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Cobalt(II)-Catalyzed Regio- and Stereoselective Hydroarylation of Alkynes with Organoboronic Acids

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The transition-metal-catalyzed addition reactions of organometallic reagents to alkynes are a convenient route for the synthesis of substituted olefins.[1] Organoboron, -silane, -stannane, -magnesium, and -lithium reagents are commonly employed as the transmetallating agents in this type of addition reaction;[1c,2] of these, organoboron reagents have gained much attention because of their various advantageous properties.[3] Palladium, nickel and rhodium complexes are known to catalyze the addition of organoborons to alkynes. When palladium complexes[4] and [Ni(cod)$_2$][5] were used as the catalysts, various types of addition products with different ratios of organoboron to alkyne were observed. Simple 1:1 coupling of organoboronic acids with alkynes to give hydroarylation products were found when rhodium(I) complexes were used as the catalysts.[6] Although the type of addition greatly depends on the nature of the metal catalysts, all of these metal-catalyzed reactions of organoborons to alkynes gave addition products with *syn* stereoselectivity. Our continuous interest in developing new reactions using less expensive and conveniently handled nickel and cobalt complexes as catalysts prompted us to investigate the addition of organoboronic acids to various π components with cobalt complexes as the catalyst.[7] Herein, we report a series of cobalt(II)-catalyzed, highly regio- and stereoselective hydroarylations of alkynes using organoboronic acids as reagents.

When phenylboronic acid (**1a**) was treated with methyl oct-2-ynoate (**2a**) in the presence of 5 mol% [Co(acac)$_2$]/dppe (acac = acetylacetonate, dppe = 1,2-bis(diphenylphosphine)ethane) in CH$_3$CN/THF (4:1) at 80 °C for 12 h, the hydroarylation product **3aa** was obtained in 93% isolated yield (Table 1, entry 1). In addition, a small amount of benzene, the protodeboronation product of **1a**, was also observed by GC–MS analysis. There was no biphenyl formed in this reaction, which indicated that the cobalt(II) had not been reduced.[8] This reaction is highly regio- and stereoselective, with the phenyl group of **1a** adding to the n-C$_5$H$_{11}$-substituted alkyne carbon to give exclusively the *E* stereoisomer. Note that this is the first report of a cobalt-catalyzed addition reaction of an organoboronic acid with an alkyne.

To gain insight into this cobalt-catalyzed addition reaction, the reaction between **1a** and **2a** was examined under various conditions. No formation of product **3aa** was observed if [Co(acac)$_2$] alone was used as the catalyst. The reaction was then carried out in the presence of [Co(acac)$_2$] and various phosphine ligands in CH$_3$CN/THF (4:1) at 80 °C for 12 h. The use of dppe (1 equiv with respect to the cobalt complex) gave **3aa** in quantitative 99% yield as determined by the ^{1}H NMR integration method. Note that under the same reaction conditions in pure CH$_3$CN, the hydroarylation product **3aa** was obtained in 81% yield, and in pure THF the protodeboronation product of **1a** was observed. The presence of THF appears to increase the solubility of the arylboronic acid and dppe ligand, whereas the use of CH$_3$CN presumably facilitates the alkyne insertion and thus the formation of **3aa**. Use of bidentate bis(diphenylphosphino)methane (dppm) and 1,3-bis(diphenylphosphino)propane (dppp) afforded **3aa** in 14 and 65% yield, respectively.[9] Two other bidentate phosphine ligands, 1,4-bis(diphenylphospheno)butane (dppb) and 1,1′-bis(diphenylphosphino)ferrocene (dppf), and the monodentate phosphane ligand PPh$_3$ were ineffective in the reaction. The cobalt(II) complexes [Co(OAc)$_2$] and CoCl$_2$ were also tested in the presence of dppe. The former gave product **3aa** in 80% yield, but the latter was inactive. Surprisingly, the hydroarylation did not proceed by using Co(OH)$_2$ in the presence of dppe as the catalyst, but the reaction took place smoothly by the addition of acacH into the system to afford **3aa** in 95% yield.[9] The activity of the cobalt(III) complex, [Co(acac)$_3$], was also examined in the presence of one equivalent of dppe. The reaction gave **3aa** in 7% yield at 80 °C and 33%

