Pd-Catalyzed Addition of Organoboronic Acids to Alkynes at Room Temperature

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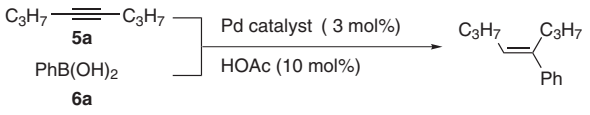
Abstract: Combination of $Pd(OAc)_2$ with 2-bromo-1,3-bis-[diphenylphosphenomethyl)]benzene (**1**) or 2-bromo-1,3-bis-[di-*tert*-butylphosphenomethyl)]benzene (**3**) catalyzed hydroarylations and hydroalkenylations of various alkynes more efficiently in terms of reaction time and temperature.

Key words: palladium, organoboronic acids, alkynes, catalyst, hydroarylation, hydroalkenylation

Pd-catalyzed cross-coupling reaction of organoboronic acids with various aryl halides, called the Suzuki reaction, has provided a variety of stereodefined biaryls,[1] alkadienes,[2] and trienes.[3] Since organoboron compounds become readily available or can be easily prepared, much attention has been devoted to developing a new aspect of organoboron chemistry.

Addition reactions of organoboronic acids to alkynes can also provide a general entry to stereodefined alkadiene or arylated alkenes. Such hydroarylation and hydroalkenylation have been attained by palladium-, rhodium-, and nickel-catalyzed addition of organometallic compounds to the alkynes,[4] or by titanium-catalyzed hydrozincation of alkynes.[5] There is still a continuing need for simple and versatile synthetic methods for this important class of compounds. In continuation of our research interest in hydroarylation and hydroalkenylation of alkynes and allenes by organoboron compounds,[6] we are very much interested in finding more efficient catalysts. In this regard, we have observed that ligands coordinating to palladium could play a vital role in catalytic activities. At first we started the present study with 4-octyne (**5a**) and phenylboronic acid (**6a**) under palladium catalysis (Equation 1) and summarized our results in Table 1. Previously, we have reported this reaction catalyzed by $[Pd(PPh_3)_4]$, where it required 60–80 °C and a long reaction time (24 h) for completion (entry 1). During the course of scrutinizing the reaction conditions by combination of various palladium compounds with different ligands, it was interesting to observe that the reaction was complete at lower temperature and in shorter time when bidentate ligands such as dppe and dppb were employed in combination with $Pd(OAc)_2$ without much change in reaction efficiency (entries 2–4). It is noteworthy that palladium acetate combined with



Equation 1

monodentate ligands did still require higher temperatures (80 °C) and ligand-free palladium acetate did not catalyze this transformation (entries 5–7). These observations inspired us to search for yet more efficient ligands, which would make the reaction possible at even lower temperatures. It has been postulated that excellent catalytic activities have arisen from the use of bidentate ligands with an aromatic ring spacer which were used as precursors in the synthesis of pincer complexes in variety of reactions.[7] Hence, we have prepared three ligands **1**–**3** and one Pd-pincer complex **4** for our study (Figure 1).

Table 1 Addition of Phenylboronic Acid (**6a**) to 4-Octyne (**5a**) under Various Conditions

