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On the regioselectivity of Pd-catalyzed additions of organoboronic acids to unsymmetrical alkynes

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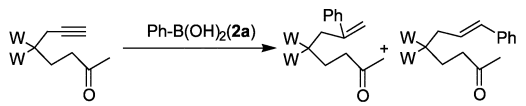
The Pd-catalyzed reaction of unsymmetrical alkynes 1 with organoboronic acids 2 gave a mixture of products 3 and 4, whose ratios were controlled by the electronic as well as steric effects of the substrates 1.

Transition-metal catalyzed addition of organometallic compounds to alkynes has been a subject of intensive work in the area of organic and organometallic chemistry.[1] It has been attained by copper catalyzed addition of lithium diorganocuprates, nickel-catalyzed additions of arylmagnesium or arylzinc reagents into the alkynes or by titanium-catalyzed hydrozincations of alkynes.[2] The rhodium-catalyzed hydroarylation was independently accomplished by Miura, Hyashi, and Lautens.[3] Although the Rh-catalyzed hydroarylation of alkynes has advantages over other methods due to high *syn*-selectivity and high efficiency, this reaction is only applicable to internal alkynes and arylboronic acids.

Recently, we reported Pd-catalyzed hydroarylation and hydroalkenylation which are widely applicable to terminal as well as internal alkynes.[4] The hydroarylation of internal alkynes with organoboronic acids, however, gave a mixture of regioisomeric products. In further studies even with a terminal alkyne bearing a remote keto-group, we isolated the unexpected regioisomer as a minor product (eqn. (1)).

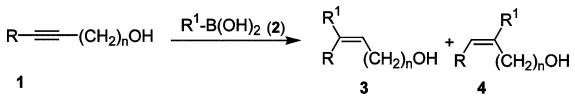


(1)

W = COOEt

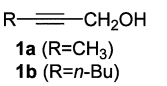
cond:Pd(PPh$_3$)$_4$ (3mol%), AcOH (10mol%), 80 °C, 12h, 1,4-Dioxane, 70%.

We postulated that incorporation of a specific functional group or a sterically bulky group into the alkynes could play a role in controlling regioselectivity. Mechanistically, we anticipated that oxygen or nitrogen atoms present in the alkyne substrate would bind the Lewis acidic RB(OH)$_2$ group and thereby direct the addition site. On the other hand, bulky substituents might block addition to one end of the alkyne. A similar directing effect has been used in developing molecular color sensors for monosaccharides.[5] Here we wish to report the palladium catalyzed hydroarylation (and hydroalkenylation) of unsymmetrical alkynes, where high regioselectivity and *syn*-stereoselectivity can be attained by properly incorporating a directing group or a bulky group (eqn. (2)).

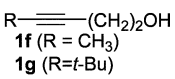


(2)

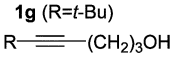
cond: Pd(PPh$_3$)$_4$ (3mol%), AcOH (10mol%), 60-80 °C, 1,4-Dioxane.
2a : PhB(OH)$_2$; **2b** : *n*-C$_4$H$_9$CH=CHB(OH)$_2$



1a (R=CH$_3$)
1b (R=*n*-Bu)
1c (R=TBSOCH$_2$)
1d (R=*iso*-Pr)
1e (R=*t*-Bu)



1f (R = CH$_3$)
1g (R=*t*-Bu)



1h (R = CH$_3$)
1i (R=*t*-Bu)

The –OH, –OAc, 2-Py- and 4-Py- moieties were tested as the directing groups. Methyl-, *n*-butyl, *i*-propyl, or *t*-butyl was attached to the other site of the alkyne. Our results are summarized in Table 1.

