A Transition-Metal-Free Cross-Coupling Reaction of Allylic Bromides with Aryl- and Vinylboronic Acids

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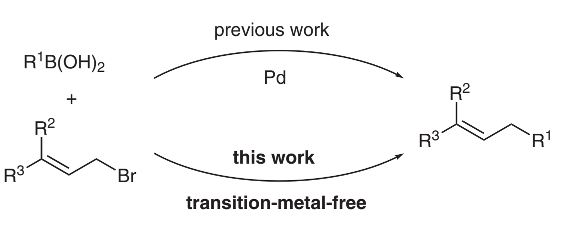
Abstract: A cross-coupling reaction between aryl- and vinylboronic acids and various allylic bromides proceeded without the use of a transition-metal catalyst to give the corresponding allylated products in moderate to good yields. The use of an inorganic base (KF or Cs_2CO_3) and a small amount of water is crucial in obtaining good performance in the present transition-metal-free reaction.

Key words: transition-metal-free, C–C bond formation, aryl- and vinylboronic acids

The palladium-catalyzed cross-coupling reaction of allylic halides,[1] esters,[2] and alcohols[3] with organoboronic acids provides a magnificent tool for organic synthesis. With this method, we generally rely on the use of precious transition metals, such as Pd complexes, as the catalyst.[4] In 2005, Kabalka and co-workers reported that a cross-coupling reaction of secondary allylic alcohols with alkenylboron dihalides proceeded in the absence of a transition metal, in which typically stoichiometric *n*-BuLi was used as a base.[5] This work suggests the possibility of a metal-free process in the cross-coupling reaction of organoboron compounds, however, to the best of our knowledge, no related studies on the transition-metal-free cross-coupling reaction of organoboron compounds with allylic halides have not been reported.[6,7]

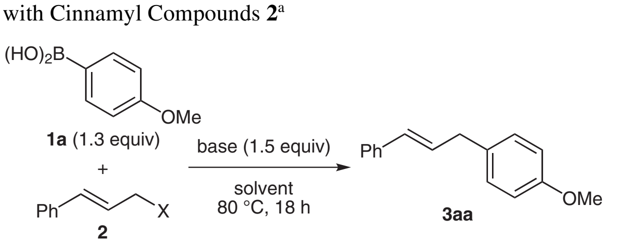
Herein, we wish to report a Suzuki–Miyaura-type cross-coupling reaction of allylic bromides with aryl- and vinylboronic acids that proceeded under metal-free conditions (Scheme 1). Concurrently with our work, Scrivanti and co-workers reported a similar metal-free cross-coupling reaction, in which they used potassium carbonate as a base. However, the reaction reported in this work has a broader scope and generality than expected from their work.[8]



Scheme 1 A transition-metal-free cross-coupling reaction of allylic bromides with organoboronic acids

In our first investigation, treatment of cinnamyl bromide (**2a**) with 4-methoxyphenylboronic acid (**1a**; 1.3 equiv) and KF (1.5 equiv) in THF at 80 ºC for 18 hours gave (*E*)-3-(4-methoxyphenyl)-1-phenyl-1-propene (**3aa**) in a 49% yield (Table 1, entry 1).[9] Interestingly, the addition of H_2O (THF–H_2O, 10:1) remarkably improved the yield (87%; entry 2). To improve this process, we then surveyed the effects of the base, solvent, and leaving groups of allylic substrates. The use of K_2CO_3 in THF–H_2O (10:1) gave **3aa** in a 66% yield (entry 3). Further improvement in the yield was achieved by using Cs_2CO_3 in THF–H_2O (10:1; 90%; entry 4).[10] An experiment without a base resulted in no reaction (entry 5). Switching the solvent from THF–H_2O to DMF–H_2O and toluene–H_2O at 80 °C gave

Table 1 Screening of Reaction Conditions for the Transition-Metal-Free Cross-Coupling Reaction of 4-Methoxyphenylboronic Acid (**1a**) with Cinnamyl Compounds **2**[a]