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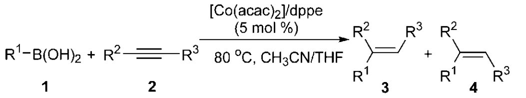
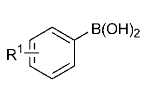
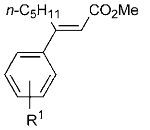
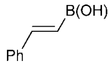
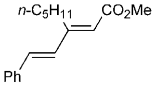
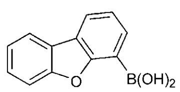
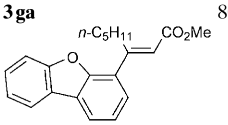
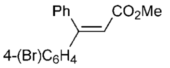
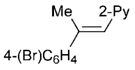
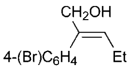
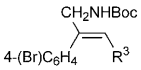
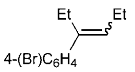
Table 1. Cobalt-catalyzed addition of organoboronic acids **1** to alkynes **2**.[a]



Entry	**1**	**2**	Product **3** or **4**	Yield[b] [%]
1	 **1a** $R^1 = H$	**2a** $R^2 = n\text{-}C_5H_{11}$ $R^3 = CO_2Me$	 **3aa**	93 (99)[c]
2	**1b** $R^1 = 4\text{-OMe}$	**2a**	**3ba**	96
3	**1c** $R^1 = 3\text{-OMe}$	**2a**	**3ca**	91
4	**1d** $R^1 = 3\text{-CHO}$	**2a**	**3da**	94
5	**1e** $R^1 = 3\text{-NO}_2$	**2a**	**3ea**	67
6	**1f** $R^1 = 4\text{-Br}$	**2a**	**3fa**	93
7	 **1g**	**2a**	 **3ga**	80[d]
8	 **1h**	**2a**	 **3ha**	88[d]
9	**1f**	**2b** $R^2 = Ph$ $R^3 = CO_2Me$	 **3fb**	90
10	**1f**	**2c** $R^2 = Me$ $R^3 = 2\text{-pyridine}$	 **3fc**	86
11	**1f**	**2d** $R^2 = CH_2OH$ $R^3 = Et$	 **4fd**	82[e]
12	**1f**	**2e** $R^2 = CH_2NHBoc$ $R^3 = p\text{-}CO_2Et\text{-}C_6H_4$	 **4fe** $R^3 = 4\text{-}(CO_2Et)C_6H_4$	78[e]
13	**1f**	**2f** $R^2 = R^3 = Et$	 **3ff/4ff** (1:1)	79

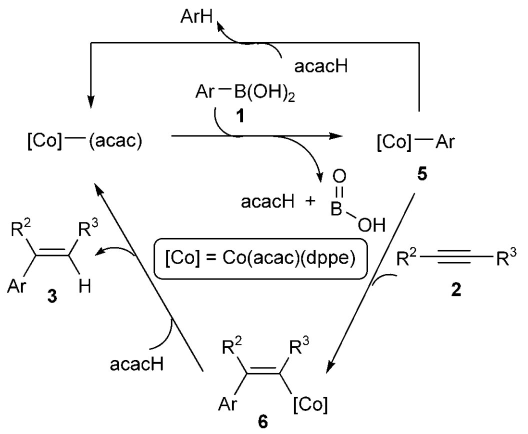
[a] Unless otherwise stated, all reactions were carried out with organoboronic acid **1** (2.0 mmol), alkyne **2** (1.0 mmol), [Co(acac)$_2$] and dppe (5 mol%) in CH_3CN/THF (4:1; 2.0 mL) at 80°C for 12 h. [b] Isolated yield. [c] Yield in parenthesis was determined by the ^{1}H NMR integration method with mesitylene as an internal standard. [d] The reaction was carried out in CH_3CN/THF (3:1). [e] The reaction time was extended to 24 h.

yield when held at 90°C for 24 h. Based on these studies, we chose [Co(acac)$_2$] and dppe in a mixture of CH_3CN/THF (4:1) at 80°C for 12 h as the standard conditions for the coupling reactions (see Table 1).

Next, we examined the scope of organoboronic acids **1** and alkynes **2** in the addition reaction under the standard reaction conditions. Both **1b** and **1c** efficiently underwent hydroarylation with **2a** to give products **3ba** and **3ca** in 96 and 91% yields, respectively (Table 1, entries 2 and 3). In contrast, 2-methoxyphenylboronic acid was inactive. Under similar reaction conditions, **1d**, **1e**, and **1f** also efficiently coupled with **2a** to provide the corresponding hydroarylation products **3da–fa** in 94, 67, and 93% yields, respectively (Table 1, entries 4–6). The particularly low yield of **3ea** (Table 1, entry 5) is probably attributed to the strong electron-withdrawing effect of the nitro group, leading to low nucleophilicity of the 3-nitrophenyl moiety. Alkenylboronic acids also worked well for the reaction. Thus, *trans*-2-phenylvinylboronic acid (**1g**) reacted with **2a** to afford the substituted 1,3-diene product **3ga**, both regio- and stereoselectively in 80% yield (Table 1, entry 7). Interestingly, unlike 2-methoxyphenylboronic acid, the *ortho*-substituted heteroaromatic boronic acid (**1h**) afforded the expected product **3ha** in 88% yield (Table 1, entry 8). In all of the above cobalt-catalyzed reactions that involve **2a** as the alkyne substrate, the addition is regio- and stereoselective to give only the *cis*-hydroarylation products. Under the reaction conditions employed, a small amount of the protodeboronation products of the organoboronic acids were produced, even when a 1:1 ratio of organoboronic acid and alkyne was used.

