doi:10.1246/cl.2011.1453
Published on the web December 5, 2011

Diaryl Ketone Synthesis by [RuHCl(CO)(PPh$_3$)$_3$]-catalyzed Coupling Reaction of Arylboronic Acids with Aryl Aldehydes

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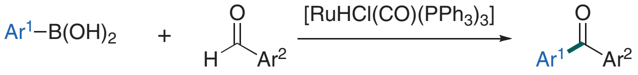
[RuHCl(CO)(PPh$_3$)$_3$] was found to be an efficient catalyst for the coupling reaction of arylboronic acids with aryl aldehydes. The reaction proceeded smoothly in the presence of K_2CO_3 and H_2O to give diaryl ketones in good yields. Diaryl ketones were obtained from primarily formed alcohols via Ru-catalyzed transfer hydrogenation reaction.



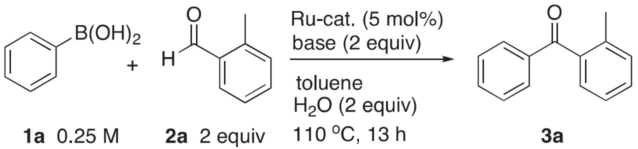
Scheme 1. [RuHCl(CO)(PPh$_3$)$_3$]-catalyzed coupling reaction of arylboronic acids with aldehydes.

Diaryl ketone frameworks are found in a variety of biologically active compounds[1] and organic materials with potential use in optical, magnetic, and electronic applications.[2] Diaryl ketones are typically prepared by addition of organometallic compounds, such as arylmagnesium or aryllithium reagents, to aryl aldehydes, followed by oxidation. These reactions require stoichiometric amounts of organometallic reagents and oxidants. Cross-coupling reaction of aryl aldehydes with aryl halide represents a straightforward approach to access diaryl ketones. It has been reported that palladium[3] and nickel[4] can catalyze such coupling reactions. Recent work revealed that arylboronic acids can also serve as a coupling partner of aryl aldehydes in Rh-,[5] Pd-,[6] and Pt-catalyzed reactions[7] in diaryl ketone synthesis.

Recently, we reported that a ruthenium hydride complex, [RuHCl(CO)(PPh$_3$)$_3$] catalyzed the reaction of aldehydes with α,β-unsaturated ketones[8] or dienes[9,10] leading to 1,3-diketones or β,γ-unsaturated ketones, in which addition of ruthenium–carbon species to aldehydes followed by β-hydride elimination from a ruthenium alkoxide intermediate would be involved as the key steps. Herein we report that [RuHCl(CO)(PPh$_3$)$_3$][11] can effectively catalyze the coupling reaction of aldehydes with arylboronic acids, resulting in good yields of diaryl ketones (Scheme 1).[12] During the course of our study, Wan and co-workers reported a similar [RuCl$_2$(CO)$_3$]$_2$/P(t-Bu)$_3$-catalyzed coupling reaction of aldehydes with arylboronic acids to give aryl ketones. In this case the Ru–H species formed in situ was proposed to be the key catalytic species.[13,14]

The reaction of phenylboronic acid (**1a**) with *o*-tolualdehyde (**2a**) was investigated as a model reaction. Thus, when the reaction of **1a** with **2a** was carried out in the presence of a catalytic amount of [RuHCl(CO)(PPh$_3$)$_3$] (5 mol %) and H_2O (2 equiv) in toluene at 110 °C for 13 h, the coupling product, 2-methylbenzophenone (**3a**), was obtained in 13% yield (Table 1, Entry 1). Addition of K_2CO_3 was found to be effective to give **3a** in 62% yield (Entry 4). When the reaction was conducted in the absence of H_2O only a trace amount of **3a** was formed (Entry 5). Increasing the concentration of substrate (0.5 M of **1a**) also improved the yield of **3a** up to 66% (Entry 6). Other ruthenium hydride complexes, such as [RuH$_2$(CO)(PPh$_3$)$_3$], [RuH$_2$(PPh$_3$)$_4$], and [RuHCl(PPh$_3$)$_3$] were less effective for the present coupling reaction (Entries 7–9).

