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Rhodium-Catalyzed Addition/ Ring-Opening Reaction of Arylboronic Acids with Cyclobutanones

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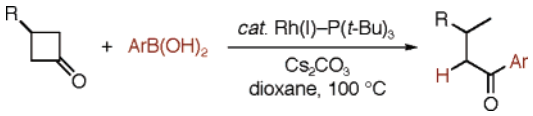
ABSTRACT



Cyclobutanones react with arylboronic acids in the presence of a catalytic amount of Rh(I) complex to afford butyrophenone derivatives through the addition of an arylrhodium(I) species to the carbonyl group, followed by ring-opening of the resulting rhodium(I) cyclobutanolate.

Carbon−carbon bond cleavage by means of transition metals has attracted much attention because it may achieve a new transformation that is otherwise difficult.[1] We have been studying the catalytic C−C bond-cleaving reactions of cyclobutanones, wherein a rhodium(I) complex undergoes insertion between the carbonyl carbon and the α-carbon.[2] On the other hand, rhodium-catalyzed addition reactions of arylboronic acid derivatives to unsaturated organic functionalities have been recently developed.[3,4] An arylrhodium(I) species formed by transmetalation is assumed as the intermediate in these reactions. We expected that an arylrhodium(I) species is more electron-rich than a rhodium(I) halide or a cationic rhodium(I) complex and, hence, is more easily oxidized to a rhodium(III) species during insertion between the carbonyl and α carbons. Thus, we examined the rhodium(I)-catalyzed reaction of cyclobutanones with arylboronic acids.

In an initial attempt, 3-phenylcyclobutanone (**1a**) was reacted with *o*-tolylboronic acid (**2a**, 3 equiv) in the presence of a rhodium(I) catalyst bearing tri-*tert*-butylphosphine (5 mol % Rh, Rh:P = 1:2) and Cs_2CO_3 (1 equiv).[5,6] After heating at 100 °C for 3 h, **1a** was completely consumed and butyrophenone derivative **3aa** and tertiary cyclobutanol **4aa** were formed (**3aa**:**4aa** = 90:10). The structure of the major product **3a** could arise from the cleavage of the C(acyl)−C(α) bond of **1a** and bonding of the *o*-tolyl group of **2a** to the acyl carbon. The minor product **4aa** resulted from the addition of the aryl group of **2a** to the carbonyl group of **1a**.

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(4) For reviews: (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

(5) Use of $[RhCl(cod)]_2$ or $[Rh(OH)(cod)]_2$ resulted in low conversion (<40%), while $[Rh(cod)_2]BF_4$ was totally ineffective. The orders of the influence of several phosphines and bases on the reactivity are as follows: P(*t*-Bu)$_3$ > P(*c*-Hex)$_3$ ≫ PPh_3 > DPPP, DPPB; Cs_2CO_3 ≥ KOH > KF > $NaHCO_3$ ≈ none.

(6) Reaction with *o*-tolylboronic acid was slower in the absence of Cs_2CO_3, whereas Cs_2CO_3 showed little accelerating effect for the reaction with less sterically hindered phenylboronic acid.

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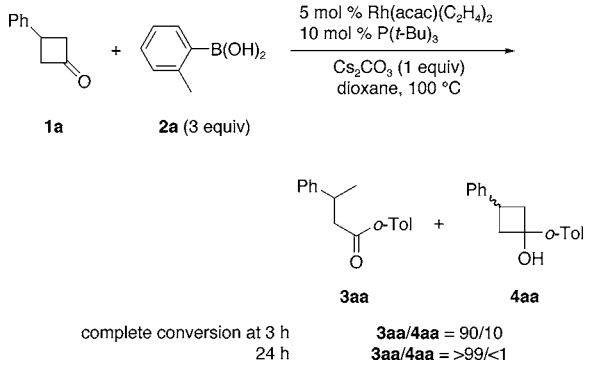
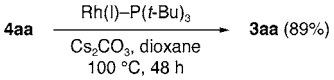
Scheme 1



When the reaction mixture was heated for 24 h, only the product **3aa** remained, indicating that **4aa** isomerized to **3aa**.

