Palladium-Catalyzed Addition of Organoboronic Acids to Conjugated Alkynecarboxylates

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Miyaura discovered the addition of organoboronic acids to α,β-unsaturated ketones by a rhodium-phosphine complex in 1997.[1] Since then, transition metal-catalyzed addition to unsaturated bonds with organometallic compounds has been a subject of intensive work in the area of organic and organometallic chemistry. Use of the chiral BINAP-rhodium catalyst was further demonstrated to achieve asymmetric additions of organoboronic acids to various carbonyl compounds.[2] The rhodium-catalyzed addition of arylboronic acids to unactivated alkenes and alkynes were also accomplished.[3] Similar hydroarylations have been attained by nickel-catalyzed addition of organometallic compounds to the alkynes[4] or by titanium-catalyzed hydrozincation of alkynes.[5]

Although the Rh-catalyzed hydroarylation of alkynes has advantages over other methods due to high syn-selectivity and high efficiency, this reaction has a severe limitation applicable to only internal alkynes and arylboronic acids. Recently, we reported Pd-catalyzed hydroarylation which has widely applicable to terminal alkynes as well as internal alkynes.[6] In continuation of our research program, we have carried out a study aimed toward developing regio- and stereoselective Pd-catalyzed hydroarylation and hydroalkenylation of unsymmetrical alkynes.

Here we wish to report that palladium complexes catalyze hydroarylation (and hydroalkenylation) of conjugated alkynecarboxylates, where high regioselectivity and syn-stereoselectivity can be attained by properly choosing the ligand and the reaction conditions. First, we reexamined the reaction of alkyne **1a** with phenylboronic acid **2a** under a variety of conditions to obtain better regioselectivity (Table 1). When the reaction of alkyne **1a** with phenylboronic acid **2a** in the presence of 3 mol% $Pd(PPh_3)_4$ and 10 mol% AcOH was conducted in 1,4-dioxane at 50 °C for 15h, a 19 : 1 mixture of the addition products **3aa** and **4aa** was isolated in combined 97% yield (entry 1). This reaction worked quite well in both protic solvent such as ethanol and aprotic solvents such as THF, chloroform, although toluene resulted in a little lower yield of the products (entry 2-5). Among these solvents we tested, 1,4-dioxane and chloroform turned out to be the best in terms of reaction efficacy and regioselectivity. Next, the catalytic activity of palladium acetate toward this reaction was screened in combination with various ligands. Palladium complexes formed with palladium acetate and triphenylphosphine catalyzed this reaction in almost same manner as $Pd(PPh_3)_4$ (entry 6). The bidentate ligands, dppe, dppp, dppb, or dppf, have shown a dramatic increase in regioselectivity (entry 7-10). A combination of $Pd(OAc)_2$ and dppe catalyzed this reaction to give the product **3aa** in 96% isolated yield and 99% isomeric purity in gram-scale reaction (entry 7).

This implied that the catalytic activity of palladium

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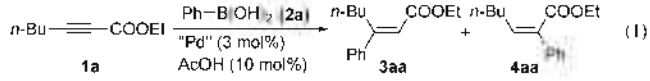
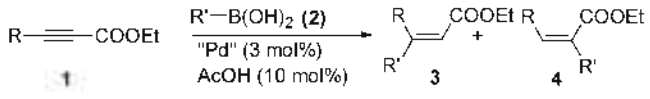
Table 1. Pd-Catalyzed Hydroarylation/alkenylation of Alkynes **1a** with Organoboronic Acids **2a** at 50 °C under various conditions



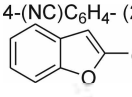
entry	Pd compds (3 mol%) Ligands (6 mol%)	Solvent	Time (h)	Isolated Yield, %	3 : 4 ratio[a]
1	$Pd(PPh_3)_4$	1,4-dioxane	15	97	95:5
2	$Pd(PPh_3)_4$	ethanol	15	83	90:10
3	$Pd(PPh_3)_4$	toluene	15	72	90:10
4	$Pd(PPh_3)_4$	THF	15	86	85:15
5	$Pd(PPh_3)_4$	chloroform	15	97	97:3
6	$Pd(OAc)_2/PPh_3$	chloroform	15	95	20:1
7	**$Pd(OAc)_2$/dppe**	**chloroform**	**5**	**96**	**99:1**
		1,4-dioxane	**5**	**93**	**99:1**
8	$Pd(OAc)_2$/dppp	chloroform	5	80	98:2
9	$Pd(OAc)_2$/dppb	chloroform	5	76	98:2
10	$Pd(OAc)_2$/dppf	chloroform	5	72	92:8
11	$Pd(OAc)_2/(t\text{-}Bu)_3P$	chloroform	5	82	1:1
12	$Pd(OAc)_2/(t\text{-}Bu)_3P$	1,4-dioxane	5	89	1:4
13	**$Pd(OAc)_2/(t\text{-}Bu)_3P$**	**THF**	**5**	**78**	**1:6**

[a]The prpduct ratios were determined by integrations of specific peaks in ^1H NMR spectra of the crude products.



