5358 *J. Am. Chem. Soc.* **2001,** *123,* 5358−5359

Rhodium-Catalyzed Coupling Reactions of Arylboronic Acids to Olefins in Aqueous Media

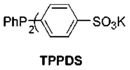
Mark Lautens,* Amélie Roy, Koichiro Fukuoka,
Keith Fagnou, and Belén Martín-Matute

Davenport Research Laboratories, Department of Chemistry
University of Toronto, Toronto, Ontario, Canada M5H 3H6

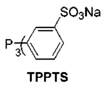
Received February 15, 2001

In recent years, significant advances have been made in the area of rhodium-catalyzed additions of arylboronic acids to activated olefins.[1] A common requirement for these transformations is the activation of the olefin by an electron-withdrawing group, which also facilitates the hydrolysis of the organorhodium intermediate. These constraints impose a limit on the substrate scope and lead the reactions to occur with net addition of carbon and hydrogen across the olefin.

We now report a new rhodium-catalyzed reaction that occurs in aqueous media[2] that overcomes both of these constraints. By performing these reactions in water, substrates that are otherwise unreactive in organic media can now be coupled in high yield. When vinyl heteroaromatic compounds **3** are used, the addition products **5** arising from an addition-hydrolysis pathway are obtained in high yield. When styrenyl olefins **1** are used, 1,2-diarylethylenes **4** are produced which must arise from a "Heck-type" addition-βH elimination process, an unprecedented mode of reactivity for rhodium. This methodology expands the scope of rhodium-catalyzed addition reactions and opens new doors for the catalytic formation of carbon−carbon bonds. Initial experiments focused on the development of a rhodium catalyst that would function in an aqueous environment. A variety of rhodium complexes (4 mol % catalyst) were combined with the commercially available water-soluble phosphine ligands TPPDS and TPPTS[3] in water and reacted with olefin **1a**, 2.5 equiv of phenylboronic acid **2a**, and 2.5 equiv of Na_2CO_3 at 80 °C for 15 h (Table 1, entries 1−4). The best results were obtained with $[Rh(COD)Cl]_2$ and TPPDS which gave **4a** in 77% yield (entry 1).[4]



TPPDS



TPPTS

Scheme 1

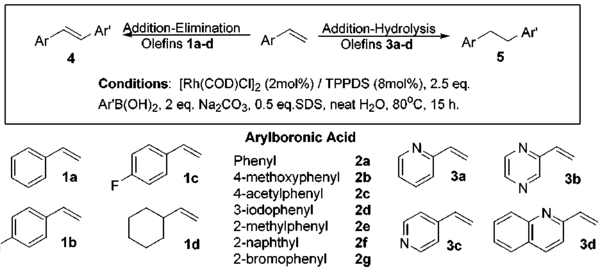
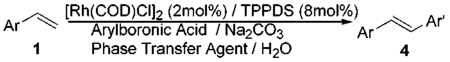


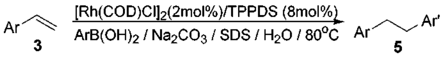
Table 1. Rh-Catalyzed Addition of Arylboronic Acids to Olefins[g]



entry	alkene	boronic acid	phase trans.	product	yield(%)[a]
1	**1a**	**2a**	none	**4a**	77
2	**1a**[b]	**2a**	none	**4a**	>10
3	**1a**[c]	**2a**	none	**4a**	>10
4	**1a**[d]	**2a**	none	**4a**	40
5	**1a**	**2a**	SDS	**4a**	80
6	**1a**	**2b**	none	**4b**	>20[e]
7	**1a**	**2b**	SDS	**4b**	85
8	**1a**	**2c**	none	**4c**	>20[e]
9	**1a**	**2c**	SDS	**4c**	73
10	**1a**	**2d**	SDS	**4d**	72
11	**1a**	**2e**	SDS	**4e**	86
12	**1a**	**2f**	SDS	**4f**	67
13	**1b**	**2a**	SDS	**4b**	76
14	**1c**	**2a**	SDS	**4g**	81
15	**1d**	**2a**	SDS	**4h**	20[f]

[a] Isolated yield. [b] $[Rh(CO)_2Cl]_2$ (2 mol %) used as the rhodium source. [c] $[Rh(CO)_2(acac)]$ (2 mol %) used as the rhodium source. [d] TPPTS (4 mol %) used as the water-soluble ligand. [e] Remainder is unreacted starting material due to competivive hydrolytic deboronation. [f] Olefin isomerisation was a competing side process leading to complex reaction mixtures and lower isolated yields. [g] **Conditions**: $[Rh(COD)Cl]_2$ (2 mol %), TPPDS (8 mol %), 2.5 equiv Ar′B(OH), 2 equiv Na_2CO_3, 0.5 equiv SDS, neat H_2O (0.2 M), 80 °C, 15 h.