Entry	X		Base	Solvent	Yield (%)[b]
1	Br	**2a**	KF	THF	49
2	Br	**2a**	KF	THF–H_2O (10:1)	87
3	Br	**2a**	K_2CO_3	THF–H_2O (10:1)	66
4	Br	**2a**	Cs_2CO_3	THF–H_2O (10:1)	90
5	Br	**2a**	none	THF–H_2O (10:1)	0
6	Br	**2a**	Cs_2CO_3	DMF–H_2O (10:1)	92
7	Br	**2a**	Cs_2CO_3	toluene–H_2O (10:1)	95
8[c]	Br	**2a**	Cs_2CO_3	CH_2Cl_2–H_2O (10:1)	99 (95)[d]
9[c]	Cl	**2b**	Cs_2CO_3	CH_2Cl_2–H_2O (10:1)	(42)[d]
10[c]	OAc	**2c**	Cs_2CO_3	CH_2Cl_2–H_2O (10:1)	0
11[c]	OH	**2d**	Cs_2CO_3	CH_2Cl_2–H_2O (10:1)	0

[a] Reaction conditions: **1a** (1.3 equiv), **2** (1.0 equiv), base (1.5 equiv), solvent (0.3 M), 80 °C, 18 h.
[b] NMR yield of **3aa**. Tetrachloroethane was used as an internal standard.
[c] The reaction was carried out at 60 ºC.
[d] Isolated yield of **3aa**.

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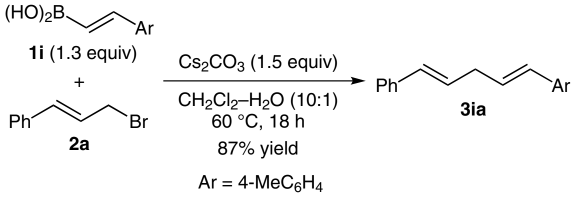
3aa in 92% and 95% yields, respectively (entries 6 and 7). The reaction using CH_2Cl_2–H_2O as a solvent at 60 °C afforded **3aa** in a 95% isolated yield (entry 8). We also examined some other cinnamyl substrates. Whereas cinnamyl chloride (**2b**) reacted with **1a** to afford **3aa** in a moderate yield (entry 9), no reaction took place with cinnamyl acetate (**2c**) and cinnamyl alcohol (**2d**; entries 10 and 11).

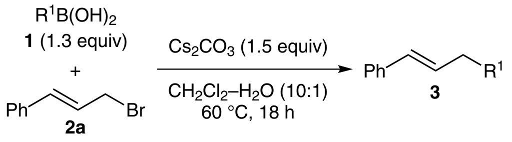
With the optimized reaction conditions, represented in entry 8 (Table 1), in hand, the scope of the transition-metal-free cross-coupling reaction with respect to various organoboronic acids was investigated using **2a** as a coupling partner (Table 2). 2-Methoxyphenylboronic acid (**1b**) and 3,4-dimethoxyphenylboronic acid (**1c**) showed a comparable reactivity with 4-methoxyphenylboronic acid (**1a**; entries 2 and 3). The reaction of 4-benzyloxyphenylboronic acid (**1d**) with **2a** also gave the corresponding product **3da** in a 91% yield (entry 4). Nitrogen-substituted phenylboronic acid (**1e**) was also applicable albeit in a modest yield (entry 5). 4-Methylphenylboronic acid (**1f**) reacted with cinnamyl bromide (**2a**) to give **3fa** in a good yield (77%; entry 6). The reaction of 4-fluorophenylboronic acid gave **3ga** in a 56% yield (entry 7). The reaction of unsubstituted phenylboronic acid (**1h**) gave **3ha** in a 79% yield under the reaction conditions involving KF and toluene–H_2O at 90 °C (entry 8).[11]