Table 1. Ru–H-catalyzed coupling reaction of **1a** with **2a**[a]

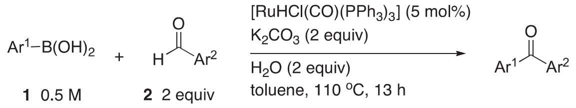


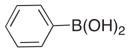
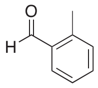
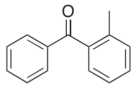
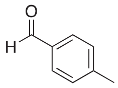
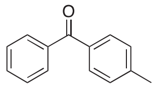
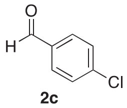
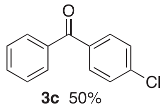
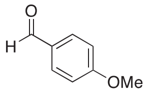
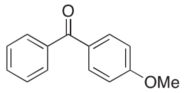
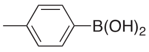
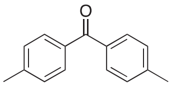
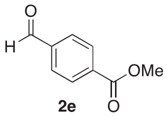
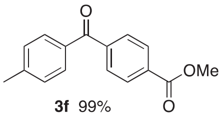
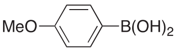
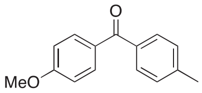
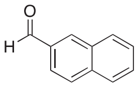
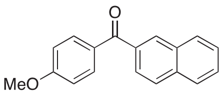
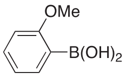
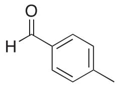
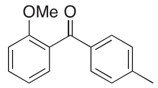
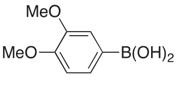
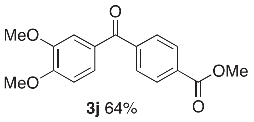
Entry	Ru-cat.	Base	Yield[b]/%
1	[RuHCl(CO)(PPh$_3$)$_3$]	none	13
2	[RuHCl(CO)(PPh$_3$)$_3$]	Cs_2CO_3	28
3	[RuHCl(CO)(PPh$_3$)$_3$]	t-BuOK	2
4	[RuHCl(CO)(PPh$_3$)$_3$]	K_2CO_3	62
5[c]	[RuHCl(CO)(PPh$_3$)$_3$]	K_2CO_3	trace
6[d]	[RuHCl(CO)(PPh$_3$)$_3$]	K_2CO_3	66[e]
7	[RuH$_2$(CO)(PPh$_3$)$_3$]	K_2CO_3	37
8	[RuH$_2$(PPh$_3$)$_4$]	K_2CO_3	17
9	[RuHCl(PPh$_3$)$_3$]	K_2CO_3	4

[a]Conditions: **1a** (0.5 mmol), **2a** (1 mmol), Ru-cat. (5 mol %), base (1 mmol), H_2O (1 mmol), toluene (2 mL), 110 °C, 13 h. [b]NMR yield using anisole as an internal standard. [c]Reaction without H_2O. [d]0.5 M. [e]Isolated yield by flash chromatography on SiO_2.

With optimized reaction conditions in hand, we then investigated the scope of [RuHCl(CO)(PPh$_3$)$_3$]-catalyzed coupling reactions of a variety of arylboronic acids with aryl aldehydes. The results are shown in Table 2.[15] The reaction of **1a** with para substituted benzaldehydes **2b**, **2c**, and **2d** gave the corresponding diaryl ketones **3b**, **3c**, and **3d** in moderate to good yields (Entries 2–4). The reaction of *p*-tolylboronic acid (**1b**) with **2b** gave 4,4′-dimethylbenzophenone (**3e**) in 49% yield (Entry 5). *p*-Methoxycarbonyl-substituted benzaldehyde **2e** exhibited high reactivity, giving the corresponding product **3f** in quantitative yield (Entry 6). Several methoxy-substituted phenylboronic acids **1c**–**1e** were examined, which gave the corresponding diaryl ketones in good yields (Entries 7–10). The reactions of arylboronic acids with aliphatic aldehydes, such as 1-heptanal and pivalaldehyde, were sluggish to give the corresponding alkyl aryl ketones in less than 20% yields. Alkylboronic acids and heteroaromatic boronic

