

# Simple and Efficient Protocol for the Synthesis of Functionalized Styrenes from 1,2-Dibromoethane and Arylboronic Acids

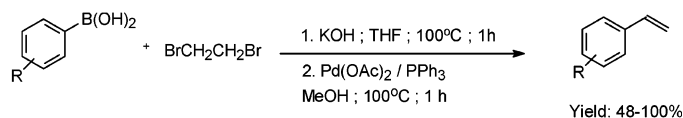
Vanusa R. Lando and Adriano L. Monteiro\*

Laboratory of Molecular Catalysis, Instituto de Química, UFRGS,  
Av. Bento Gonçalves, 9500 Porto Alegre 91501-970, CP 15003, RS, Brazil

almonte@iq.ufrgs.br

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## ABSTRACT



A simple and efficient protocol for the preparation of functionalized styrenes is disclosed that employs the palladium-catalyzed cross-coupling reaction of arylboronic acids with vinyl bromide, generated in situ from 1,2-dibromoethane. The reaction is carried out under mild reaction conditions. Compared with the cross-coupling reactions usually employed to obtain vinylarenes, this protocol is very simple, overcomes the inconvenience of using of ethylene under pressure, and uses air-stable and widely available arylboronic acids instead of vinyl organometallic reagents.

Functionalized styrenes are employed for the synthesis of important compounds such as new polymeric materials and herbicide, sunscreen, antiinflammatory, and antiasthma agents.<sup>1</sup> The palladium-catalyzed cross-coupling reaction is one of the most efficient methods for the construction of functionalized styrene bonds, by reacting aryl halides with a variety of reagents.<sup>2</sup> For instance, Heck<sup>3</sup> and Stille<sup>4</sup> cross-coupling reactions have been widely exploited in synthetic organic procedures. However, the Heck reaction uses ethylene under high pressure, and the Stille reaction necessitates the use of vinyltin reagents that can be toxic or generate toxic organotin residues. Vinylmagnesium bromide,<sup>5</sup> vinyl trimethylsilane,<sup>6</sup>

and vinylpolysiloxanes<sup>7</sup> have been also used in the cross-coupling with aryl iodides. The Suzuki cross-coupling reaction is an obvious alternative since organoboron derivatives are nontoxic reagents and can react not only with aryl iodides but also with bromides and chlorides. However, there are considerable problems specific to alkenylboronic acids and esters in Suzuki couplings. The Pd-catalyzed cross-coupling of vinylboronate esters and aryl iodides and bromides furnishes a mixture of Heck- and Suzuki-type products with the selectivity strongly dependent upon the reaction conditions.<sup>8</sup> Furthermore, vinylboronic acid is readily polymerized and cannot be isolated and its use in the Suzuki reaction gives very poor reproducibility.<sup>9</sup>

Recently, two procedures have been developed to overcome these problems by using a 2,4,6-trivinylcycloboroxane-

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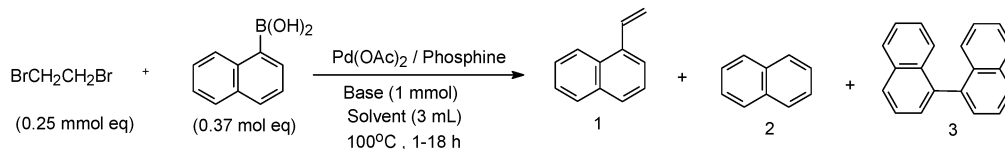
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**Table 1.** Effect of the Reaction Conditions on the Pd-Catalyzed Cross-Coupling Reaction of 1,2-Dibromoethane with 1-Naphthylboronic Acid

