ORGANIC LETTERS

2002
Vol. 4, No. 1
123−125

Regioselective Rhodium-Catalyzed Addition of Arylboronic Acids to Alkynes with a Pyridine-Substituted Water-Soluble Ligand

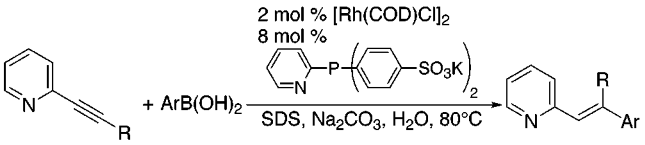
Mark Lautens* and Masahiro Yoshida

*Davenport Research Laboratories, Department of Chemistry, University of Toronto,
Toronto, Ontario, Canada M5S 3H6*

mlautens@chem.utoronto.ca

Received November 6, 2001

ABSTRACT



Alkynyl heteroaromatic compounds reacted with arylboronic acids to give addition products in the presence of [Rh(COD)Cl]$_2$ and pyridine-substituted water-soluble ligand. The reactions proceed to give trisubstituted alkenes with high regioselectivity.

The formation of carbon−carbon bonds using a transition metal catalyst in water represents an attractive strategy in organic synthesis.[1] Recently, we reported the rhodium-catalyzed reactions of various arylboronic acids to aromatic or heteroaromatic olefins[2] using the water-soluble ligand TPPDS **1**.[3] We sought to determine whether a modified ligand system could promote the addition to other unsaturated compounds. Herein we report the rhodium-catalyzed addition reactions of arylboronic acids to alkynes in water. In this reaction, the regioselective addition of arylboronic acids to alkynyl heteroaromatic compounds successfully proceeded in the presence of the novel water-soluble ligand **3**,[4] which has a pyridyl phosphine moiety.

Initial experiments focused on finding a catalyst system that would promote the addition. When the reaction of 2-(1-hexynyl)pyridine **4** with phenylboronic acid **5a** was carried out in the presence of 2 mol % [Rh(COD)Cl]$_2$, 8 mol % TPPDS **1**,[5] Na$_2$CO$_3$, and sodium dodecyl sulfate (SDS) in water at 80 °C for 3 h, the corresponding addition product **6a** was formed in 25% yield (35% yield based on recovered starting material) (Table 1, entry 1). The reaction using TPPTS **2**[5] failed completely (entry 2). Recently, we found the rhodium-catalyzed reaction of arylboronic acids to vinyl heteroaromatic compounds effectively proceeds in the presence of pyridine.[6] On the basis of this result, we examined the pyridine-substituted water-soluble ligand **3**, which improved the yield of **6a** to 51% (entry 3). A series of substituted arylboronic acids were then subjected to these

---

[1] For reviews of organic synthesis in water, see: (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blacky Academic and Professional: London, 1998. (b) Li, C. J.; Chan, T. H. *Organic Reactions in Organic Media*; John Wiley and Sons: New York, 1997. (c) Cornils, B.; Herrmann, W. A. *Aqueous Phase Organometallic Chemistry: Concepts and Applications*; Wiley-VCH: Weinheim, 1998. (d) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. (e) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149. (f) Li, C. J. *Tetrahedron* **1996**, *52*, 5643.

[2] Other examples of the rhodium-catalyzed additions of arylboronic acids to olefins. For additions to enones, see: (a) Sakai, M.; Hayashi, M.; Miyaura, N. *Organometallics* **1997**, *16*, 4229. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579. For additions to α,β-unsaturated esters, see: (c) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951. For additions to vinyl phosphonates, see: (d) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591. For additions to vinyl nitro compounds, see: (e) Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716.

[3] Lautens, M.; Roy, A.; Fukuoka, K.; Fagnou, K.; Martín-Matute, B. *J. Am. Chem. Soc.* **2001**, *123*, 5358.

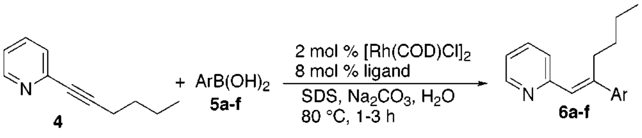
[4] Synthesis of ligand **3**: Herd, O.; Langhans, P. K.; Stelzer, O. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1058.