R= $CH_3(CH_2)_4$- (**1a**)
TBSOCH$_2$-(**1b**)
$(CH_3)_3C$- (**1c**)
Ph- (**1d**)

R'= C_6H_5- (**2a**)
3,5-$(CH_3)_2C_6H_3$- (**2b**)
4-$(CH_3O)C_6H_4$- (**2c**)
n-C_4H_9CH=CH- (**2d**)
C_6H_5CH=CH- (**2e**)
4-$(NC)C_6H_4$- (**2f**)



Scheme 1

Table 2. Pd-Catalyzed Hydroarylation/alkenylation of Alkynes **1a-d** with Organoboronic Acids **2** in the presence of 10 mol% AcOH

#	Alkynes (1)	$RB(OH)_2$ (2)	conditions, temp (°C), time (h)	Products	% Yield (ratio)	#	Alkynes (1)	$RB(OH)_2$ (2)	conditions, temp (°C), time (h)	Products	% Yield (ratio)
1	1a	2b	A, 60, 12	**3ab**	89	7	1b	2c	A, 50, 10[a]	**3bc, 4bc**	75 (3:1)
			B, 60, 8	**3ab, 4ab**	53 (1:20)				B, 60, 4	**3bc, 4bc**	95 (1:4)
2	1a	2c	A, 60, 27[a]	**3ac, 4ac**	71 (7:1)	8	1b	2d	A, 50, 10	**3bd, 4bd**	80 (5:1)
			B, 60, 4	**3ac, 4ac**	88 (1:5)				B, 60, 4	**3bd, 4bd**	86 (1:3)
3	1a	2d	A, 50, 20	**3ad**	86 (20:1)	9	1c	2c	A, 80, 24[a]	**3cc, 4cc**	75 (1:50)
			B, 35, 24	**3ad, 4ad**	89 (1:6)				B, 60, 20	**3cc, 4cc**	71 (1:50)
4	1a	2e	A, 50, 22	**3ae**	67	10	1c	2d	A, 80, 24[a]	**3cd, 4cd**	51 (1:4)
			B, 50, 12	**3ae, 4ae**	98 (1:3)				B, 60, 4	**4cd**	94
5	1a	2f	A, 50, 20	**3af**	83	11	1d	2c	A, 70, 8[a]	**3dc, 4dc**	98 (5:1)
			B, 60, 4	**3af, 4af**	51 (1:7)				B, 60, 8	**3dc, 4dc**	89 (1:2)
6	1a	2g	A, 60, 20[a]	**3ag, 4ag**	88 (5:1)	12	1d	2d	A, 70, 4[a]	**3dd, 4dd**	98 (4:1)
			B, 60, 5	**3ag, 4ag**	86 (1:3)				B, 50, 24	**3dd, 4dd**	94 (1:2)

[a]Reactions were done in 1,4-dioxane in stead of in chloroform.

complexes as well as the regioselectivity in the present reaction is associated with steric and electronic nature of the phosphine ligand. When we tested tri(tert-butyl)phosphine as a ligand under the present conditions, the regioisomeric ratio of the products **3aa** and **4aa** was changed to 1 : 1 (entry 11). The regioselectivity in the products **3aa** and **4aa** was further reversed to 1 : 4 ratio when this reaction was conducted in 1,4-dioxane. This reverse regioselectivity was increased up to 1 : 6 in THF solvent. Thus, these two different conditions have been applied to a series of conjugated alkynecarboxylates **1a-d** with arylboronic acids (**2a-c**) and alkenylboronic acids (**2d** and/or **2e**) (Scheme 1). Our results are summarized in Table 2. When a combination of palladium acetate and dppe in chloroform or in 1,4-dioxane (**method A**) was subjected to **1a** with various organoboronic acids **2b-g**, the products **3ab-ag** were obtained as major products.

In the other hand, when a combination of palladium acetate and tri(tert-butyl)phosphine in THF (**method B**) was subjected to **1a** with the same organoboronic acids, the products **4ab-ag** were obtained as major products along with the products **3ab-3ag** as minor products, ranging from 3 : 1 to 20 : 1 ratios.

The reverse regioselectivities are very interesting. Thus, we chose two organoboronic acids, 4-methoxyphenylboronic acid (**2c**) and hexenylboronic acid (**2d**) and tested three alkynecarboxylates **1b-1d**. When **1b** was reacted with the boronic acid **2c** under **condition A**, the reaction furnished the product **3bc** and the **4bc** in a ratio of 3 to 1 (entry 7). The same reaction under **condition B** resulted in reverse regioselectivity of 1 to 4. The substrate **1b** with hexenylboronic acid **2d** resulted in the similar trend, where **condition A** gave the products **3bd** and **4bd** in 5 : 1 ratio, while **condition B** gave the reverse regioselectivity of 1 : 3. Then, we prepared a sterically hindered substrate **1c**.[7] When **1c** was reacted with the boronic acid **2c** under **condition A**, the reaction furnished the **4cc** almost exclusively (entry 9). The same reaction under **condition B** resulted in exclusive formation of the **4cc**. The substrate **1c** with hexenylboronic acid **2d** resulted in the similar trend, where both **condition A** and **condition B** gave the **4cd** as a major product.

Finally, we prepared ethyl phenylacetylenecarboxylate **1d** and tested with the boronic acid **2c** and **2d**. As expected, the reaction of **1d** with **2c** and with **2d** under **condition A** gave the products **3dc** and **3dd**, respectively. Similarly, the same reaction with **2c** and with **2d** under **condition B** gave the products **4dc** and **4dd** as major products, respectively (entry 12).

In conclusion, we have shown dramatic change in regioselectivity when organoboronic acids added to alkynecarboxylates under palladium catalysis.

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