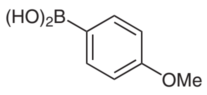
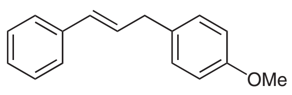
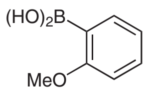
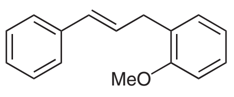
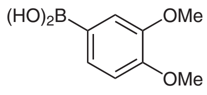
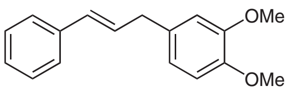
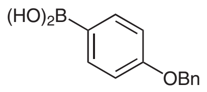
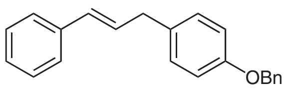
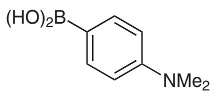
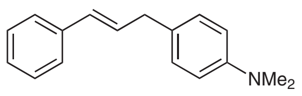
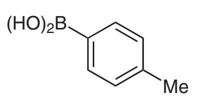
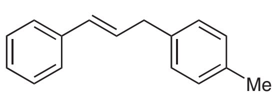
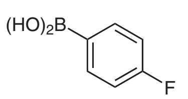
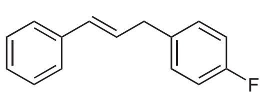
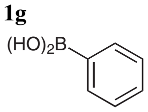
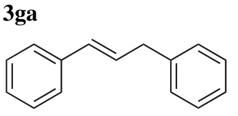
Importantly, these conditions were applicable to the cross-coupling reaction of vinylboronic acids. For example, *trans*-2-(4-methylphenyl)vinylboronic acid (**1i**) reacted with **2a** to give the expected 1,4-diene **3ia** in a 87% yield (Scheme 2).



Scheme 2 Transition-metal-free cross-coupling reaction of *trans*-2-(4-methylphenyl)vinylboronic acid (**1i**) with cinnamyl bromide (**2a**)

Table 2 Transition-Metal-Free Cross-Coupling Reaction of Organoboronic Acids **1** with Cinnamyl Bromide (**2a**)[a]



Entry	$R^1B(OH)_2$ **1**	Product **3**	Yield (%)[b]
1	 **1a**	 **3aa**	95
2	 **1b**	 **3ba**	85
3	 **1c**	 **3ca**	74
4	 **1d**	 **3da**	91
5	 **1e**	 **3ea**	52
6	 **1f**	 **3fa**	77
7	 **1g**	 **3ga**	56
8[c]	 **1h**	 **3ha**	79

[a] Reaction conditions: **1** (1.3 equiv), **2a** (1.0 equiv), Cs_2CO_3 (1.5 equiv), CH_2Cl_2–H_2O (10:1, 0.3 M), 60 °C, 18 h.

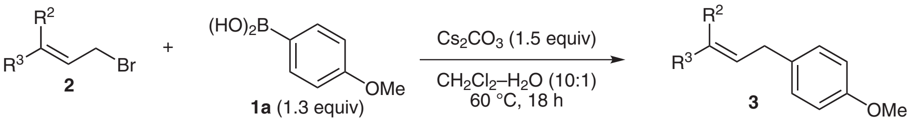
[b] Isolated yield of **3**.

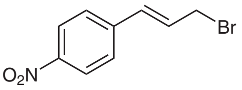
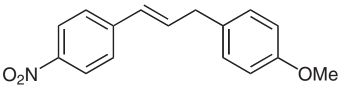
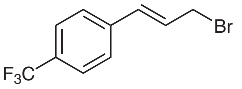
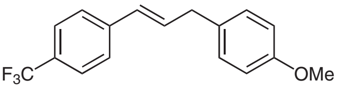
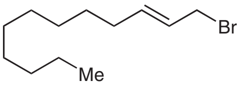
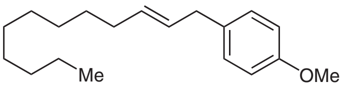
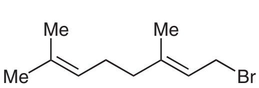
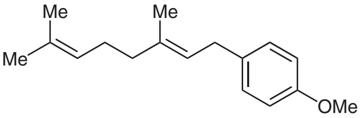
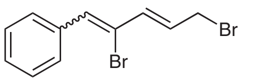
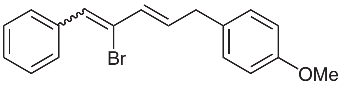
[c] KF (1.5 equiv), toluene–H_2O (10:1, 0.3 M), 90 °C, 18 h.