[5] These ligands are available commercially from Strem Chemicals.

[6] Additives such as pyridine were found to influence the ratio of Heck-type products to addition products in some substrates. A detailed description of these results will appear in the full paper on this reaction.

10.1021/ol010261t CCC: $22.00

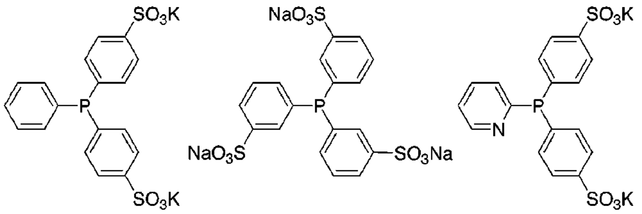
Table 1. Reactions of Alkyne **4** with Various Arylboronic Acids[a]



entry	boronic acid	ligand	product	yield (%)
1	phenyl **5a**	1	**6a**	25 (35)
2	phenyl **5a**	2		nr
3	phenyl **5a**	3	**6a**	51
4	2-methylphenyl **5b**	3	**6b**	81
5	2,6-dimethylpenyl **5c**	3	**6c**	86
6	1-naphthyl **5d**	3	**6d**	72
7[a]	4-methoxyphenyl **5e**	3	**6e**	57
8[a]	4-methoxy-2-methyl-phenyl **5f**	3	**6f**	83

[a] Using 4 mol % [Rh(COD)Cl]$_2$, 16 mol % **3**, and 5 equiv of boronic acid.

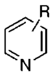
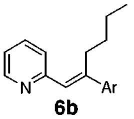
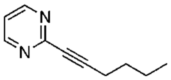
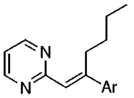
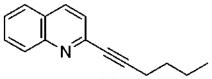
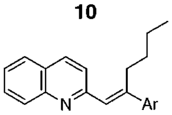
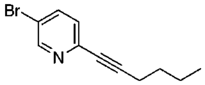
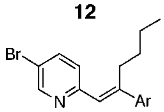
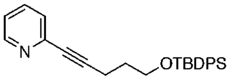
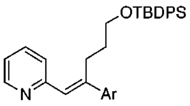
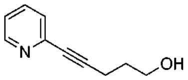
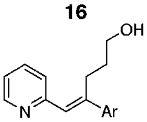
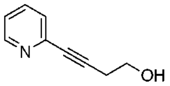
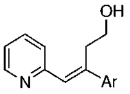
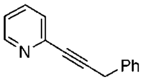
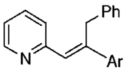
reaction conditions to further define the reaction scope. Substitution in the *ortho* position gave better results (entries 4−6), and the yield was increased to 86% when 2,6-dimethylphenylboronic acid **5c** was used (entry 5). When the reactions with arylboronic acids **5e** and **5f** bearing a methoxyl group were carried out, the corresponding products **6e** and **6f** were obtained in good yield (entries 7 and 8). All adducts **6a−f** were isolated as the sole products, and it was clear by NMR that the reactions proceed with high regioselectivity.



1 **2** **3**

Some results of rhodium-catalyzed reactions of various alkynyl heteroaromatic compounds with 2-methylphenylboronic acid in the presence of **3** are summarized in Table 2. In contrast to the reaction of **4** (entry 1), the reactions of **7** and **8**, which have the alkynyl group at the *meta* and *para* positions on the pyridine ring, did not undergo the addition (entries 2 and 3). However, when alkynes **9** and **11** bearing a pyrimidyl and quinolyl group were subjected to the reactions, the corresponding products **10** and **12** were obtained in good yield (entries 4 and 5). The bromoalkyne **13** reacted to afford **14** in 66% yield demonstrating chemoselectivity (entry 6). A substrate containing a siloxyl group within the alkyl side chain **15** was successfully transformed to **16** (entry 7), and substrates with a free hydroxyl group **17** and **19** were converted to **18** and **20** in moderate yields (entries 8 and 9). The reaction of **21** having a phenyl group at the propargyl position also proceeded to give **22** (entry 10).