Several features are noteworthy. First, a large directing effect was observed from a hydroxyl group when it was located in the propargylic position. Substitution at the 3-position of propargylic alcohol affected regioselectivities in Pd-catalyzed additions. 2-Butyn-1-ol (**1a**) reacted with phenyl- and *n*-hexenylboronic acid under the Pd-catalysis to give the addition products **3aa** and **3ab** in 65% and 70% yields, respectively (entry 1).[6] As the alkyl substituent became bulkier from methyl, *n*-butyl, *i*-propyl to finally *t*-butyl, the formation of regioisomer **4** became predominant. Note that reaction of 4,4-dimethyl-2-pentyn-1-ol (**1e**) with both **2a** and **2b** gave only **4ea** and **4eb**, respectively. Second, as the distance between the hydroxyl group and the triple bond increases, the regioselectivity becomes worse. Substrate **1f**, which has two carbons between the –OH group and the triple bond, showed reasonably good regioselectivities in these addition reactions (entry 6). Substrate **1g**, bearing a *t*-butyl at the 4-position of 3-butyn-1-ol, gave exclusive formation of the addition products **4ga** and **4gb**, respectively (entry 7). The substrates **1h** and **1i**, which have three carbons between the –OH and the triple bond, showed a little regioselectivity.

Third, we tested acetylated substrates of **1a** and **1e** in order to confirm the –OH effect. The absence of the –OH group decreased the regioselectivity dramatically for the present additions (eqn. (3)). The substrate **5a** with phenylboronic acid (**2a**) under the present conditions gave a 5 : 1 mixture of the products **6aa** and **7aa** in 60% yield. Even *tert*-butyl-substituted alkyne **5e** gave a 5 : 1 mixture of the products **6ea** and **7ea** in 75% yield.

Table 1 Reactions of organoboronic acids **2** with alkynes **1**

Entry	Alkyne	R^{1}B(OH)$_2$	Temp. (°C)/ time (h)	Products	Yield (%)[a]	Ratio (**3** : **4**)[b]
1	**1a**	**2a**	60/5	**3aa**	65	Only **3**
		2b	60/5	**3ab**	70	Only **3**
2	**1b**	**2a**	60/5	**3ba, 4ba**	50	3 : 1
		2b	60/5	**3bb, 4bb**	71	2 : 1
3	**1c**	**2a**	80/12	**3ca, 4ca**	80	3 : 1
		2b	60/30	**3cb, 4cb**	60	2 : 1
4	**1d**	**2a**	80/12	**3da, 4da**	75	2 : 3
		2b	80/15	**3db, 4db**	78	1 : 2
5	**1e**	**2a**	80/12	**4ea**	75	Only **4**
		2b	80/15	**4eb**	82	Only **4**
6	**1f**	**2a**	80/12	**3fa, 4fa**	75	10 : 1
		2b	80/12	**3fb, 4fb**	73	5 : 1
7	**1g**	**2a**	80/12	**4ga**	95	Only **4**
		2b	80/12	**4gb**	80	Only **4**
8	**1h**	**2a**	80/12	**3ha, 4ha**	81	2 : 1
		2b	80/15	**3hb, 4hb**	84	2 : 1
9	**1i**	**2a**	80/20	**3ia, 4ia**	87	1 : 3
		2b	80/20	**3ib, 4ib**	91	1 : 2

[a] Isolated yields. [b] Ratios were determined by ^{1}H NMR analysis of the crude products.

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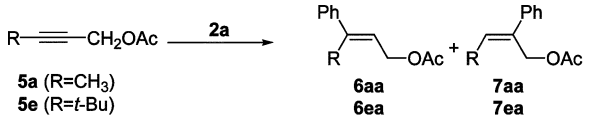
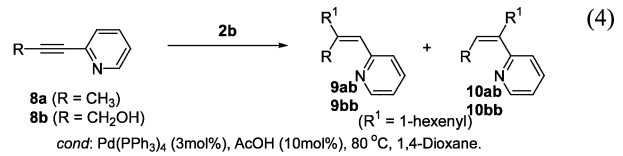


(3)

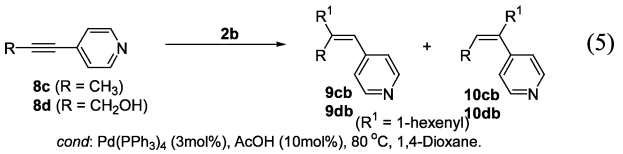
cond: $Pd(PPh_3)_4$ (3mol%), AcOH (10mol%), 80 °C, 1,4-Dioxane.