In addition to **2a**, compounds **2b** and **2c** also reacted with **1f** to provide hydroarylation products **3fb** and **3fc** (90 and 86% yield, respectively) with *cis* stereoselectivity. The high regioselectivity of these reactions with alkynes **2a–c** indicates that the addition belongs to a Michael-type addition, with the aryl or styryl group adding to the β carbon of the alkyne moiety. Surprisingly, unlike the reactions using alkynes **2a–c**, the hydroarylation of propargyl alcohol **2d** and propargyl carbamate **2e** provided *trans* addition products **4fd** and **4fe** in 82 and 78% yields, respectively after 24 h, in a highly regio- and stereoselective manner. In contrast, compound **2f** afforded a 1:1 mixture of the *cis* and *trans* addition products **3ff** and **4ff** in a 79% combined yield. Shorter reaction times are necessary for activated alkynes **2a–c** and longer reaction times are required for propargyl alcohol **2d** and propargyl carbamate **2e**.

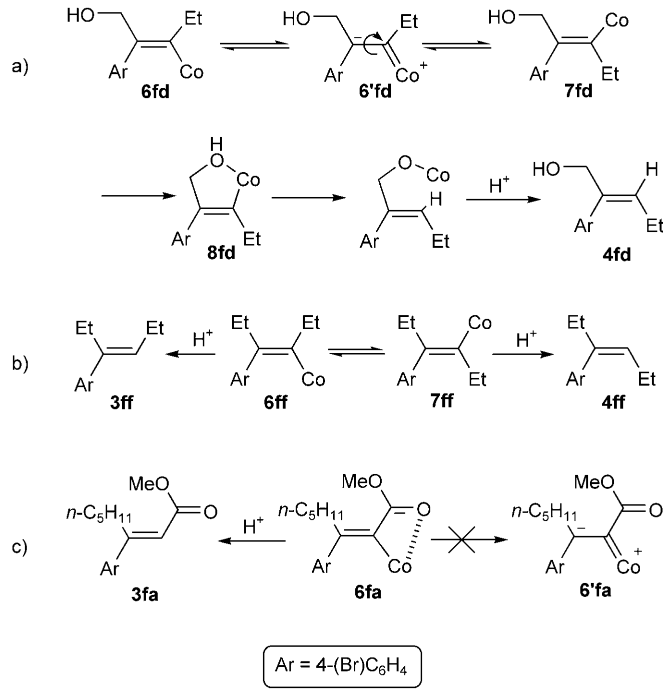
Based on the known metal-catalyzed couplings of organometallic reagents and alkynes, a possible reaction mechanism for the present hydroarylation reaction has been proposed (Scheme 1).[4,6] Transmetallation of an arylboronic acid **1** with [Co(acac)$_2$]/(dppe) gives an aryl cobalt(II) intermediate **5**, together with acacH and HOBO.[10] Coordinative carbocobaltation of alkyne **2** with the cobalt–aryl bond of **5** provides the cobalt–alkenyl intermediate **6**. Protonolysis of intermediate **6** by acacH affords hydroaryla-



Scheme 1. Proposed mechanism for the coupling of organoboronic acids **1** and alkynes **2**.

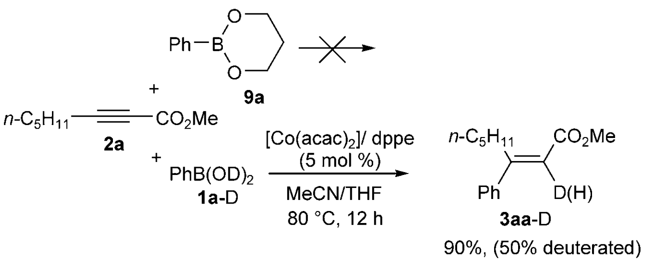
tion product **3** and regenerates the active cobalt(II) species for further catalytic cycles. A competitive pathway through protonolysis of the cobalt(II)–aryl bond in species **5** by acacH leads to the observed protodeboronation product, ArH, of arylboronic acid **1**. This accounts for the requirement of extra arylboronic acid (2 equiv) for this reaction.

