

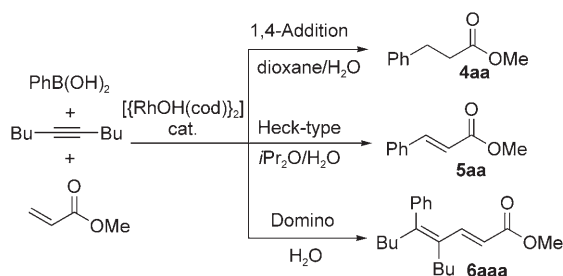
Intermolecular Rhodium-Catalyzed Carbometalation/Heck-Type Reaction in Water**

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In recent years, organic reactions in aqueous media have received particular attention for environmental and safety reasons. Furthermore, water often exhibits profound effects on the rate and selectivity of organic reactions through enhanced hydrophobic interactions and the enrichment of organic substrates in the local environment as a result of its unique physical and chemical properties.^[1,2] A recent report by Sharpless and co-workers clearly demonstrates that water can accelerate some types of intermolecular addition reactions, even under heterogeneous conditions with insoluble organic components.^[3] Such an intriguing effect should also be valid for transition-metal-catalyzed reactions, thus leading to novel transformations that are difficult in conventional reaction media. Herein, we wish to describe a novel rhodium-catalyzed coupling reaction of aryl boronic acids with internal alkynes and acrylates in water to afford functionalized dienes through an aryl rhodation/Heck-type addition sequence. Although a number of rhodium-catalyzed domino processes with organoboron reagents and unsaturated functionalities have been reported,^[4-6] a fully intermolecular version is quite rare.

α,β -Unsaturated carbonyl compounds are highly reactive substrates in the rhodium-catalyzed addition of boronic acid derivatives. Aryl rhodation also occurs to alkynes, but the reactivity is lower than that of conjugated enones and enoates. The rhodium-catalyzed addition of aryl boronic acids to α,β -unsaturated carbonyl compounds can proceed at room temperature, whereas the addition to alkynes often requires elevated temperatures.^[7] Consequently, one can anticipate that an aryl rhodium intermediate predominantly adds to unsaturated carbonyl compounds, even in the presence of alkynes. Not surprisingly, the 1,4-addition product **4aa** was

formed as the major product in 58% yield in organic solvents such as wet THF and dioxane. The reaction in a biphasic system (water/diisopropyl ether) yielded the Heck-type product **5aa** as the major product in 61% yield. Curiously, however, when the same reaction was conducted in aqueous media, a three-component assembly reaction took place to afford 1,3-diene **6aaa** in 81% yield along with the simple Heck-type product **5aa** (11%) and 1,4-addition product **4aa** (3%; Scheme 1): an emulsion of phenylboronic acid (**1a**),



Scheme 1. Addition of phenylboronic acid to methyl acrylate and 5-decyne.

5-decyne (**2a**), methyl acrylate (**3a**), and 4 mol % of $[\{\text{Rh(OH)(cod)}\}_2]$ (cod = 1,5-cyclooctadiene) in water was allowed to stand at ambient temperature for 12 h without stirring to provide 4-butyl-5-phenylnona-2,4-dienoic acid methyl ester (**6aaa**; see Supporting Information).^[8] Note that arylation proceeds at ambient temperature with an unactivated alkyne. Importantly, the domino reaction takes place only in an emulsion of substrates with water, as far as we investigated. As Lautens et al. already reported, the use of surfactants (i.e., sodium decyl sulfate) to homogenize the reaction system resulted in the exclusive formation of the Heck product **5aa**.^[9] Water-soluble phosphine ligands, such as trisodium triphenylphosphine-3,3',3''-trisulfonate, disodium triphenylphosphine-4,4'-disulfonate, and cyclohexyl amphos chloride, were not effective. Thus, the course of the reaction was found to be quite sensitive to the conditions.

Boronic acids with electron-donating (**1b** and **1c**) or -withdrawing groups (**1d**) gave the corresponding product **6** as the predominant product in moderate yields (Table 1). 2-Naphthylboronic acid (**1e**) also reacted with **2a** and **3a** to furnish the corresponding diene **6ea** in 45% yield. In this case, the emulsion of the substrates in water seemed not to be as stable as that obtained from **1a**. The reactions of **1a** and **3a** with various alkynes were also examined. Alkynes, such as 4-octyne, 6-dodecyne, and 7-tetradecyne, reacted to furnish the corresponding dienes **6**. The sparingly water-soluble toluene (**2e**) sluggishly reacted to give **6bea** in 31% yield. The miscibility of substrates seems to be critical for the successful reaction.^[10] The configuration of diene **6bea** was unambiguously confirmed by an X-ray crystal structure analysis (see Supporting Information). Consequently, the arylation of alkynes in this reaction proceeds in a *syn* fashion.

