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Authors: Gerald B. Hammond, Bo Xu, Shiwen Liu, and Xiaojun Zeng

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# COMMUNICATION

# Mild Base Promoted Nucleophilic Substitution of Unactivated *sp*<sup>3</sup>-Carbon Electrophiles with Alkenylboronic Acids

Shiwen Liu,<sup>[a]</sup> Xiaojun Zeng,<sup>[a]</sup> Gerald B. Hammond<sup>[b], \*</sup> and Bo Xu<sup>[a], \*</sup>

<sup>[a]</sup> Key Laboratory of Science and Technology of Eco-Textiles, Ministry of Education, College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, Shanghai 201620, China. <sup>[b]</sup> Department of Chemistry, University of Louisville, Louisville, KY 40292, USA.

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**Abstract.** Diverse <u>alkenylboronic</u> acids react smoothly with various  $sp^3$ -carbon electrophiles such as unactivated alkyl triflates in the presence of mild bases such as K<sub>3</sub>PO<sub>4</sub>. The reaction protocol is very mild and thereby enables high functional group tolerance. This transition metal-free condition is orthogonal towards the classic transition metal catalyzed Suzuki coupling.

**Keywords:** Transition metal-free, cross-coupling, alkenylboronic acids, *sp*<sup>3</sup>-carbon electrophiles

### Introduction

The transition metal-catalyzed cross-coupling between organometallic reagents and carbon electrophiles is an extremely important carboncarbon bond formation protocol in organic synthesis.<sup>[1]</sup> In this context, the Suzuki-Miyaura coupling is by far the most widely used crosscoupling protocol due to its good functional group tolerance and the low toxicity of organoboron reagents.  $^{[1\text{-}2]}$  In general,  $C_{sp2}\text{-}C_{sp2}$  (aryl-aryl, alkenylalkenyl or aryl-alkenyl) bond formations via Suzuki couplings are highly efficient, while cross-coupling of  $sp^3$  carbon electrophiles with <u>organoborons</u> are more problematic due to the low reactivity and side reactions such as  $\beta$ -hydride elimination.<sup>[3]</sup> In the last two decades, there has been meaningful progress on Pd/Ni,<sup>[2-4]</sup> Cu,<sup>[5]</sup> Fe<sup>[6]</sup> catalyzed or metal-free<sup>[7]</sup> crosscouplings of  $sp^3$  carbon electrophiles (Scheme 1a). Notable examples include Fu and coworkers' Nicatalyzed stereoconvergent Suzuki reaction using 9-BBN reagents<sup>[8]</sup> and Falck and coworkers' Pdcatalyzed stereospecific Suzuki cross-coupling of alkyl a-cyanohydrin triflates with organoboronic acids<sup>[1g]</sup> (Scheme 1a).





### Scheme 1. Literature background.

Despite the progress summarized above, limitations still exist for the cross-coupling of  $sp^3$ -carbor electrophiles. To overcome side reactions such as  $\beta$ -hydride elimination, a highly optimized metal/ligand combination is needed, which leads to a lack of general and mild conditions. Also, reactive/sensitive organoborons, such as R-BBN, and air-sensitive ligands have been often utilized.<sup>[2b]</sup> The loading of expensive metal/ligand is frequently high (e.g. >5%), which is a problem when transition metal residues matter in the synthesis of biologically active compounds.

Pioneering work on transition metal-free coupling<sup>[9]</sup> of alkenyl or aryl boronic acids has been

reported by the groups of Tang, Wang, Huang and Ryu (Scheme 1b).<sup>[9d, 10]</sup> However, most of these protocols are still limited to relatively reactive sp3carbon electrophiles such as benzyl or allyl electrophiles. We envision that a nucleophilic substitution between alkenylboronic acids with diverse unactivated  $sp^3$ -carbon electrophiles could be viable through a careful choice of bases and leaving groups. Herein, we are glad to report a versatile base promoted nucleophilic substitution protocol of alkenyl boronic acids with a diverse range of  $sp^3$ carbon electrophiles, including unactivated alkyl triflates. A significant advantage of our protocol is the simple and mild conditions needed, which is the result of employing a mild metal phosphate base.