Having examined the substrate scope of organoboronic acids with cinnamyl bromide (**2a**), we next turned our attention to the allylic bromides **2e**–**2i** (Table 3). A range of electron-withdrawing ring substituents of cinnamyl bromides **2e** and **2f** tolerated the reaction conditions well enough to furnish the corresponding cross-coupling product **3** in good yields (entries 1 and 2). Straight-chain aliphatic allylic bromide **2g** also reacted with **1a** to afford **3ag** in a 68% yield (entry 3). Geranyl bromide (**2h**) participated in the reaction with **1a** to afford the desired product **3ah** in a 94% yield (entry 4). Interestingly, conjugated allylic bromide **2i** containing vinyl bromide reacted with **1a** to give only monosubstituted product **3ai** in a 76% yield (entry 5), since it is known that the substrate containing both vinyl and allylic bromide react with organoboronic acid to afford the bis-substituted cross-coupling product as a major product under palladium-catalyzed cross-coupling conditions.[12]

The addition of radical scavengers, such as 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and 1,4-dinitrobenzene (an ET scavenger),[13] did not affect the yield of the reaction of **1a** with **2a** (Scheme 3). Therefore, it seems unlikely that the reaction proceeded by a radical mechanism. Although the mechanistic details of this reaction remain to be elucidated, an ionic substitution mechanism including an *ipso*-attack of organoboronic acid is shown in Scheme 4.[14] As a first step, **1a** is converted to a borate an-

Table 3 Transition-Metal-Free Cross-Coupling Reaction of 4-Methoxyphenylboronic Acid (**1a**) with Allylic Bromides **2**[a]

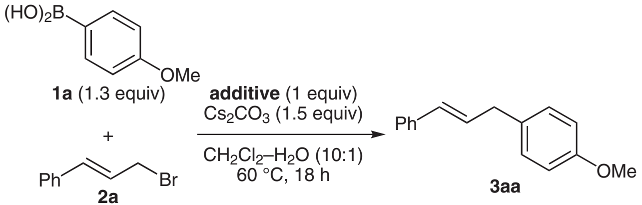


Entry	Allyl bromide **2**	Product **3**	Yield (%)[b]
1	 **2e**	 **3ae**	68
2	 **2f**	 **3af**	52
3	 **2g**	 **3ag**	68
4	 **2h**	 **3ah**	94
5	 **2i**	 **3ai**	76

[a] Reaction conditions: **1a** (1.3 equiv), **2** (1.0 equiv), Cs_2CO_3 (1.5 equiv), CH_2Cl_2–H_2O (10:1, 0.3 M), 60 °C, 18 h.

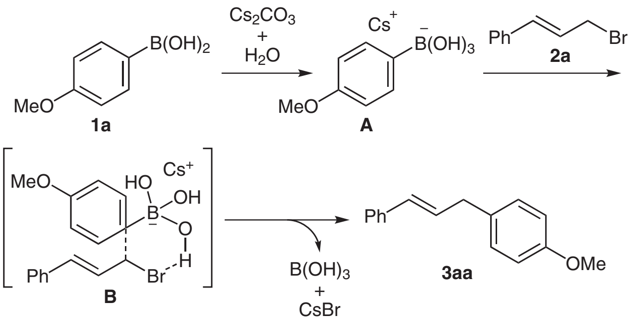
[b] Isolated yield of **3**.

ion **A** by an hydroxide anion attack. The borate anion **A** could then react with cinnamyl bromide (**2a**) through a transition state **B** to give the cross-coupling product **3aa** with the liberation of boronic acid.