We propose the following mechanism for this domino reaction (Scheme 2). Both the alkyne and acrylate coordinate to the aryl–rhodium species **B**, which is generated through the

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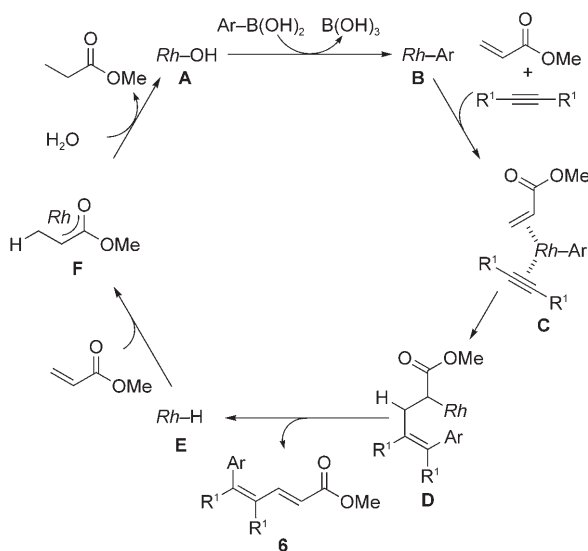


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Table 1: Rhodium-catalyzed domino carbometalation/Heck-type reaction of aryl boronic acids to alkynes and methyl acrylate in water.^[a]

Ar	R ¹	Yield [%] 6 ^[b]	Yield [%] 4 ^[c]	Yield [%] 5 ^[c]
Ph (1a)	Bu (2a)	81 (6aaa)	3 (4aa)	11 (5aa)
4-Me-C ₆ H ₄ (1b)	Bu (2a)	66 (6baa)	5 (4ba)	5 (5ba)
4-MeO-C ₆ H ₄ (1c)	Bu (2a)	50 (6caa)	10 (4ca)	14 (5ca)
4-CF ₃ -C ₆ H ₄ (1d)	Bu (2a)	72 (6daa)	12 (4da)	11 (5da)
2-Naphthyl (1e)	Bu (2a)	45 (6eaa)	3 (4ea)	44 (5ea)
Ph (1a)	Pr (2b)	61 (6aba)	3 (4aa)	7 (5aa)
Ph (1a)	C ₅ H ₁₁ (2c)	53 (6aca)	11 (4aa)	8 (5aa)
Ph (1a)	C ₆ H ₁₃ (2d)	57 (6ada)	6 (4aa)	5 (5aa)
4-Me-C ₆ H ₄ (1b)	Ph (2e)	31 (6bea)	3 (4ba)	59 (5ba)

[a] The reaction was carried out with **1** (0.2 mmol), **2** (0.1 mmol), and **3** (0.2 mmol) in water (1 mL) in the presence of $[\{\text{RhOH}(\text{cod})\}_2]$ (0.004 mmol) at ambient temperature for 12 h. [b] Yield of the isolated products. [c] Yields were determined by the ¹H NMR signals of the crude products with dibromomethane as an internal standard.



Scheme 2. A plausible mechanism for the rhodium-catalyzed domino reaction.

transmetalation of hydroxo-rhodium species **A** with aryl boronic acid **1**. The resulting complex **C** then undergoes an addition to the carbon-carbon triple bond of alkyne **2** and the double bond of acrylate **3** in either a concerted or stepwise manner to yield alkyl-rhodium species **D**.^[11] We suppose that acrylate **3** acts not only as the third coupling component but also as a good π -acid ligand to promote the addition of aryl boronic acids to alkynes, as the reaction of **1a** and **2a** without **3** under the same conditions provided a trace of the phenylation product of **2a**. Compound **D** affords product **6** and hydrido-rhodium species **E** through β -hydride elimination. The hydrido-rhodium **E** reacts with **3** to form oxa- π -allyl-

rhodium species **F**, which is hydrolyzed to complete the catalytic cycle. This mechanism is consistent with the fact that quantitative formation of the 1,4-reduction product, methyl propanoate, was observed by ¹H NMR spectroscopic analysis in the reaction mixture.^[12]

Although conclusive discussion of the role of water in this reaction is difficult at present, we performed several experiments to obtain some information. Whereas the reaction under solvent-free conditions provided the three-component coupling product **6aaa** in only 15% yield and Heck product **5aa** as the major product (31%), application of high pressure (140 atm) doubled the yield of **6aaa** under the same conditions but produced **5aa** (33%) in an unchanged yield (Scheme 3). The domino reaction is more pressure-dependent

1a + 2a + 3a	$[\{\text{RhOH}(\text{cod})\}_2]$ (4 mol%)	neat, RT, 24 h	6aaa	4aa	5aa
	N ₂ (1 atm)		15%	<1%	31%
	N ₂ (140 atm)		27%	<1%	33%

Scheme 3. Pressure dependence under neat conditions.

than the Heck-type reaction. This fact indicates that the rate-determining step of the domino reaction, which would be the C-C bond-forming step of the reaction of aryl rhodium with alkyne and acrylate species (**C**→**D**), has a negative activation volume (ΔV^\ddagger). Importantly, water often enhances reaction rates for reactions, such as the Diels-Alder reaction and Claisen rearrangement, for which the activation volumes are negative.^[13] This behavior implies that high internal pressure of water may be one of the reasons for this phenomenon. However, the heterogeneous nature of the present reaction may call for other explanations, such as specific interactions between hydrophobic molecules at the microscopic water-oil phase boundary.

In summary, we have demonstrated that the reaction of aryl boronic acids with internal alkynes and acrylate units can be performed by rhodium catalysis in water to give the domino coupling products. Although the role of water is unclear at this stage, the present reaction demonstrates that water offers us not only the possibility to optimize known reactions but also to discover novel transformations. Investigations to expand the scope and limitations of this procedure along with the mechanistic elucidation are currently in progress.

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