The hydroarylation of alkynes with a -CH$_2$OH or -CH$_2$NH(Boc) group show unusual selectivity for *trans* addition.[11] This stereoselectivity has not been reported so far in the metal-catalyzed hydroarylation of alkynes with arylboronic acids,[5,6] and may be explained based on the proposed process illustrated in Scheme 2. It is likely that intermediate **6fd**, obtained from the carbocobaltation of **2d**, undergoes facile *E*–*Z* isomerization to intermediate **7fd** via a cobalt carbene species **6′fd** (Scheme 2a). The presence of the hydroxymethyl group in **7fd** stabilizes the cobalt intermediate by forming a five-membered oxametallocycle (**8fd**). The latter becomes the major cobalt intermediate among **6–8fd** in the catalytic solution, and is protonated to give the observed *trans*-hydroarylation product **4fd** stereoselectively. A similar explanation can be applied to the hydroarylation of alkyne **2e** to give **4fe**. For the carbocobaltation of 3-hexyne, facile *E*–*Z* isomerization of intermediates **6ff** and **7ff** also occurs (Scheme 2b). In the absence of a chelating heteroatom, protonation of the two intermediates leads to a 1:1 mixture of *E* and *Z* isomers **3ff** and **4ff**, respectively. On the other hand, intermediate **6fa** from the carbocobaltation of **2a** does not form the metal carbene species **6′fa** due to the electron-withdrawing property of the ester group (Scheme 2c). Thus, no *E*–*Z* isomerization occurs and only the *cis*-hydroarylation product **3fa** was obtained. The analogous regio- and *cis*-stereoselective hydroarylation of **2c** is attributed to the coordination of the pyridyl group to the metal center during the carbocobaltation of the alkyne.[6b]



Scheme 2. Proposed key pathways for the observed stereochemistry of the hydroarylation of various alkynes.

In the reaction, the organoboronic acid appears to play a dual role, acting as both a transmetallating agent and a proton source.[4g,12] The dual role of the organoboronic acid is illustrated by the treatment of phenylboroxine or **9a** with **2a** in the presence of the [Co(acac)$_2$]/dppe system, which did not give the hydroarylation product. However, treating phenylboroxine with D$_2$O (3 equiv) to provide PhB(OD)$_2$ (**1a**-D), followed by treatment with **2a** in the presence of the [Co(acac)$_2$]/dppe system gave the deuterated coupling product **3aa**-D in 90% isolated yield, in which approximately 50% of the vinyl protons were deuterated based on ^{1}H NMR spectroscopy results (Scheme 3).[6a,12]



Scheme 3. Illustrating the dual role of the organoboronic acid, which acts as both a transmetallating agent and a proton source.

In conclusion, we have demonstrated a series of cobalt(II)-catalyzed cross-coupling reactions of organoboronic acids with alkynes. The reaction provides a convenient method for the synthesis of highly substituted olefins by using less expensive cobalt complexes as catalysts under base-free conditions. In addition, these are the first cobalt-catalyzed addition reactions of organoboronic acids to alkynes. An unusual *trans* stereochemistry for the hydroarylation of substituted propargyl alcohol and amine was observed, due to the formation of five-membered oxa- or azametallacycles during the catalytic reaction. It is likely that the catalytic reaction involves cobalt(II) as the active catalyst because the reaction proceeds smoothly with [Co(acac)$_2$]/dppe, but becomes very slow if [Co(acac)$_3$]/dppe is used as the catalyst. The organoboronic acid plays a dual role, acting both as a carbon nucleophile as well as a proton source in the reaction.

Experimental Section

General procedure for the addition reaction of 1 with 2: A sealed tube containing [Co(acac)$_2$]/dppe (1 equiv dppe to [Co(acac)$_2$]; 0.050 mmol, 5.0 mol %) and arylboronic acid **1** (2.00 mmol) was evacuated and purged with nitrogen gas three times. Freshly distilled CH_3CN (1.6 mL), THF (0.4 mL), and alkyne **2** (1.00 mmol) were added to the system. The dark-red reaction mixture was stirred at 80 °C for 12 h. The mixture was then filtered through a short Celite and silicagel pad and was thoroughly washed with dichloromethane. The filtrate was concentrated, and the residue was purified on a silicagel column using hexane/ethyl acetate as the eluent to afford the desired addition product **3**.

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Keywords: alkynes · cobalt · cross-coupling · hydroarylation · organoboronic acids

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[9] In the presence of $Co(OH)_2$ and HacacR, R = Me, CF_3, Ph, *t*Bu, the addition product **3aa** was obtained in 95, 99, 82, and 43 % yield, respectively (80 °C for 24 h).

[10] The observation of $B(OH)_3$ was confirmed by ^{11}B NMR spectroscopy; for the transmetallation from the boron atom to the metal by β-aryl elimination, see: P. Zhao, C. D. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.* **2007**, *129*, 1876.

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