No	Catalyst	Solvent	Temp (°C)/ time (h)	Yield (%)
1	$Pd(Ph_3P)_4$	1,4-Dioxane	60, 48	93
2	$Pd(OAc)_2$dppe	1,4-Dioxane	50, 15	85
3	$Pd(OAc)_2$dppb	1,4-Dioxane	50, 15	78
4	$Pd(OAc)_2$dppf	1,4-Dioxane	50, 15	71
5	$Pd(OAc)_2$, $(cy)_3P$	1,4-Dioxane	80, 18	63
6	$Pd(OAc)_2$, $(t\text{-}Bu)_3P$	1,4-Dioxane	80, 15	67
7	$Pd(OAc)_2$	1,4-Dioxane	100, 24	7
8	Complex **3**	1,4-Dioxane	120, 48	N.R
9	**$Pd(OAc)_2$, 1**	**1,4-Dioxane**	**25, 5**	**95**
10	$Pd(OAc)_2$, **1**	Toluene	25, 24	63
11	$Pd(OAc)_2$, **1**	$CHCl_3$	25, 8	75
12	Pd $(OAc)_2$, **1**	THF	25, 10	82
13	$Pd(OAc)_2$, **1**	DMF	25, 12	71
14	$PdCl_2$, **1**	1,4-Dioxane	100, 24	N.r.
15	$Pd_2(dba_3)$, **1**	1,4-Dioxane	100, 24	Trace
16	$Pd(OAc)_2$, **2**	1,4-Dioxane	80, 24	61

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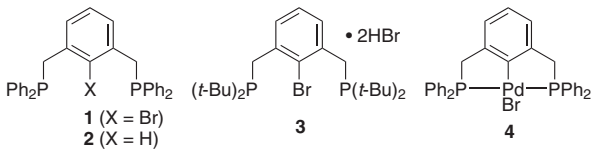
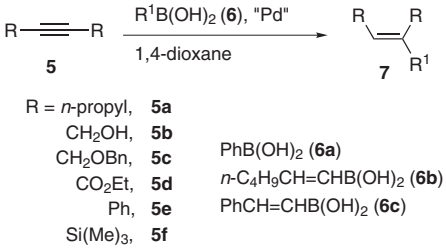


Figure 1



Equation 2

These ligands **1**, **2**, and **3**, and the Pd-pincer complex **4** were prepared according to known methods. First, we tested the catalytic activity of Pd-pincer complex **4** for the hydrophenylation of 4-octyne (**5a**) with phenylboronic acid. To our surprise, the reaction did not afford the addition product **7aa** even at higher temperature (entry 8). On the other hand, the same reaction occurred by mixing the ligand **1** in combination with $Pd(OAc)_2$ in situ in a 1:1 ratio. GC analysis showed that the reaction was completed at room temperature within five hours. Product **7aa** could be isolated in 95% yield (entry 9).

The present reaction was scrutinized in various solvents such as toluene, chloroform, THF, and DMF, and by other palladium compounds such as $PdCl_2$ and $Pd_2(dba)_3$ (entries 10–15). It was observed that the optimal conditions to yield product **7aa** were a combination of $Pd(OAc)_2$ (3mol%), ligand **1** (3 mol%), and acetic acid (0.10 equiv) in 1,4-dioxane at room temperature.[8] The combination of $Pd(OAc)_2$ with ligand **2** required higher temperature (80 °C) and a prolonged reaction time (24 h) to afford the product **7aa** in only 61% yield. It implies that the presence of a bromide group in ligand **1** on the aromatic ring could greatly enhance the catalytic activity.

This experimental protocol was applied to various types of symmetrical alkynes **5a–f** such as a non-polar alkyne **5a**, polar alkynes **5b** and **5c**, an electron deficient alkyne **5d**, a sterically hindered alkyne **5e**, and an electron-rich alkyne **5f** toward three different types of organoboronic acids **6a–c** (Equation 2). We have compared two catalytic systems: the previously reported conditions A, catalyzed by $Pd(PPh_3)_4$, and the present conditions B, catalyzed by $Pd(OAc)_2$ ligand **1**. Our results are summarized in Table 2. Under the present conditions B, 4-octyne (**5a**) and 2-butyne-1,4-diol (**5b**) underwent the reactions very smoothly with **6a–c** at room temperature to give **7aa–ac** and **7ba–bc** in good to excellent yields, respectively (entries 1–8). The reactions of **5c** with **6a–c** gave products **7ca–7cc** in high yields without debenzylation (entries 9–11), in contrast to our observations during the reaction of **5c** with **6a**,**b** under $Pd(PPh_3)_4$-catalyzed reaction. As we expected, diethyl acetylenecarboxylate (**5d**) with the three boronic acids **6a–c** gave **7da**, **7db**, and **7dc** in 91%, 66% and 74% yields, respectively (entries 12–14).