Table 2. Rh-Catalyzed Addition of Arylboronic Acids to Vinyl Heteroaromatic Compounds[b]



entry	alkene	boronic acid	product	yield(%)[a]
1	**3a**	**2a**	**5a**	84
2	**3a**	**2b**	**5b**	77
3	**3a**	**2e**	**5c**	87
4	**3a**	**2f**	**5d**	88
5	**3a**	**2g**	**5e**	60
6	**3b**	**2a**	**5f**	84
7	**3c**	**2a**	**5g**	80
8	**3d**	**2e**	**5h**	70

[a] Isolated yield. [b] **Conditions**: $[Rh(COD)Cl]_2$ (2 mol %), TPPDS (8 mol %), 2.5 equiv $Ar'B(OH)_2$, 2 equiv Na_2CO_3, 0.5 equiv SDS, neat H_2O (0.2 M), 80 °C, 15 h.

This reaction was then examined with respect to the scope of the boronic acid. While both electron-rich and electron-deficient arylboronic acids are compatible, the presence of polar functional groups on the arylboronic acid caused an increased amount of

---

(1) 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. Additions to α,β-unsaturated amides have also been reported: (d) Preliminary results were discussed at The Xth International Conference on Boron Chemistry; Durham, July 11−15, 1999 and at the (e) Symposium on Organic and Inorganic Syntheses via Boranes; 218th National Meeting of the American Chemical Society, New Orleans, Aug 22−25, 1999. For additions to vinyl phosphonates, see: (f) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591. For additions to vinyl nitro compounds, see: (g) Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716. For additions to aldehydes, see: (h) Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3279. (i) Uead, M.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 4450. For additions to aldimines, see: (j) Ueda, M.; Miyaura, N. *J. Organomet. Chem.* **2000**, *595*, 31. It has also been found that arylstannanes will add to aldimines in ee values up to >90%, see: (k) Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976. Parallel reactivity has also been shown for potassium aryltrifluoroborates, see: (l) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683.

(2) 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 Organmetallic Chemistry: Concepts and Applications*; Wiley-VCH: Weinheim, 1998.

(3) These ligands are commercially available from Strem Chemicals.

(4) It is interesting to note that these reactions are heterogeneous. Upon completion, the product can be easily separated from the aqueous phase by simple extraction.

10.1021/ja010402m CCC: \$20.00

hydrolytic deboronation. This resulted in consumption of the boronic acid before the reaction could proceed to completion. To overcome this undesirable side reaction, the use of phase transfer reagents was examined. Addition of 0.5 equiv of sodium dodecyl sulfate (SDS) as a phase transfer agent served to accelerate the reaction and reduce the amount of deboronation. For example, while reaction of **1a** with **2b** and **2c** does not result in complete conversion in the absence of a phase transfer agent (Entries 6 and 8), in the presence of 0.5 equiv of SDS, they react efficiently to generate **4b** and **4c** in 85 and 73% yield, respectively (entries 7 and 9).[5] More sterically hindered systems are also compatible as exemplified by reaction of **1a** with **2e** to give **4e** in 86% yield. Of particular interest is the use of the 3-iodophenylboronic acid **2d** to produce **4d** in 72% yield (entry 10), illustrating that insertion of rhodium into the aryliodide bond is not a competitive process. The chemoselectivity exhibited by this system could be used to generate compounds capable of participating in subsequent metal-catalyzed coupling reactions.

Varying degrees of electron donation are tolerated in the olefin moiety as well. For example, **1b** and **1c** react with **2a** to produce **4b** and **4g** in 76 and 81% yields, respectively. We also examined the use of nonstyrenyl olefin **1d**. While complete consumption of **1d** occurred, olefin isomerization was a competing process resulting in complex reaction mixtures and lower isolated yields of the coupled product **4h** (Entry 15).

When 2-vinylpyridine **3a** was reacted under the standard conditions, a dramatic change in reactivity was observed. Instead of obtaining the Heck-type product, **5a** was generated exclusively arising from an addition-hydrolysis pathway (Table 1, entry 1). This pattern was found to be general for a variety of arylboronic acids (entries 2−5). Again, competitive insertion into the arylbromide bond was not observed when 2-bromopheylboronic acid **2g** was used (entry 5). In addition to the use of **3a**, several other vinyl heteroaromatics **3b**−**d** reacted analogously to produce the addition products **5f**−**h**.