Table 2. [RuHCl(CO)(PPh$_3$)$_3$]-catalyzed coupling reaction of arylboronic acids with aryl aldehydes[a]

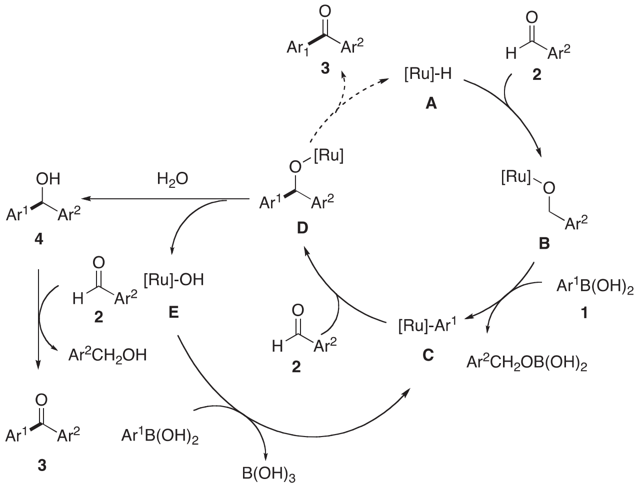


Entry	Boronic acid	Aldehyde	Product, Yield[b]
1	 **1a**	 **2a**	 **3a** 66%
2	**1a**	 **2b**	 **3b** 71%
3	**1a**	 **2c**	 **3c** 50%
4	**1a**	 **2d**	 **3d** 49%
5	 **1b**	**2b**	 **3e** 49%
6	**1b**	 **2e**	 **3f** 99%
7	 **1c**	**2b**	 **3g** 80%
8	**1c**	 **2f**	 **3h** 57%
9	 **1d**	 **2f**	 **3i** 56%
10	 **1e**	**2e**	 **3j** 64%

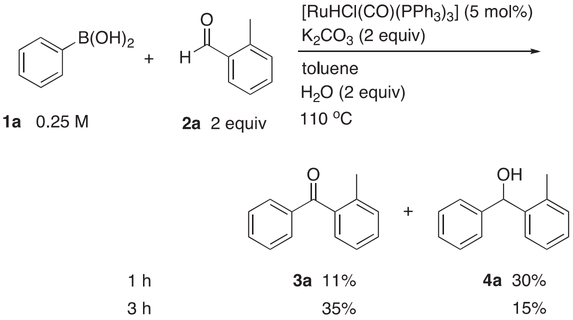
[a]Conditions: **1** (0.5 mmol), **2** (1 mmol), [RuHCl(CO)(PPh$_3$)$_3$] (5 mol %), K$_2$CO$_3$ (1 mmol), toluene (1 mL), H$_2$O (1 mmol), 110 °C, 13 h. [b]Isolated yield after flash chromatography on SiO$_2$.

acid, such as 3-pyridylboronic acid did not give any coupling products.

Interestingly, in the cross-coupling reaction of **1a** with **2a**, after 1 h 2-methyldiphenylmethanol (**4a**) was observed as the major product, whereas after 3 h, the diaryl ketone **3a** was the major product (eq 1).



Scheme 2. A proposed reaction mechanism.