entry	Pd(OAc) <sub>2</sub> (mol %)	ligand <sup>a</sup>	ligand/Pd	base	solvent <sup>b</sup>	<i>t</i> (h)	selectivity (%)		
							1	2	3
1	4	PPh <sub>3</sub>	4	NaOH	THF/H <sub>2</sub> O	18	81	14	5
2	4	PPh <sub>3</sub>	4	<i>t</i> -BuONa	DMA	18	43	57	0
3	4	PPh <sub>3</sub>	4	<i>t</i> -BuONa	THF/MeOH	18	76	14	10
4	4	PPh <sub>3</sub>	4	NaOH	THF/MeOH	18	55	38	7
5	4	PPh <sub>3</sub>	4	K <sub>3</sub> PO <sub>4</sub>	THF/MeOH	18	33	22	45
6	4	PPh <sub>3</sub>	4	K <sub>2</sub> CO <sub>3</sub>	THF/MeOH	18	73	20	7
7	4	PPh <sub>3</sub>	4	KOH	THF/MeOH	18	73	11	16
8	4	PCy <sub>3</sub>	4	KOH	THF/MeOH	18	72	20	8
9	4	P( <i>o</i> -tol) <sub>3</sub>	4	KOH	THF/MeOH	18	0	97	3
10	4	dppe	2	KOH	THF/MeOH	18	77	18	5
11	4	dppf	2	KOH	THF/MeOH	18	49	44	7
12	1	PPh <sub>3</sub>	4	KOH	THF/MeOH	18	47	38	15
13	6	PPh <sub>3</sub>	4	KOH	THF/MeOH	18	77	7	16
14	10	PPh <sub>3</sub>	4	KOH	THF/MeOH	18	87	6	7
15	6	PPh <sub>3</sub>	4	KOH	THF/MeOH	1	82	10	8
16 <sup>c</sup>	1	PPh <sub>3</sub>	2	KOH	THF/MeOH	1	83	16	1
17 <sup>c</sup>	2	PPh <sub>3</sub>	2	KOH	THF/MeOH	1	87	9	4
18 <sup>c</sup>	4	PPh <sub>3</sub>	2	KOH	THF/MeOH	1	90	6	4

<sup>a</sup> BrCH<sub>2</sub>CH<sub>2</sub>Br = 1,2-dibromoethane; PPh<sub>3</sub> = triphenylphosphine; PCy<sub>3</sub> = tricyclohexylphosphine; P(*o*-tol)<sub>3</sub> = tri-*o*-tolylphosphine; dppe = 1,2-bis(diphenylphosphino)ethane; dppf = 1,1'-bis(diphenylphosphino)ferrocene. <sup>b</sup> THF/H<sub>2</sub>O and THF/MeOH = 1. <sup>c</sup> Dehydrobromination carried out prior to cross-coupling reaction (see ref 12).

pyridine complex<sup>9</sup> or potassium vinyltrifluoroborate.<sup>10</sup> Herein we present a simple and efficient alternative for obtaining styrene derivatives from the Pd-catalyzed Suzuki cross-coupling between arylboronic acids and vinyl bromide, generated in situ from 1,2-dibromoethane.<sup>11</sup>

A set of experiments were performed in order to determine the feasibility of the Pd-catalyzed Suzuki cross-coupling between arylboronic acids and vinyl bromide, generated in situ from 1,2-dibromoethane. Initially, we investigated the coupling of 1,2-dibromoethane with 1-naphthylboronic acid using Pd(OAc)<sub>2</sub> as the catalyst in the presence of phosphine ligands, a variety of different bases, and different solvents (Table 1). In addition to the expected vinylnaphthalene, products generated from the homocoupling and reduction of 1-naphthylboronic acid were also observed. Among the solvents and bases examined, the best results were obtained using KOH or *t*-BuONa as the base in a mixture of THF/MeOH (entries 1–7, Table 1). We chose to follow the optimization with KOH as the base. Good yields in vinylnaphthalene were achieved by using triphenylphosphine (entry 7, Table 1), tricyclohexylphosphine (entry 8, Table 1), and 1,2-diphenylphosphineethane (entry 10, Table 1) as phos-

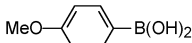
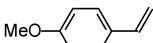
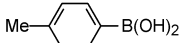
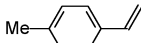
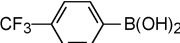
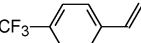
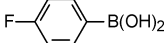

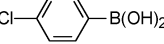

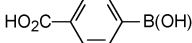
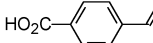
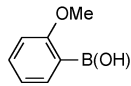

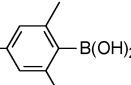
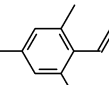
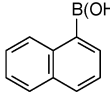

