

## Double Suzuki Reactions of Organoboronic Acids with 1,1-Dibromides

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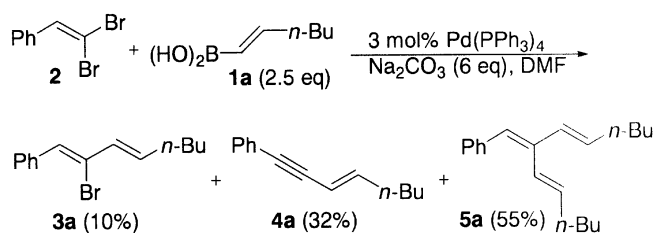
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The palladium-catalyzed cross-coupling of organoboronic acids with alkenyl or aryl halides, known as the Suzuki reaction, has a great potential in synthetic organic chemistry.<sup>1</sup> Recently, asymmetric C-C cross-couplings between aryl halides and aryl boronates were also reported to give binaphthalene derivatives in up to 85% enantiomeric excess.<sup>2</sup> Because a variety of organoboron derivatives are now readily available, much attention has been focused on the use of Suzuki reaction for the syntheses of stereodefined biaryls,<sup>3</sup> alkadienes<sup>4</sup> and trienes.<sup>5</sup> Since the two carbon-Br bonds in 1,1-dibromo-1-alkenes have different reactivities under metal-catalyzed reactions, the Suzuki reactions of 1,1-dibromo-1-alkenes with alkenyl- or arylboronic acids were possible to give stereoselective formation of (*Z*)-1-aryl- or (*Z*)-alkenyl-1-bromo-1-alkenes.<sup>6</sup> To our best knowledge, there have been no successful methods for the double cross-couplings of such 1,1-dihalo-1-alkenes with two equivalents of organoboronic acids. Instead, a few methods for the synthesis of branched enynes by sequential cross-couplings have been published.<sup>7</sup> Contrast to 1,1-dihalo-1-alkenes, a few 1,2-dihalo-1-alkenes reacted with two-equivalents of arylboronic acids to give the double-cross-coupling products.<sup>8</sup> Since literature survey prompted us to secure efficient synthetic methods by extending Suzuki reactions, we have initiated a systematic study on double Suzuki reaction as a research program and here wish to report our results. At the initial stage, we required diverse organoboronic acids **1a-e** by known procedures (Figure 1).<sup>9</sup>

Organic diacceptors we employed in this study were 1,1-dibromo-1-alkene,<sup>10</sup> 1,2-dibromo-1-alkene,<sup>11</sup> *o*-bromobenzyl bromide as a 1,3-diacceptor. The Suzuki reaction of 1,1-dibromo-1-alkene was known to afford (*Z*)-1-alkenyl-1-bromo-1-alkenes.<sup>12</sup> The higher reactivity of the E-bromide over *Z*-bromide in 1,1-dibromoalkene seemed to come from steric factor. Thus, an initial attempt for double Suzuki reactions of 1,1-dibromoalkene with 2.5 equivalents of 1-hexenylboronic acid (**1a**) was made in the presence of 3 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> and excess sodium carbonate in *N,N*-dimethylformamide to give a mixture of the double-coupled product **5a** (55%) along with the mono-coupled diene **3a**



**Scheme 1**

(10%) and the enyne **4a** (32%) as shown in Scheme 1.

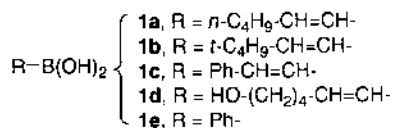
To accomplish the double-Suzuki reactions with 1,1-dibromo-1-alkenes **2**, we have attempted to optimize the reaction conditions by changing reaction temperature, reaction time, base, solvent, and amount of organoboronic acids. The best result for the intended double-Suzuki reaction was obtained when four equivalents of organoboronic acids were employed. Thus, when a mixture of 1,1-dibromo-1-alkene and four equivalents of organoboronic acids **1a-e** was stirred at 50 °C in the presence of 3 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> and excess sodium carbonate, the corresponding double cross-coupled products **5a-d** were isolated in 66%, 58%, 40%, 54%, and 56% yields, respectively, as shown in Table I.

Since conjugated enynes are frequently found not only in natural products but also in synthetic intermediates, synthetic chemists have been seeking efficient synthetic methods of

**Table I.** Palladium-catalyzed cross-coupling of 1,1-dibromoalkene **2** with organoboronic acids **1a-e**

Reaction scheme for Table I: 1,1-dibromo-1-alkene **2** reacts with organoboronic acid **1a-e** in the presence of 3 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> and Na<sub>2</sub>CO<sub>3</sub> in DMF to yield products **4** and **5**.