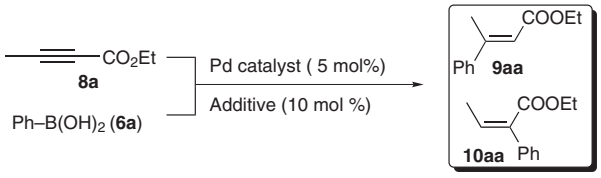
The reaction of diphenylacetylene (**5e**) with phenylboronic acid **6a** in the presence of $Pd(PPh_3)_4$ was completed at 80 °C in 12 hours (entry 15). The same reaction under conditions B was successfully completed within five hours at ambient temperature (entry 16). The similar reactivity was observed with *n*-hexenylboronic acid (**6b**) and phenylvinylboronic acid (**6c**) to give **7eb** and **7ec** (entries 17–19). Finally, the highly electron-dense alkyne **5f** did not undergo an addition reaction even under harsh conditions (entry 20).

Next we have applied this strategy to conjugated alkyne carboxylates. Once again, we attempted to optimize the reaction conditions for addition of phenylboronic acid (**6a**) to ethyl-2-butynoate (**8a**) as shown in Equation 3 and Table 3.

Table 2 Addition of Organoboronic Acids **6a–c** to Symmetrical Alkynes **5a–f**

	R	R^1	Reaction conditions[a]	Temp (°C)/ time (h)	Product	Yield (%)
1	**5a**	**6a**	A	60, 48	**7aa**	95
2			B	25, 5	**7aa**	93
3		**6b**	A	80, 24	**7ab**	89
4			B	25, 6	**7ab**	78
5		**6c**	B	25, 6	**7ac**	82
6	**5b**	**6a**	B	25, 8	**7ba**	86
7		**6b**	B	25, 10	**7bb**	76
8		**6c**	B	25, 10	**7bc**	79
9	**5c**	**6a**	B	25, 10	**7ca**	82
10		**6b**	B	25, 10	**7cb**	72
11		**6c**	B	25, 10	**7cc**	74
12	**5d**	**6a**	B	25, 3	**7da**	91
13		**6b**	B	25, 4	**7db**	76
14		**6c**	B	25, 4	**7dc**	74
15	**5e**	**6a**	A	80, 12	**7ea**	91
16		**6b**	B	45, 5	**7ea**	85
17			A	80, 12	**7eb**	75
18			B	45, 7	**7eb**	78
19		**6c**	B	50, 7	**7ec**	76
20	**5f**	**6d**	B	100, 24	**7fa**	N.r.

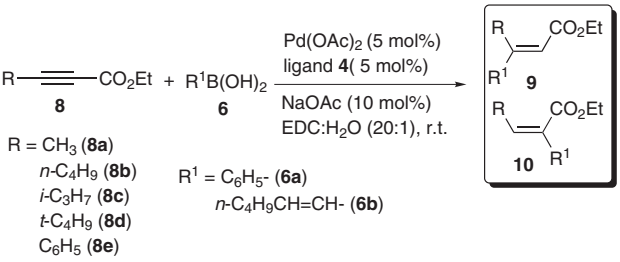
[a] Condition A: $Pd(PPh_3)_4$ (3 mol%), HOAc (10 mol%) in 1,4-dioxane at 60–80 °C. Condition B: $Pd(OAc)_2$ (3 mol%), ligand **1** (3 mol%), HOAc (10 mol%) in 1,4-dioxane at r.t.