The use of water as the solvent for these transformations deserves comment. In each case, addition of other cosolvents to the reaction mixture or use of organic solvents with the sulfonated ligands or with triphenylphoshine resulted in either no reaction after 15 h or less than 10% conversion. This clearly illustrates the differences in reactivity that can be obtained by changing to an aqueous environment. We were also gratified to learn that competitive rhodium-catalyzed hydrolytic deboronation of the arylboronic acid can be kept at a minimum. In previous reports of additions to activated olefins, where organic solvents containing as little as 10% water were used, degradation of the boronic acid nucleophiles could become problematic and result in the need to use up to 10 equiv of the boronic acid. When the coupling reactions described herein are run in neat water with SDS, only 3 equiv of the boronic acids are required, indicating that this side-process is not accelerated to a noticeable degree and does not preclude the use of water as a solvent as may have been anticipated.[6]

The mechanisms of these transfomations are the focus of continuing study. The sequence of steps in the Heck-type additions is particularly intriguing. If the olefin is regenerated via a β-hydride elimination in an analogous fashion to the palladium-catalyzed Heck reaction, the intermediacy of a rhodium hydride must be involved. How this species can be converted to an active catalyst capable of undergoing transmetalation with the arylboronic acids is not presently known.[7] The reaction mechanism for the addition reactions is likely similar to those proposed for the conjugate addition reactions whereby the presence of an enolizable nitrogen functionality allows isomerization of the C-bound rhodium species to an N-bound form that can then undergo hydrolysis and regenerate the active catalyst complex.[8]

In conclusion, we have developed an aqueous rhodium-catalyzed coupling reaction of arylboronic acids and olefins. Use of water as the solvent is crucial since these substrates do not react under analogous conditions in organic solvents. Two types of reactivity are observed. First, when styrenyl olefins are used, the reaction proceeds to give the Heck-type products. This type of reactivity is unprecedented in rhodium catalysis. When an enolizable functionality is present within the aromatic ring, the addition-hydrolysis pathway occurs to give the hydrophenylated compounds. These results should broaden the scope of rhodium-catalyzed addition reactions and have the potential to open the door to new possibilities for asymmetric transformations.

Acknowledgment. We would like to thank NSERC, the ORDCF, and the University of Toronto for valuable support of our programs. A.R. and K.F. would like to thank NSERC for postgraduate scholarships. B.M.-M. thanks the MEC (Ministerio de Educación y Ciencia) for a predoctoral fellowship. We also thank Takeda Chemical Industries for providing a research leave for K.F.

Supporting Information Available: Experimental details and characterization data including ^{1}H and ^{13}C NMR, IR, and mass spectroscopy data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA010402M

---

[5] Representative experimental procedure: To a mixture of $[Rh(COD)Cl]_2$ (4.3 mg, 2 mol %) and TPPDS (17.5 mg, 8 mol %) in H_2O (2.2 mL, 0.2 M) at room temperature was successively added phenylboronic acid (133 mg, 1.09 mmol), Na_2CO_3 (97 mg, 0.916 mmol), SDS (63 mg, 0.228 mmol), and styrene (50 μL, 0.436 mmol). The reaction mixture was heated at 80 °C for 15 h. After cooling to room temperature the colored solution was poured into Et_2O (25 mL) and the reaction flask was carefully rinsed with Et_2O. The heterogeneous mixture was vigorously stirred at room temperature for 2 h. The two phases were separated, the aqueous phase was extracted with Et_2O (3 × 30 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated to dryness. The crude residue was purified by flash chromatography.

[6] Experimental evidence for the deboronation process being mediated by water was obtained by running the reactions in D_2O. In these cases, the only product detected (in addition to the desired coupling product) was the deboronated aryl species where the boron had been exchanged for a deuterium atom.

[7] We have attempted to address whether the arylboronic acid is being used as a sacrificial hydride acceptor via an oxidative addition of the Rh−H species into the aryl−boron bond with subsequent reductive elimination of an aryl−H compound. This was done by running the reaction in D_2O. In this case, only deuterated aryl compounds were produced from deuteriolytic deboronation of the boronic acid. If the arylboronic acid were acting as a hydride acceptor, 1 equiv of the aryl−H compound should have been produced.

[8] Preliminary mechanistic investigations support this hypothesis. When the reaction is run in D_2O, deuterium is incorporated quantitatively at the benzylic position of the product adjacent to the heteroaromatic ring.