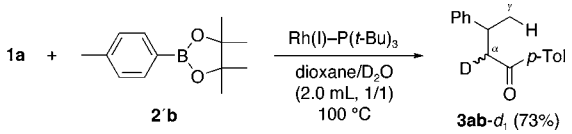
In fact, heating of **4aa**[7] in the presence of the rhodium(I) catalyst gave the ring-opening product **3aa**. On the other hand, no reaction occurred on heating **4aa** in the absence of the rhodium(I) catalyst, suggesting that the ring-opening reaction was also catalyzed by the rhodium(I) (Scheme 2). These results indicated that the reaction proceeded via the addition of arylrhodium to the carbonyl group of **1a** followed by the ring-opening of the resulting rhodium alcoholate through β-carbon elimination, rather than via the direct insertion of rhodium(I) between the carbonyl carbon and the α-carbon.

Scheme 2



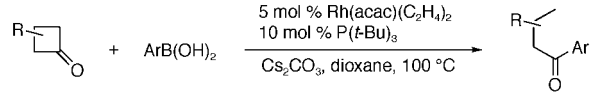
When the boronic ester **2′b** was used instead of boronic acid, no reaction occurred in dioxane. In contrast, the addition of water to the solvent effectuated the reaction. It is likely that protic hydrogens are requisite for the regeneration of the rhodium(I) catalyst from the product by protonolysis. Much to our surprise, when the reaction was carried out in dioxane/D_2O (1:1), deuterium was incorporated not at the γ-position of the produced ketone but at the α-position exclusively (Scheme 3).[8]

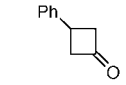
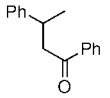
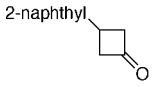
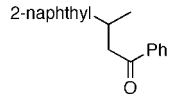
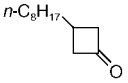
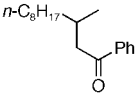
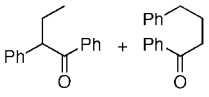
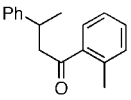
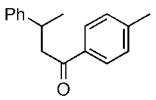
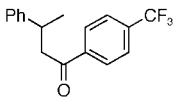
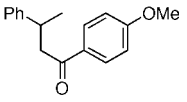
Scheme 3



On the basis of the experimental results mentioned above and the previous reports on the rhodium(I)-catalyzed addition of arylboronic acids to aldehydes,[3d,e] the mechanism illustrated in Scheme 4 seems to be plausible. The catalytic cycle involves (i) addition of arylrhodium species **5** to cyclobutanone **1**, (ii) ring-opening of rhodium cyclobutano-

Table 1. Rh-Catalyzed Addition/Ring-Opening Reaction of Arylboronic Acids **2** with Cyclobutanones **1**[a]



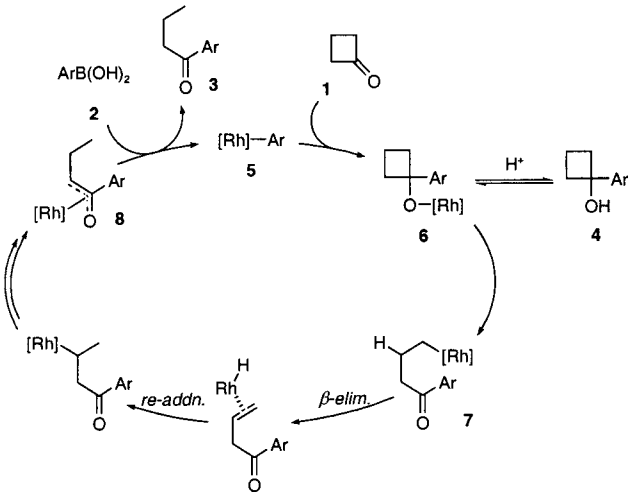
entry	cyclobutanone **1**	boronic acid Ar (**2**)	product **3**	%yield[b]
1	 **1a**	Ph (**2c**)	 **3ac**	95
2	 **1b**	**2c**	 **3bc**	78
3	 **1c**	**2c**	 **3cc**	75
4[c]	 **1d**	**2c**	 **3dc** **3′dc** (77:23)	52
5	**1a**	*o*-MeC_6H_4 (**2a**)	 **3aa**	72
6	**1a**	*p*-MeC_6H_4 (**2b**)	 **3ab**	82
7	**1a**	*p*-$CF_3C_6H_4$ (**2d**)	 **3ad**	39
8	**1a**	*p*-$MeOC_6H_4$ (**2e**)	 **3ae**	42