 (1)

In addition to this, in the absence of water, the reaction did not proceed (Table 1, Entry 5). Taking these results into consideration, we propose a mechanism, in which an alcohol can serve as a precursor for the corresponding diaryl ketone (Scheme 2). Thus, hydroruthenation of **A** to an aldehyde would give a ruthenium alkoxide intermediate **B**. Transmetalation between **B** and arylboronic acid would give aryl ruthenium intermediate **C**, which would then react with an aldehyde **2** to give a ruthenium alkoxide **D**. Hydrolysis of **D** (by the added water) would result in the formation of a free alcohol **4** and Ru–OH **E**. **E** is then able to undergo transmetalation with arylboronic acid to give **C**. Ru–H catalyzed transfer hydrogenation of **4** with an aldehyde **2** would give the desired ketone **3** and a primary alcohol by-product.[11b,11d]

In conclusion, [RuHCl(CO)(PPh$_3$)$_3$] was found to be an efficient catalyst for the coupling reaction of arylboronic acids with aryl aldehydes to give the corresponding diaryl ketones. Results over the time course of the reaction suggest that diaryl ketones are obtained via Ru-catalyzed transfer hydrogenation reaction of secondary aryl alcohols. Other applications and mechanistic studies are currently underway in this laboratory.

We thank JSPS and MEXT, Japan for financial support of this work.

This paper is in celebration of the 2010 Nobel Prize awarded to Professors Richard F. Heck, Akira Suzuki, and Ei-ichi Negishi.

References and Notes

1 For selected examples, see: a) N. Hsu, D. Cai, K. Damodaran, R. F. Gomez, J. G. Keck, E. Laborde, R. T. Lum, T. J. Macke, G. Martin, S. R. Schow, R. J. Simon, H. O. Villar, M. M. Wick, P. Beroza, *J. Med. Chem.* **2004**, *47*, 4875. b) K. M. Henry, C. A. Townsend, *J. Am. Chem. Soc.* **2005**, *127*, 3300. c) M. Pecchio, P. N. Solís, J. L. López-Pérez, Y. Vásquez, N. Rodríguez, D. Olmedo, M. Correa, A. S. Feliciano, M. P. Gupta, *J. Nat. Prod.* **2006**, *69*, 410. d) Y. Deng, Y.-W. Chin, H. Chai, W. J. Keller, A. D. Kinghorn, *J. Nat. Prod.* **2007**, *70*, 2049. e) H. S. Tae, J. Hines, A. R. Schneekloth, C. M. Crews, *Org. Lett.* **2010**, *12*, 4308.

2 a) T. Itoh, T. Maemura, Y. Ohtsuka, Y. Ikari, H. Wildt, K. Hirai, H. Tomioka, *Eur. J. Org. Chem.* **2004**, 2991. b) D. D. Andjelkovic, V. V. Sheares, *Macromolecules* **2007**, *40*, 7148. c) W. Sharmoukh, K. C. Ko, C. Noh, J. Y. Lee, S. U. Son, *J. Org. Chem.* **2010**, *75*, 6708.

3 a) T. Satoh, T. Itaya, M. Miura, M. Nomura, *Chem. Lett.* **1996**, 823. b) L. Adak, S. Bhadra, B. C. Ranu, *Tetrahedron Lett.* **2010**, *51*, 3811. For Pd/Ru catalyst system, see: c) S. Ko, B. Kang, S. Chang, *Angew. Chem., Int. Ed.* **2005**, *44*, 455. For coupling reaction of aryl halides with aliphatic aldehydes, see: d) J. Ruan, O. Saidi, J. A. Iggo, J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 10510. e) A. Zanardi, J. A. Mata, E. Peris, *Organometallics* **2009**, *28*, 1480. f) P. Álvarez-Bercedo, A. Flores-Gaspar, A. Correa, R. Martin, *J. Am. Chem. Soc.* **2010**, *132*, 466. g) P. Colbon, J. Ruan, M. Purdie, J. Xiao, *Org. Lett.* **2010**, *12*, 3670.

4 Y.-C. Huang, K. K. Majumdar, C.-H. Cheng, *J. Org. Chem.* **2002**, *67*, 1682.

5 a) G. Mora, S. Darses, J.-P. Genet, *Adv. Synth. Catal.* **2007**, *349*, 1180. b) N. Imlinger, K. Wurst, M. R. Buchmeiser, *J. Organomet. Chem.* **2005**, *690*, 4433. c) N. Imlinger, M. Mayr, D. Wang, K. Wurst, M. R. Buchmeiser, *Adv. Synth. Catal.* **2004**, *346*, 1836. Also see: d) M. Pucheault, S. Darses, J.-P. Genet, *J. Am. Chem. Soc.* **2004**, *126*, 15356. e) O. Chuzel, A. Roesch, J.-P. Genet, S. Darses, *J. Org. Chem.* **2008**, *73*, 7800.