In order to maximize the site selectivity, we postulated that a certain type of nitrogen might be a better directing group than oxygen. Among the many possible nitrogen-containing directing groups, we have chosen the nitrogen of pyridine. Thus, 1-(2-pyridyl)propyne **8a** under these conditions gave **9ab** exclusively in 87% yield, whereas 1-(4-pyridyl)propyne **8c** gave a 1 : 1 mixture of products **9cb** and **10cb** in 75% yield. Substitution with the 2- and 4-pyridyl group at the 3-position of propargyl alcohol showed a dramatic effect on regioselectivity. Notably, an interesting directing group effect was observed in 2-pyridyl-substituted propargyl alcohol. While the 4-pyridyl-substituted propargyl alcohol **8d** with **2b** gave an almost 1 : 1 mixture of the corresponding products in 84% yield, 2-pyridyl-substituted propargyl alcohol **8b** with **2a** under these conditions gave the product **9bb** exclusively in 70% yield.



(4)

cond: $Pd(PPh_3)_4$ (3mol%), AcOH (10mol%), 80 °C, 1,4-Dioxane.



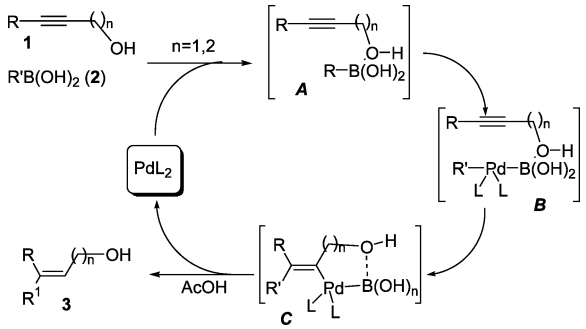
(5)

cond: $Pd(PPh_3)_4$ (3mol%), AcOH (10mol%), 80 °C, 1,4-Dioxane.

Here the catalytic reaction was highly stereoselective with the organic group on boronic acid adding to the triple bond in *syn* fashion. The stereochemistry of the products was confirmed by a NOESY study. We observed the formation of *E*-isomer solely for all cases. A plausible explanation for the formation of the compound **3** is shown in Scheme 1.

Organoboronic acids (**2**) can interact with the hydroxyl group of the substrate **1** attractively to form intermediate **A**. Oxidative addition of the intermediate **A** into PdL_2 forms the intermediate **B**. The intermediate **B** can undergo carbopalladation regioselectively to form **C**. Cleavage of the C–Pd bond by a proton from either acetic acid or boronic acid gives the product **3**. As the size of the R-group in the substrate **1** increases, carbopalladation of **B** might be retarded to eventually form the product **4**.

In conclusion, we have shown an electronic factor and steric factors that control the regioselectivity in Pd-catalyzed additions of organoboronic acids to unsymmetrical alkynes. Strong directing groups such as –OH and 2-pyridyl groups might control the site of addition by chelation as shown in Scheme 1 and bulky groups such as *tert*-butyl give the regioisomer **4** by blocking one site. Although



Scheme 1

mechanistic studies are needed to figure out the origin of the regioselectivities shown here, the present work could have a good synthetic applicability in preparing stereo- and regiodefined trisubstituted olefins from readily available alkynes.

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Notes and references

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6 General procedure: A 10 mL round-bottomed flask was charged with 2-butynol (**1a**, 45.0 mg, 0.64 mmol), phenylboronic acid (**2a**, 93.6 mg, 0.77 mmol), and $Pd(PPh_3)_4$ (22.1 mg, 0.019 mmol) and then 1,4-dioxane (1.0 mL) was added at 0 °C. The mixture was purged with a dry argon gas and was treated with acetic acid (3.7 μL, 0.064 mmol) *via* a 10 μL gastight syringe at 0 °C. Then the mixture was stirred at 60 °C for 5 h. On completion of the reaction, the mixture was allowed to cool to 0 °C, quenched with water, and then extracted with ether. The organic portion was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate–hexane = 1 : 4) to give **3aa** (61.7 mg, 65%) as a colorless oil. The structures of the products have been satisfactorily characterised by means of FT-IR, ^{1}H NMR, ^{13}C NMR, HRMS and stereochemistry was assigned by NOESY experimentation.