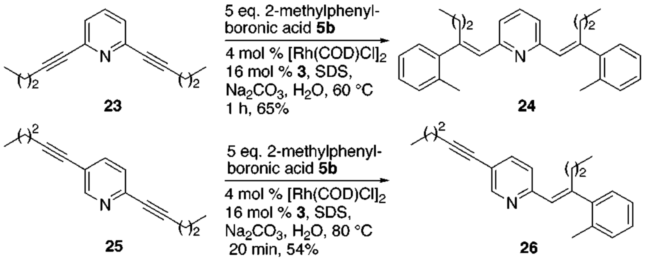
Table 2. Reactions of Various Alkynes with 2-Methylphenylboronic Acid[a]

entry	substrate	product[b]	yield (%)
1	 **4** R = 2-(1-hexynyl)	 **6b**	81
2	**7** R = 3-(1-hexynyl)		N.R.
3	**8** R = 4-(1-hexynyl)		N.R.
4[c]	 **9**	 **10**	69
5	 **11**	 **12**	63
6[d]	 **13**	 **14**	66
7	 **15**	 **16**	83
8	 **17**	 **18**	79
9	 **19**	 **20**	60
10[d]	 **21**	 **22**	66

[a] Reactions were carried out in the presence of 2 mol % [Rh(COD)Cl]$_2$, 8 mol % **3**, and 2.5 equiv of 2-methylphenylboronic acid, SDS, and Na$_2$CO$_3$ in H$_2$O at 80 °C for 1−3 h. [b] Ar = 2-methylphenyl. [c] The reaction was carried out at 60 °C. [d] Using 4 mol % [Rh(COD)Cl]$_2$, 16 mol % **3**, and 5 equiv of 2-methylphenylboronic acid **5b**.

We next tried the reaction of **23** and **25**, in which two alkynyl groups were present on the pyridine ring (Scheme 1). When **23** was treated with 5 equiv of 2-methylphenylboronic acid **5b** in the presence of 4 mol % [Rh(COD)Cl]$_2$ and 8 mol % **3**, the double addition product **24** was produced

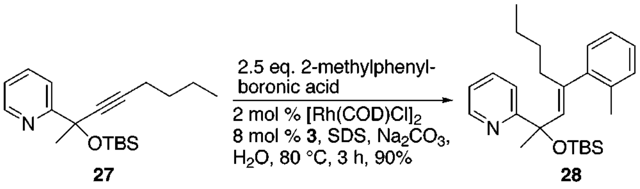
Scheme 1



in 65% yield. Interestingly, substrate **25**, which has an alkynyl group at both an *ortho* and *meta* position, was selectively converted into the mono adduct **26** in 54% yield, demonstrating it was possible to distinguish two alkynes within a single molecule. From these results, it is clear that the *ortho*-positioned alkyne is far more reactive than an alkyne at the *meta* position.

The reaction was also applicable to **27**, which has a triple bond one carbon away from the pyridyl group. The product **28** was obtained in 90% yield from the reaction of **27** with 2-methylphenylboronic acid **5b** (Scheme 2).

Scheme 2



Very recently, Hayashi has reported the rhodium-catalyzed addition of arylboronic acids to alkynes.[7] We note several differences between these two apparently similar reactions. First, the reaction can be carried out in neat water under our conditions compared to 10/1 dioxane/H_2O solvent in Hayashi's conditions. Second, we find the addition occurs with heteroaryl-containing alkynes and not with dialkyl or diaryl alkynes. Third, the presence of the pyridyl nitrogen has a dramatic effect in the regiochemistry as we obtain a single regioisomer, whereas Hayashi found that addition to 1-phenylpropyne gave a 3:1 mixture of regioisomers. Finally Hayashi reported an unusual D-labeling result ,whereas we see no such products. We found that deuterium was incorporated quantitatively at the alkenyl position when the reaction of **4** with **5b** was run in D_2O.