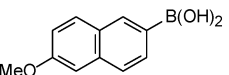
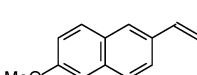
phine ligands. Between these three options, we decided to use PPh<sub>3</sub>, considering its lower cost and lower sensitivity to oxygen. 1,1'-Bis(diphenylphosphino)ferrocene (entry 11, Table 1) gave lower yields in cross-coupling product, whereas the use of tri-*o*-tolylphosphine (entry 9, Table 1) gave only naphthalene and binaphthyl. Since the cross-coupling product is formed from the reaction between the arylboronic acid and vinyl bromide, generated in situ from 1,2-dibromoethane, the yield could be improved by performing the dehydrobromination prior to the cross-coupling reaction. In entry 16, a mixture of 1,2-dibromoethane and KOH in THF was stirred at 100 °C for 1 h. Then, a solution containing 1-naphthylboronic acid, Pd(OAc)<sub>2</sub>, and PPh<sub>3</sub> was added and the mixture was stirred at 100 °C for an additional hour, furnishing 1-vinylnaphthalene in 83% selectivity and 91% yield based on the starting 1,2-dibromoethane. Using this protocol allowed the amount of palladium and phosphine to be decreased and the cross-coupling product was obtained in 90% selectivity and a quantitative yield based on 1,2-dibromoethane (entry 18, Table 1).<sup>12</sup>

The coupling of vinyl bromide, generated in situ from the dehydrobromination of 1,2-dibromoethane, with a variety of aryl boronic acids was examined under optimized reaction conditions (Table 2). Under these conditions, 1-vinylnaphthalene was isolated in 87% yield (entry 9, Table 2). It is

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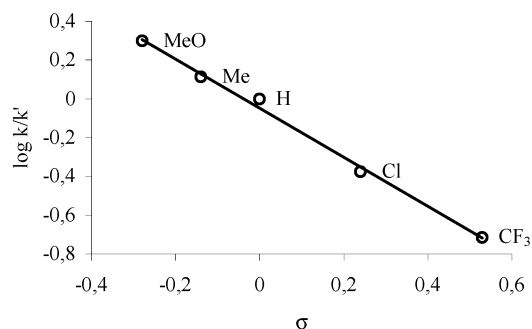
**Table 2.** Pd-Catalyzed Cross-Coupling Reaction of 1,2-Dibromoethane with Arylboronic Acids<sup>a</sup>

entry	aryl boronic acid	product	yield (%) <sup>b</sup>
1			94 (82)
2			86
3			48
4			62 (64)
5			58
6			(69)
7			89 (81)
8			63 (54)
9			100 (87)
10			72 (66)

<sup>a</sup> Reaction conditions: (1) Dehydrobromination: 1 mmol of BrCH<sub>2</sub>CH<sub>2</sub>Br, 4 mmol of KOH, THF (2.5 mL), 100 °C, 1 h. (2) Cross-coupling reaction: 1.5 mmol of ArB(OH)<sub>2</sub>, 0.04 mmol of Pd(OAc)<sub>2</sub>, 0.08 mmol of PPh<sub>3</sub>, MeOH (2.5 mL), 100 °C, 1 h. <sup>b</sup> GC yields (isolated yields are given in parentheses).

interesting to note that a lower yield was achieved (25%) when the reaction with 1-naphthylboronic acid was carried out in an open reflux setup. Aryl boronic acids containing electron-donating groups in the para position (entries 1 and 2, Table 2) are efficiently coupled to provide the corresponding vinyl arenes in excellent yields. Lower yields were obtained with aryl boronic acids containing electron-withdrawing groups in the para position (entries 3–6, Table 2). *ortho*-Methoxy-substituted phenyl boronic acid gave a

(12) In a typical experiment, an oven-dried resealable Schlenk flask was evacuated and back-filled with argon and charged with KOH (225 mg, 4 mmol). The flask was evacuated and back-filled with argon, and then tetrahydrofuran (2.5 mL) and 1,2-dibromoethane (87  $\mu$ L, 1 mmol) were added. The reaction mixture was stirred at 100° for 1 h. The solution was then allowed to cool to room temperature, and 1-naphthylboronic acid (258 mg, 1.5 mmol), PPh<sub>3</sub> (21 mg, 0.08 mmol), Pd(OAc)<sub>2</sub> (9.0 mg, 0.04 mmol), and methanol (2.5 mL) were added. The reaction mixture was stirred at 100 °C for 1 h. The solution was then allowed to cool to room temperature, taken up in ether (20 mL), and washed with aqueous NaOH (1 M, 5 mL) and brine (2  $\times$  5 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo, and then the crude material was purified by flash chromatography on silica gel.