Equation 3

When we employed the previously reported conditions, the reaction was complete at 50 °C in 15 hours to give a 85:15 mixture of the expected products **9aa** and **10aa** in combined 91% yield (entry 1). Compared to $Pd(PPh_3)_4$, $Pd(OAc)_2$ with a phosphine ligand such as PPh_3 or tri(*n*-butyl)phosphine resulted in better regioselective phenylation (entries 2 and 3). We were very gratified that an 1:1 mixture of bidentate phosphine ligands and $Pd(OAc)_2$ dramatically improved the regioselectivity. While 1,4-bis(diphenylphosphine)butane (dppb) gave a 97:3 mixture of **9aa** and **10aa** in 76% yield, 1,4-bis(diphenyl-phosphine)ethane (dppe) gave **9aa** along with a trace of **10aa** (2%, entries 4 and 5). When the present phenylation was tried by simply employing ligand **3** in combination with $Pd(OAc)_2$, the reaction did not proceed even after 24 hours at 80 °C (entry 6). When a mixture of palladium acetate and ligand **3** in 1,4-dioxane was treated with 10 mol% of sodium acetate and additional 10% of acetic acid, the reaction occurred very smoothly at room temperature in three hours to give a 93:7 mixture of **9aa** and **10aa** (entry 7). In fact, almost complete regiospecificity was obtained when a 1:1:2 mixture of $Pd(OA)_2$, ligand **3** and sodium acetate was treated with a mixture of **8a** and **6a** in aqueous ethylene dichloride (EDC–H_2O = 20:1; entry 8).[9] The same reaction with ligand **1** resulted in moderate regioselectivity (entry 9). The conditions described for entry 8 were used for our further studies.

In order to prove the versatility and diversity of the methodology, we carried out arylation and alkenylation with five conjugated alkynecarboxylates **8a**–**e** by varying the size of alkyl groups and two different organoboronic acids (**6a** and **6b**, Equation 4).



Equation 4

Table 4 Addition Reactions of Organoboronic Acids to Alkynecarboxylate

No	Substrates	$R^1B(OH)_2$	Yields (%)	Ratio **9**:**10**
1	**8a**	**6a**	89	Only **9aa**
2		**6b**	74	Only **9ab**
3	**8b**	**6a**	85	**9ba**:**10ba** (98:2)
4		**6b**	81	**9bb**:**10bb** (94:6)
5	**8c**	**6a**	76	**9ca**:**10ca** (85:15)
6		**6b**	77	**9cb**:**10cb** (75:25)
7	**8d**	**6a**	79	Only **10da**
8		**6b**	73	Only **10db**
9	**8e**	**6a**	92	**9ea**:**10ea** (83:17)
10		**6b**	88	**9eb**:**10eb** (85:15)

Table 3 Addition of Phenylboronic Acid (**6a**) to Ethyl 2-Butynoate (**8a**) under Various Conditions

	Catalyst ligand	Additives	Solvent	Temp (°C)/time (h)	Yield (%) (**9aa**:**10aa**)
1	$Pd(PPh_3)_4$	HOAc	THF	50/15	91 (85:15)
2	$Pd(OAc)_2PPh_3$	HOAc	$CHCl_3$	50/15	95 (95:5)
3	$Pd(OAc)_2$ *n*-$(Bu)_3P$	HOAc	THF	50/5	88 (92:8)
4	$Pd(OAc)_2$dppe	HOAc	$CHCl_3$	50/5	80 (92:8)
5	$Pd(OAc)_2$dppb	HOAc	$CHCl_3$	50/5	76 (97:3)
6	$Pd(OAc)_2$, **3**	–	Dioxane	80/24	Trace
7	$Pd(OAc)_2$, **3**	NaOAc HOAc	Dioxane	r.t./2–3	91 (97:3)
8	$Pd(OAc)_2$, **3**	NaOAc	EDC–H_2O	r.t./12	89 (**9aa** only)
9	$Pd(OAc)_2$, **1**	HOAc	Dioxane	r.t./24	70 (90:10)