### **Results and discussion**

#### Table 1. Optimization of reaction conditions.<sup>a</sup>

Ph X = Br, 1 X = OTs, X = OMs, X = OTf,	R <sup>2</sup> 1 X 1b ,1c 1d	$\begin{array}{c} & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & $	Ph~ [B] = [B] = [B] =	[B] B(OH) <sub>2</sub> , <b>2a</b> B(pin) <sub>2</sub> , <b>2b</b> BF <sub>3</sub> K, <b>2c</b> 60	base solvent °C, air,12 h
entry	1	2	base	solvent	yield (%) <sup>b</sup>
1	1a	2a	KOtBu	toluene	0
2	1b	2a	KOtBu	toluene	0
3	1c	2a	KOtBu	toluene	0
4	1d	2a	KOtBu	toluene	41
5	1d	2a	$K_2CO_3$	toluene	78
6	1d	2a	$Cs_2CO_3$	toluene	84
/	10	2a	K <sub>3</sub> PO <sub>4</sub>	toluene	91
8	10	2a	Na <sub>3</sub> PO <sub>4</sub>	toluene	83
9	10	2a 2a	KOAC	toluene	5
10	10	2a 21		toluene	69
11	10 1.J	20	K <sub>3</sub> PO <sub>4</sub>	toluene	0
12	10 1.J	20	K <sub>3</sub> PO <sub>4</sub>	DCE	21
13	1d	2a 20	K <sub>3</sub> PO <sub>4</sub>	THE	30
15	1d	2a 2a	$K_{2}PO_{4}$	DME	14
16°	1d	2a 2a	K <sub>2</sub> PO <sub>4</sub>	toluene	90
17	1e	2a 2a	K <sub>3</sub> PO <sub>4</sub>	toluene	0
18	1f	 2a	K <sub>3</sub> PO <sub>4</sub>	toluene	ŏ
19	1g	2a	K <sub>3</sub> PO <sub>4</sub>	toluene	õ
20	1h	2a	K <sub>3</sub> PO <sub>4</sub>	toluene	$92^{d}$
21	1d	2a	-	toluene	0

<sup>a</sup> Conditions: **1** (0.1 mmol), **2** (0.15 mmol), base (0.2 mmol) in solvent (1 mL), 12 h. <sup>b</sup> Determined by GC-MS. <sup>c</sup> The temperature is 90°C <sup>d</sup> Isolated yield.

Our studies of nucleophilic substitution reaction were shown in Table 1. First, we investigated the reactions of relatively unreactive alkyl electrophiles (**1a-1d**) containing various leaving groups (Table 1, entries 1-4) with alkenylboronic acid **2a**. In the presence of weakly nucleophilic base KOtBu, alkyl bromide (**1a**), alkyl tosylate (**1b**) and alkyl methanesulfonate (**1c**) did not give any product (Table 1, entries 1-3). To our delight, the desired coupling product was obtained in 41% yield when alkyl triflate **1d** (Table 1, entry 4) was used. Screening of bases of different strength (Table 1, entries 4–10) revealed metal phosphate is better than stronger bases (t-BuOK) or weaker bases (Cs<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, KOAc, and KF). On the other hand, no reaction occurred when less reactive styrylboronic while ester 2b was used, potassium styryltrifluoroborate 2c gave a comparably low yield (Table 1, entries 11-12). Besides, the yield could not be further improved when the reaction temperature was raised to 90 °C (Table 1, entry 16). We also explored the reaction of secondary alkyl triflates. Similarly, excellent chemical yield was obtained for secondary triflate 1h (Table 1, entry 20), while secondary electrophiles with other leaving groups like bromide, tosylate, and methanesulfonate were unreactive (Table 1, entry 17-19). It should be noted that there was no reaction in the absence of a base.

 Table 2. Scope of reaction between alkenylboronic acids

 with primary alkyl triflate.<sup>a</sup>



<sup>a</sup> Conditions: 1 (0.1 mmol), 2 (0.15 mmol), K<sub>3</sub>PO<sub>4</sub> (0.2 mmol) in toluene (1 mL), 12 h, 60 °C; all yields are isolated yields.
 <sup>b</sup> A mixture of regioisomers were obtained.

