

Double Suzuki Reactions of Organoboronic Acids with 1,*n*-Dibromides

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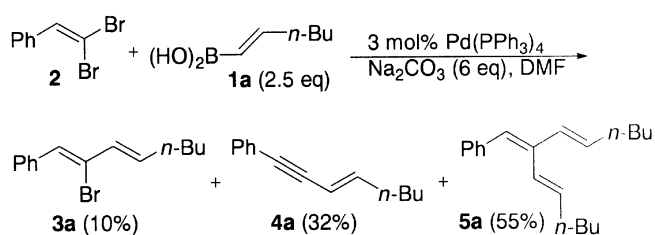
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The palladium-catalyzed cross-coupling of organoboronic acids with alkenyl or aryl halides, known as the Suzuki reaction, has a great potential in synthetic organic chemistry.¹ Recently, asymmetric C-C cross-couplings between aryl halides and aryl boronates were also reported to give binaphthalene derivatives in up to 85% enantiomeric excess.² 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,³ alkadienes⁴ and trienes.⁵ 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.⁶ 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.⁷ 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.⁸ 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).⁹

Organic diacceptors we employed in this study were 1,1-dibromo-1-alkene,¹⁰ 1,2-dibromo-1-alkene,¹¹ *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.¹² 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(PPh₃)₄ 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(PPh₃)₄ 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 1.

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

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

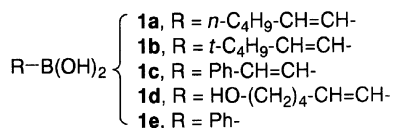
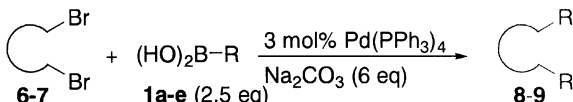
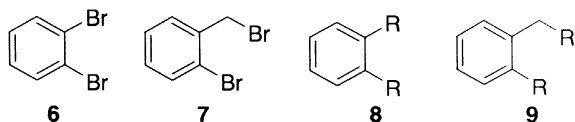


Figure 1

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	1a	90, 1	DMF	8a (84)
	1b	50, 3	Benzene	8b (87)
	1c	100, 1	DMF	8c (92)
	1d	90, 1	DMF	8d (65)
	1e	90, 3	DMF	8e (86)
7	1a	90, 1	DMF	9a (95)
	1b	90, 3	DMF	9b (72)
	1c	90, 1	DMF	9c (74)
	1d	90, 1	DMF	9d (65)
	1e	90, 3	DMF	9e (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 2.¹³

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(PPh₃)₄ 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-e** in good yields under palladium catalytic conditions.

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