
4		**1j**		**5ja**	63
5		**1k**		**3ka**	17

[a] All reactions were carried out using **1** (0.20 mmol), **2** (0.20 mmol), H_2O (0.60 mmol), $[Rh(OH)(cod)]_2$ (0.010 mmol, 10 mol% Rh), and $P(tBu)_3$ (0.06 mmol, 20 mol%) in 1,4-dioxane (1.0 mL) at 100 °C for 6 h. [b] Isolated yield.

Received: March 4, 2005
Published online: June 28, 2005

Keywords:
rhodium · boron · elimination · ketones · ring expansion

[1] a) N. A. Petasis, M. A. Patane, *Tetrahedron* **1992**, *48*, 5757 – 5821; b) C. J. Roxburgh, *Tetrahedron* **1993**, *49*, 10749 – 10784; c) G. Mehta, V. Singh, *Chem. Rev.* **1999**, *99*, 881 – 930; d) L. Yet, *Chem. Rev.* **2000**, *100*, 2963 – 3007.

[2] a) G. Illuminati, L. Mandolini, *Acc. Chem. Res.* **1981**, *14*, 95 – 102; b) C. Galli, L. Mandolini, *Eur. J. Org. Chem.* **2000**, 3117 – 3125.

[3] a) T. Matsuda, M. Makino, M. Murakami, *Org. Lett.* **2004**, *6*, 1257 – 1259; b) T. Matsuda, M. Makino, M. Murakami, *Bull. Chem. Soc. Jpn.* **2005**, in press.

[4] For intramolecular additions of an organorhodium(I) to a carbonyl group, see: a) A. Takezawa, K. Yamaguchi, T. Ohmura, Y. Yamamoto, N. Miyaura, *Synlett* **2002**, 1733 – 1735; b) R. Shintani, K. Okamoto, Y. Otomaru, K. Ueyama, T. Hayashi, *J. Am. Chem. Soc.* **2005**, *127*, 54 – 55; c) T. Miura, T. Sasaki, H. Nakazawa, M. Murakami, *J. Am. Chem. Soc.* **2005**, *127*, 1390 – 1391; d) T. Miura, M. Shimada, M. Murakami, *Synlett* **2005**, 667 – 669; For intermolecular additions, see: e) M. Sakai, M. Ueda, M. Miyaura, *Angew. Chem.* **1998**, *110*, 3475 – 3477; *Angew. Chem. Int. Ed.* **1998**, *37*, 3279 – 3281; f) C. Krug, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 1674 – 1679; g) M. Pucheault, S. Darses, J.-P. Genet, *J. Am. Chem. Soc.* **2004**, *126*, 15356 – 15357.

[5] Wittig olefination of the aldehyde with cyclopropylidenephosphorane afforded 2-bromobenzylidenecyclopropane (71%). Oxidation of the methylenecyclopropane with *m*-chloroperbenzoic acid followed by treatment with aqueous HBF_4 gave 2-(2-bromophenyl)cyclobutanone (58%). Introduction of a but-1-ynyl moiety by palladium-catalyzed coupling furnished **1a** (55%). See Supporting Information for details.

[6] Triphenylboroxin and water were used to generate phenylboronic acid in situ, see: a) T. Senda, M. Ogasawara, T. Hayashi, *J. Org. Chem.* **2001**, *66*, 6852 – 6856; b) T. Hayashi, K. Inoue, N. Taniguchi, M. Ogasawara, *J. Am. Chem. Soc.* **2001**, *123*, 9918 – 9919.

[7] a) M. Murakami, H. Igawa, *Helv. Chim. Acta* **2002**, *85*, 4182 – 4188; b) M. Lautens, M. Yoshida, *Org. Lett.* **2002**, *4*, 123 – 125; c) M. Lautens, T. Marquardt, *J. Org. Chem.* **2004**, *69*, 4607 – 4614; d) T. Miura, M. Shimada, M. Murakami, *J. Am. Chem. Soc.* **2005**, *127*, 1094 – 1095.

[8] For a review on β-carbon eliminations from palladium(II) cyclobutanolates, see: T. Nishimura, S. Uemura, *Synlett* **2004**, 201 – 216.

[9] For examples of related migrations of transition metals leading to enolates, see: a) H. Qian, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2003**, *125*, 2056 – 2057; b) S. V. Gagnier, R. C. Larock, *J. Am. Chem. Soc.* **2003**, *125*, 4804 – 4807.

[10] a) K. Oguma, M. Miura, T. Satoh, M. Nomura, *J. Am. Chem. Soc.* **2000**, *122*, 10464 – 10465; b) R. Shintani, K. Okamoto, T. Hayashi, *J. Am. Chem. Soc.* **2005**, *127*, 2872 – 2873; c) H. Yamabe, A. Mizuno, H. Kusama, N. Iwasawa, *J. Am. Chem. Soc.* **2005**, *127*, 3248 – 3249.

[11] The reaction with *o*-tolylboroxin resulted in the formation of a complex mixture of products, in which 1,2-adduct **4** was the only identifiable product.

[12] Ring expansion by β-carbon elimination failed to occur even when the isolated **5ja** was heated at 160 °C in the presence of the rhodium catalyst.