A plausible mechanism for the reaction is shown in Figure 1. It is presumed that (hydroxo)rhodium(I) complex **29**[8] exits as an active species in this reaction, and a catalytic cycle would involve the transmetalation of arylboronic acid to the rhodium species **29** to give the arylrhodium complex **30** at the initial step. Next, the coordination of alkynyl and pyridyl group of the substrate to rhodium followed by regioselective insertion into the Rh−C bond would give the alkenylrhodium complex **31**.[9] The observation that only alkynes substituted at *ortho* position reacted with arylboronic acids support a chelation-controlled insertion process. Finally the hydrolysis of the complex **31** with water would afford the product and the regenerated rhodium species **29**.

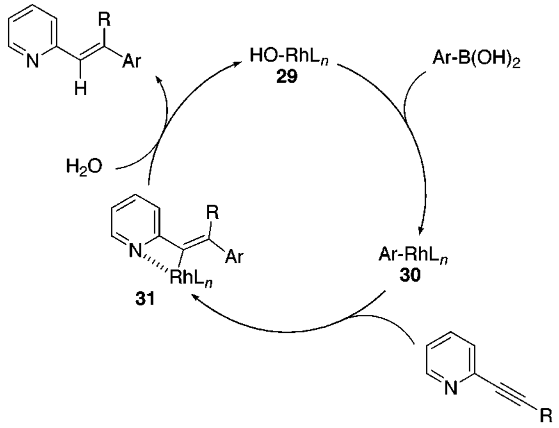


Figure 1.

In conclusion, we have developed a rhodium-catalyzed addition reaction of arylboronic acids to alkynes. The reaction enables the regioselective construction of trisubstituted olefins in water, which is a very useful methodology in view of environmental concerns. Furthermore, it was found that the reaction smoothly proceeds best in the presence of the pyridine-substituted ligand **3**. Investigation to examine the effect of pyridine moiety of **3** in this reaction and application of this catalyst to other types of reactions are now in progress.

Acknowledgment. We would like to thank NSERC, the ORDCF and the University of Toronto for valuable support of our programs. M.Y. acknowledges support in the form of a Postdoctoral Fellowship from the Uehara Memorial Foundation. We are grateful to Dr. Koichiro Fukuoka for helpful suggestions and the synthesis of ligand **3**.

Supporting Information Available: General procedures for the rhodium-catalyzed reaction and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL010261T

---

[7] Hayashi, T.; Inoue, K.; Taniguchi, N.; Ogasawara, M. *J. Am. Chem. Soc.* **2001**, *123*, 9918.

[8] (a) Brune, H.-A.; Unsin, J.; Hemmer, R.; Reichhardt, M. *J. Organomet. Chem.* **1989**, *369*, 335. (b) Uson, R.; Oro, L. A.; Cabeza, J. A. *Inorg. Synth.* **1985**, *23*, 126. (c) Grushin, V. V.; Kuznetsov, V. F.; Bensimon, C.; Alper, H. *Organometallics* **1995**, *14*, 3927 and see also ref 2c.

[9] For examples of the chelation-controlled rhodium-catalyzed reactions, see: (a) Ishiyama, T.; Hartwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 12043. (b) Jun, C.-H.; Lee, H.; Moon, C. H.; Hong, H.-S. *J. Am. Chem. Soc.* **2001**, *123*, 8600. (c) Jun, C.-H.; Lee, H.; Lim, S.-G. *J. Am. Chem. Soc.* **2001**, *123*, 751. (d) Jun, C.-H.; Lee, D.-Y.; Lee, H.; Hong, J.-B. *Angew. Chem., Int. Ed.* **2000**, *39*, 3070. (e) Jun, C.-H.; Lee, H. *J. Am. Chem. Soc.* **1999**, *121*, 880. (f) Jun, C.-H.; Lee, D.-Y.; Hong, J.-B. *Tetrahedron Lett.* **1997**, *38*, 6673. (g) Jun, C.-H.; Lee, H.; Hong, J.-B. *J. Org. Chem.* **1997**, *62*, 1200.