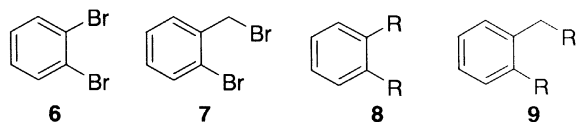
	R <sub>1</sub> B(OH) <sub>2</sub> (eq.)	Equiv. of Na <sub>2</sub> CO <sub>3</sub>	Temp (°C)	Time (h)	Products (% yield)
1	<b>1a</b> (1.2)	6	120	1	<b>4a</b> 77
2	(2.5)	12	50	3	<b>5a</b> 55
	(4.0)	12	50	3	<b>5a</b> 66
3	<b>1b</b> (1.2)	6	50	3	<b>4b</b> 82
4	(4.0)	12	50	3	<b>5b</b> 58
5	<b>1c</b> (1.2)	6	110	1	<b>4c</b> 46
6	(4.0)	12	50	3	<b>5c</b> 40
7	<b>1d</b> (1.2)	6	90	1	<b>4d</b> 70
8	(4.0)	12	50	3	<b>5d</b> 54
9	<b>1e</b> (1.2)	6	90	1	<b>4e</b> 85
10	(4.0)	12	50	3	<b>5e</b> 56



**Figure 1**

**Table 2.** Palladium-catalyzed cross-couplings of 1,2- and 1,3-diacceptors with organoboronic acids **1a-e**

Reactants	Boronic acids	Temp (°C)	Solvent	Products (% yield)
6	<b>1a</b>	90. 1	DMF	<b>8a</b> (84)
	<b>1b</b>	50. 3	Benzene	<b>8b</b> (87)
	<b>1c</b>	100. 1	DMF	<b>8c</b> (92)
	<b>1d</b>	90. 1	DMF	<b>8d</b> (65)
	<b>1e</b>	90. 3	DMF	<b>8e</b> (86)
7	<b>1a</b>	90. 1	DMF	<b>9a</b> (95)
	<b>1b</b>	90. 3	DMF	<b>9b</b> (72)
	<b>1c</b>	90. 1	DMF	<b>9c</b> (74)
	<b>1d</b>	90. 1	DMF	<b>9d</b> (65)
	<b>1e</b>	90. 3	DMF	<b>9e</b> (80)



such conjugated enynes. Simply, use of only a slight excess of alkenylboronic acids **1a** with respect to the 1,1-dibromide **2** under the palladium catalytic conditions, we could isolate the conjugated enyne **4a** in 77% yield. Under these conditions, alkenylboronic acids **1b**, and **1c** were shown to have the same reaction patterns to give the corresponding conjugated enynes **4b** and **4c** in 82% and 46% yields, respectively. The hydroxy-containing boronic acid **1d** and phenylboronic acid **1e** did also work well toward all 1,1-diacceptors to give the **4d** and **4e** in 70% and 85% yields, respectively.

Contrast to 1,1-diacceptor, both 1,2-dibromobenzene (**6**) as an 1,2-diacceptor and 2-bromobenzyl bromide (**7**) as an 1,3-diacceptor reacted two equivalents of alkenylboronic acids **1a-e** to afford the double cross-coupling products **8a-e** and **9a-e** within 3 h at below 100 °C as shown in Table 2.<sup>13</sup>

1,2-Dibromobenzene (**6**) was smoothly coupled with two molecules of organoboronic acid **1a-e**. Since there is not much steric congestion after the first coupling, the second couplings occurred well to give the double cross-coupled products **8a-e**. 2-Bromobenzyl bromide (**7**) was also doubly cross-coupled with all organoboronic acids **1a-e**. Two features are worth to be noted. First, the benzylic bromide was cross-coupled with alkenylboronic acids faster than the aryl bromide in bromobenzyl bromide (**7**). This higher reactivity of benzylic halide over aryl halide might come from electronic nature. Second, the hydroxy-containing boronic acid **1d** did also work well toward all 1,1-, 1,2-, and 1,3-diacceptors.

In summary, two equivalents of alkenylboronic acids were doubly cross-coupled with 1,1-, 1,2- and 1,3-diacceptors in the presence of excess base and 3 mol% of Pd(PPh<sub>3</sub>)<sub>4</sub> in excellent yields. Use of excess base and a slight excess of organoboronic acids **1a-e** with the 1,1-diacceptor **2** afforded to the corresponding enynes **3a-c** in good yields under palladium catalytic conditions.

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