Our results are summarized in Table 4. Ethyl 2-butynoate (**8a**) was reacted with 1-hexenylboronic acid (**6b**) to give exclusively products **9ab** in 74% yield (entry 2). Although the alkyne carboxylate **8b** is structurally similar to **8a**, there was a little difference in regioselectivity. A small amount of 1,3-addition product **10ba** was observed with phenylboronic acid (**6a**) whereas more **10bb** was formed with 1-hexenylboronic acid (**6b**, entries 3, 4) In order to find out the effect of the size of alkyl group, we replaced the methyl group in **8a** by an isopropyl group. The resulting substrate **8c** was then subjected to the same reaction conditions. While the reaction of **8c** with **6a** gave products **9ca** and **10ca** in 85:15 ratio, the reaction with **6b** gave products **9cb** and **10cb** in 75:25 ratio (entries 5, 6). Substrate **8d**, with an introduced bulky *t*-butyl group at the alkyne end, gave rise to a complete reversal of regioselectivity with both **6a** and **6b** to form the 1,3-addition product **10da** and **10bd** in 79% and 73% yields, respectively. Finally, the reaction of ethyl phenylpropynoate (**8e**) also underwent very smooth addition with both **6a** and **6b** to give products **9ea** and **10ea** in a 83:17 ratio and **9eb** and **10eb** in a 85:15 ratio, respectively.

In conclusion, we have demonstrated that combinations of $Pd(OAc)_2$ ligand **1** and $Pd(OAc)_2$ ligand **2** catalyzed hydroarylations and hydroalkenylations of various alkynes in a highly efficient manner. Particularly, ligands possessing an aromatic ring as a spacer (**1** and **3**) enhanced the rate of the Pd-catalyzed addition reactions of organoboronic acids to various alkynes greatly. More studies on influence of the bromide group in the ligands **1** and **3** are underway.

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(8) **Preparation of Compound 7; General Procedure**
A 10 mL round-bottomed flask was charged with an alkyne **5a–f** (0.40 mmol), organo boronic acid **6a–c** (0.48 mmol), ligand **1** (3 mol%), $Pd(OAc)_2$ (3 mol%) and then 1,4-dioxane (1.0 mL) at 0 °C. The reaction mixture was purged with dry argon gas and was treated with HOAc (0.04 mmol) via a 10 μL gastight syringe at 0 °C. The mixture was stirred at 25 °C as described in Table 2. On completion of the reaction, the mixture was cooled to 0 °C, quenched with H_2O, and then extracted with Et_2O. The organic portion was washed with sat. NaCl solution, dried over anhyd $MgSO_4$, and concentrated in vacuo. The residue thus obtained was purified by flash chromatography (EtOAc–hexane = 1:10) to give product **7**. All the isolated products were characterized by IR, ^1H NMR, ^{13}C NMR and HRMS.

(9) **Preparation of Compounds 9 and 10; General Procedure**
A 10 mL round-bottomed flask was charged with an alkyne carboxylate **8a–e**, (0.40 mmol), organoboronnic acid **6a–c** (0.48 mmol), $Pd(OAc)_2$ (5 mol%), ligand **3** (5 mol%), NaOAc (2.1 equiv, 0.48 mmol) and 0.95 mL of ethylene dichloride and 0.05 mL of H_2O. The reaction mixture was stirred vigorously until the absence of starting material was observed on TLC. Then the mixture was diluted with Et_2O (10 mL) plus H_2O (5 mL) and extracted twice with Et_2O (2 × 10 mL). The combined organic portion was washed with a sat. brine solution, dried over anhyd $MgSO_4$, and concentrated in vacuo. Finally, the residue was purified by flash chromatography (EtOAc–hexane = 1:10) to get **9** and/or **10**. The product structure was assigned by IR, ^1H NMR, ^{13}C NMR and HRMS.