**Figure 1.** Effects of substituents on aryl boronic acids *p*-XC<sub>6</sub>H<sub>4</sub>B(OH)<sub>2</sub> (X = MeO, Me, H, Cl and CF<sub>3</sub>).  $Y = -1.263x - 0.0476$ .  $R^2 = 0.995$ 

similar yield compared with its para-substituted analogue (entries 1 and 7, Table). A reasonable yield was achieved when the protocol was applied to a more sterically demanding substrate, 2,4,6-trimethylphenyl boronic acid (54% isolated yield). 2-Vinyl-6-methoxynaphthalene, a key intermediate for the production of Naproxen in the Albermale process, was obtained in 66% isolated yield (entry 10, Table 2).<sup>1c</sup>

The dependence of the substitution on the aryl boronic acid para position is also evidenced in a competitive experiment (Figure 1). A plot of the relative reactivity of substituted aryl boronic acids against the  $\sigma$  constant shows that the relative reactivity is sensitive to the electronic effects of the substituents on the aryl boronic acids. The reactivity is opposite to those observed for cross-coupling reactions with aryl halides such as Heck<sup>13</sup> and Suzuki<sup>14</sup> reactions, where higher activities are obtained with aryl halides possessing electron-withdrawing groups in the para position. Aryl boronic acids containing electron-donating groups in the para position are more reactive and the correlation yields a value of  $\rho = -1.26$ . The effect is different from those obtained for the Ni-catalyzed Suzuki cross-coupling of aryl boronic acids with aryl chlorides<sup>15</sup> and aryl tosylates,<sup>16</sup> indicating that oxidative addition is not the rate-determining step. Higher reaction rates for electron-donating substituents in the aryl boronic acid have also been observed for the Pd-catalyzed homocoupling of arylboronic acids.<sup>17</sup> To explain this behavior, the authors proposed that the transfer of the aryl group to the electron-deficient palladium should be favored by the electron-donating ability of the substituent. The Hammett correlation observed in our case can also be explained by the enhancement of the nucleophilicity of the

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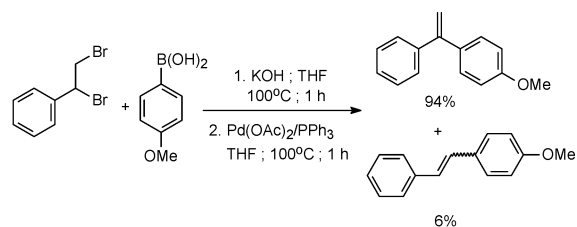
(17) Moreno-Manás, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346.

organic moiety when the electron-donating ability of the para substituent increases. Although the mechanism of the transmetalation step is less understood than the mechanism of oxidative addition and reductive elimination, two processes have been proposed for the cross-coupling reaction of organoboron compounds in alkaline solution: (A) base reacts with the organoboron reagent, forming a more reactive "ate" complex for arylation of Ar-Pd-X or (B) exchange between Ar-Pd-X and a base (R'O<sup>-</sup>) generating an alkoxo- or hydroxo-Pd(II) complex that undergoes transmetalation with organoboronic acids without the aid of a base.<sup>18</sup> Since increasing the nucleophilicity of the organic moiety should facilitate both processes, we cannot propose which process is predominant, and further mechanistic studies are currently under investigation.

Finally, we applied this protocol to a substituted dibromoethane (eq 1). (1,2-Dibromoethyl)-benzene is easily obtained from the bromination of styrene. Using the optimized procedure generated the corresponding 1,1-arylethylene in 94% yield with 6% yield of 1,2-regioisomers. The regioselectivity is maintained in the cross-coupling reaction since it was the same as that observed for the first step, the dehydrobromination ( $\alpha$ -: $\beta$ -bromostyrene = 94:6). In summary, we have developed a simple protocol for the synthesis of functionalized styrenes from 1,2-dibromoethane and arylboronic acids. Compared with the cross-coupling reactions usually employed to obtain vinylarenes, this protocol is very simple, overcomes the inconvenience of using of ethylene under pressure, and uses air-stable and widely available arylboronic acids instead of vinyl organometallic reagents. Given that vinyl bromide is either a gas or available

(18) Miyaura, N. *J. Organomet. Chem.* **2002**, 653, 54.

Scheme 1



as a stock solution, both more expensive than 1,2-dibromoethane, this in situ protocol also circumvents the difficult manipulation of gaseous or volatile starting material. Further studies to extend this protocol to other substrates are currently under investigation in our group.

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**Note Added after ASAP Posting.** The addition of 1,2-dibromoethane was omitted from the typical experimental procedure in ref 12 and in the Supporting Information in the version posted ASAP on July 11, 2003; the corrected version was posted July 15, 2003.

**Supporting Information Available:** Detailed experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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