6 a) C. Qin, J. Chen, H. Wu, J. Cheng, Q. Zhang, B. Zuo, W. Su, J. Ding, *Tetrahedron Lett.* **2008**, *49*, 1884. b) F. Weng, C. Wang, B. Xu, *Tetrahedron Lett.* **2010**, *51*, 2593.

7 Y.-X. Liao, Q.-S. Hu, *J. Org. Chem.* **2010**, *75*, 6986.

8 T. Fukuyama, T. Doi, S. Minamino, S. Omura, I. Ryu, *Angew. Chem., Int. Ed.* **2007**, *46*, 5559.

9 S. Omura, T. Fukuyama, J. Horiguchi, Y. Murakami, I. Ryu, *J. Am. Chem. Soc.* **2008**, *130*, 14094.

10 The Krische group also reported Ru–H-catalyzed coupling reaction of dienes with aldehydes leading to β,γ-unsaturated ketones, see: F. Shibahara, J. F. Bower, M. J. Krische, *J. Am. Chem. Soc.* **2008**, *130*, 14120.

11 Our reports on $[\mathrm{RuHCl(CO)(PPh_3)_3}]$-catalyzed reactions, see: a) T. Doi, T. Fukuyama, S. Minamino, G. Husson, I. Ryu, *Chem. Commun.* **2006**, 1875. b) T. Doi, T. Fukuyama, J. Horiguchi, T. Okamura, I. Ryu, *Synlett* **2006**, 721. c) T. Doi, T. Fukuyama, S. Minamino, I. Ryu, *Synlett* **2006**, 3013. d) A. Denichoux, T. Fukuyama, T. Doi, J. Horiguchi, I. Ryu, *Org. Lett.* **2010**, *12*, 1.

12 For ruthenium-catalyzed coupling reaction using boronic acids, see: a) E. J. Farrington, J. M. Brown, C. F. J. Barnard, E. Rowsell, *Angew. Chem., Int. Ed.* **2002**, *41*, 169. b) F. Kakiuchi, S. Kan, K. Igi, N. Chatani, S. Murai, *J. Am. Chem. Soc.* **2003**, *125*, 1698. c) R. Shintani, T. Hayashi, *Chem. Lett.* **2008**, *37*, 724. d) Y. Yamamoto, K. Kurihara, N. Miyaura, *Angew. Chem., Int. Ed.* **2009**, *48*, 4414. e) K. Kitazawa, M. Kotani, T. Kochi, M. Langeloth, F. Kakiuchi, *J. Organomet. Chem.* **2010**, *695*, 1163.

13 H. Li, Y. Xu, E. Shi, W. Wei, X. Suo, X. Wan, *Chem. Commun.* **2011**, *47*, 7880.

14 Cu-Catalyzed coupling reaction of aldehydes with boronic acids was also recently reported. See: H. Zheng, J. Ding, J. Chen, M. Liu, W. Gao, H. Wu, *Synlett* **2011**, 1626.

15 Phenylboronic acid (**1a**, 61.0 mg, 0.5 mmol), *o*-tolualdehyde (**2a**, 120.1 mg, 1.0 mmol), $[\mathrm{RuHCl(CO)(PPh_3)_3}]$ (23.8 mg, 0.025 mmol), H_2O (18 mg, 1.0 mmol), K_2CO_3 (138 mg, 1.0 mmol), and toluene (1 mL) were placed in a screw-capped test tube. The test tube was purged with argon and sealed. The mixture was stirred at 110 °C for 13 h. After the reaction, the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/Et_2O = 100/1) to give **3a** (65.5 mg, 66%).