Using the newly founded reaction conditions, we first examined the substrate scope of coupling reactions of primary alkyl triflates with various organoboronic acids (Table 2). Most unactivated primary alkyl triflates gave moderate to good yields of desired products. This protocol could be used with aryl and alkyl- substituted alkenylboronic acids. Also, the functional group tolerance was good: common functional groups such as alkene (3b), aryl iodides (3d, 3p), ketone (3e), nitriles (3m, 3r), nitro (3i), alkyl bromides (**3h**, **3n**), heterocycle (**3j-3k**), hydroxyl (31) and cyclopropane (3m-3p) were well substituted tolerated. However, linear alkyl alkenylboronic acids (3q) could not react with alkyl triflates, possibly due to its lower nucleophilicity compared to aryl alkenylboronic acids. Besides, we observed the formation of regioisomers when substituted aryl boronic acids were used (Table 2, 3t).

The formation of regioisomers was consistent with Wang and coworkers' report<sup>[10b]</sup> on metal-free coupling of arylboronic acids with benzyl halides.

# Table 3. Scope of reaction between alkenylboronic acids with secondary alkyl triflates.



 $<sup>^</sup>a$  Conditions: 1 (0.1 mmol), 2 (0.15 mmol),  $K_3PO_4$  (0.2 mmol) in toluene (1 mL), 12 h. 60  $^oC$ : all vields are isolated vields.

Then, we started to investigate the coupling of unactivated secondary alkyl triflates. However, secondary alkyl triflates without a geminal electronwithdrawing group were not stable<sup>[11]</sup>, so we explored the coupling of secondary alkyl triflates with a geminal electron-withdrawing group such as nitrile. These reactions gave excellent chemical yields and showed good functional group tolerance. Functional groups such as alkenes (Table 3, 4c, 4f), organo azides (Table 3, 4d, 4ad), terminal alkyne (Table 3, 4e), thioether (Table 3, 4g), alkyl bromide (Table 3, 4h), nitro (Table 3, 4i), ether (Table 3, 4i, 4l, 4q, 4ab, 4ae), esters (Table 3, 4j, 4k, 4x), nitrile (Table 3, 4l), amide (Table 3, 4m, 4ac), thiophene (Table 3, 4p), benzothiophene (Table 3, 4y) were well tolerated. This protocol worked very well even with substrates containing a complex natural product skeleton (**3e** and **4ae**). We believed that the high functional group tolerance is due to the fact that the only reagent used is a mild base  $- K_3PO_4$ . In general, compared to reactions of  $\alpha$ -cyanohydrin triflates,  $\alpha$ -triflate aliphatic esters gave relatively lower yields (Table 3, **4af** - **4ah**). This may be due to the higher steric hindrance of ester groups.

To get some mechanistic insights, we added a cation catcher (N-methylindole)<sup>[10]</sup> and a radical quencher (TEMPO) to the reaction, both of them had no effect on the progress of reactions. This result indicated the reaction may not go through a  $S_{\rm N}1$  or a radical mechanism. Based on these experimental results, we propose a possible reaction pathway (Scheme 2). First, the base  $(K_3PO_4)$  attacks the organoboronic acid to form an ate type complex A. whose anionic nature leads enhanced to nucleophilicity.<sup>[12]</sup> When the reaction is conducted in non-polar solvents such as toluene, this complex is likely to exist as a contact ion pair.<sup>[13]</sup> Then complex A reacts with a  $sp^3$ -carbon electrophile through a  $S_N2$ like process to give the final product.



#### Scheme 2. Proposed mechanism.

It should be noted that our metal-free protocol is orthogonal to the classic transition metal catalyze Suzuki reactions. For example, reactive aryl iodides (Table 2, 3d, 3l) showed no reactivity toward alkenylboronic acids under our conditions. Alkyl bromides (Table 2, 3n, 3p, 3q; Table 3, 4h, 4aa) also were untouched. This means that our metal-free protocol and the classic Pd-catalyzed Suzuki reaction are complementary to each other. This feature could be more powerful when the two are used together (Scheme 4). For example, a building block containing both alkyl triflate  $(X^1)$  and aryl halide  $(X^2)$  (e.g., 1d) could couple with two different boronic acids in a tandem manner (Scheme 3). This strategy could be potentially used in the Suzuki reaction-based iterative synthesis of small molecules developed by Burke and coworkers.<sup>[14]</sup>



Scheme 3. Tandem metal-free coupling and classic Suzuki reactions.

### Conclusion

In conclusion, we have developed a highly versatile base promoted nucleophilic substitution protocol. Only a mild metal phosphate base is needed; the mild conditions led to excellent functional group tolerance. Our metal-free condition is orthogonal towards the transition metal catalyzed Suzuki reaction, which means that our method is complementary to the classic Suzuki coupling for the synthesis of complex target molecules.

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