[a] Unless otherwise noted, cyclobutanone **1** (0.50 mmol) and **2a** (1.5 mmol) were heated in the presence of $Rh(acac)(C_2H_4)_2$ (0.025 mmol), $P(t\text{-}Bu)_3$ (0.050 mmol), and Cs_2CO_3 (0.50 mmol) in dioxane (1.0 mL) at 100 °C for 24 h. [b] Isolated yield. [c] Reaction was carried out on 0.21 mmol scale.

(7) Tertiary cyclobutanol **4aa** was synthesized independently by the reaction of **1a** with the Grignard reagent as a diastereomeric mixture (cis: trans = 74:26).

(8) Diastereomeric ratio of **3ab**-*d* was determined to be 64:36 by ^1H NMR; however, the relative stereochemistries were not determined.

Scheme 4



late **6** by β-carbon elimination to alkylrhodium intermediate **7**,[9] (iii) successive β-hydride elimination/re-addition sequence leading to rhodium enolate **8**,[10] and (iv) protonolysis and/or transmetalation with the boronic acid **2** giving butyrophenone **3** and arylrhodium species **5**.

Other examples of the addition/ring-opening of cyclobutanones are listed in Table 1. The reaction of 3-phenylcyclobutanone (**1a**) and phenylboronic acid (**2c**) afforded the product **3ac** in high yield (entry 1). In the reaction of 2-phenylcyclobutanone (**1d**), β-carbon elimination took place either at C(1)−C(4) or C(1)−C(2) bond to yield two products **3dc** and **3′dc**, with the former predominating (entry 4). *o*-Tolyl- and *p*-tolylboronic acids (**2a** and **2b**) also gave the corresponding butyrophenones (**3aa** and **3ab**) in good yield (entries 5 and 6). However, phenylboronic acids having trifluoromethyl and methoxy groups at the *p*-position (**2d** and **2e**) resulted in unsatisfactory yields (entries 7 and 8).

Whereas an arylboronic acid adds to a ketone *intramolecularly*,[3f] there has been no report on the *intermolecular* addition to a ketone. In fact, no reaction occurred with 4-phenylcyclohexanone under the present reaction conditions. Therefore, it is of note that an arylboronic acid adds to the ketonic carbonyl group of cyclobutanone intermolecularly. The increased reactivity is ascribed to the strain of the four-membered ring;[11] the carbonyl sp^2 carbon changes to an sp^3 carbon on addition of the arylrhodium, thereby diminishing the ring strain. The β-carbon elimination step would be also promoted by the release of the ring strain.

In summary, we have developed a new catalytic ring-opening of cyclobutanones with arylboronic acids. Contrary to our initial expectation, the reaction involved the addition of the Rh−C bond to the ketonic carbonyl group followed by β-carbon elimination from the resulting rhodium alcoholate.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) For β-carbon elimination from Pd(II) cyclobutanolate, see: (a) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 11010. (b) Nishimura, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2001**, *66*, 1455. (c) Matsumura, S.; Maeda, Y.; Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **2003**, *125*, 8862.

(10) For transition metal-hydride elimination followed by re-addition with opposite regiochemistry, see: (a) Yoshida, K.; Hayashi, T. *J. Am. Chem. Soc.* **2003**, *125*, 2872. (b) Gagnier, S. V.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 4804. (c) Suginome, M.; Matsuda, T.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11015. (d) Ittel, S. D.; Johnson, L. K. *Chem. Rev.* **2000**, *100*, 1169.

(11) For synthetic applications of cyclobutane derivatives, see: Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485.