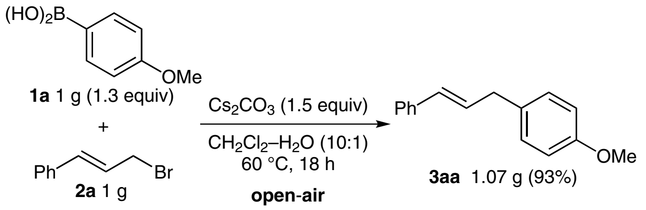


Additive	Yield (%)
none	95
none (dark)	95
TEMPO	77
1,4-dinitrobenzene	89

Scheme 3 Effect of additives on transition-metal-free cross-coupling reaction of 4-methoxyphenylboronic acid (**1a**) with cinnamyl bromide (**2a**)



Scheme 4 Plausible mechanism for the formation of **3aa**



Scheme 5 Gram-scale transition-metal-free C–C bond-forming reaction

The distinction of this transition-metal-free C–C bond-forming reaction is very easy to handle. In this reaction, purifications of commercial solvents and reagents are not required, and an open-air condition is tolerated. Thus, we performed a gram-scale reaction with cinnamyl bromide (**2a**; 1 g, 5.1 mmol), 4-methoxyphenylboronic acid (**1a**; 1 g, 6.6 mmol), and Cs_2CO_3 (2.5 g, 7.65 mmol) in CH_2Cl_2–H_2O (15.5 mL/1.5 mL) at 60 °C, which gave **3aa** in a 93% yield (1.07 g; Scheme 5).

In summary, we have developed an efficient transition-metal-free carbon–carbon bond-forming reaction with various allylic bromides using aryl- and vinylboronic acids under the mild reaction conditions.[15] A transition-metal-free cross-coupling reaction has some benefits such as low cost, environmental benignity, easy operation, and avoidance of the need to eliminate trace metals from the final compounds. Therefore, we believe that the present transition-metal-free system will be a useful tool in cross-coupling chemistry.

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(10) The use of Cs_2CO_3 in the absence of H_2O gave **3aa** in a moderate yield (60%).

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(15) **Typical Procedure for a Transition-Metal-Free Cross-Coupling Reaction of Allylic Bromides with Aryl- and Vinylboronic Acids**: A mixture of 4-benzyloxyphenyl boronic acid (**1d**; 0.65 mmol, 1.3 equiv), cinnamyl bromide (**2a**; 0.5 mmol), and Cs_2CO_3 (0.75 mmol, 1.5 equiv) in CH_2Cl_2–H_2O (1.65 mL, 10:1) was stirred at 60 °C for 18 h.

After the reaction was completed, the reaction mixture was treated with aq 1 N HCl, extracted with CH_2Cl_2 and dried over $MgSO_4$. The organic layer was concentrated and the resulting residue was purified by column chromatography on silica gel (hexane–EtOAc, 100:1) to give (*E*)-3-(4-benzyloxyphenyl)-1-phenyl-1-propene (**3da**) as a white solid in 91% yield (136.6 mg, 0.455 mmol); mp 44–48 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.49 (d, *J* = 6.9 Hz, 2 H), 5.05 (s, 2 H), 6.34 (dt, *J* = 15.6, 6.9 Hz, 1 H), 6.43 (d, *J* = 15.6 Hz, 1 H), 6.93 (d, *J* = 8.7 Hz, 2 H), 7.16 (d, *J* = 8.7 Hz, 2 H), 7.20 (t, *J* = 7.4 Hz, 1 H), 7.27–7.39 (m, 7 H), 7.43 (d, *J* = 6.9 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.6, 70.2, 115.0, 126.2, 127.2, 127.6, 128.0, 128.6, 128.7, 129.7 (two peaks overlap), 130.9, 133.0, 137.3, 137.6, 157.4. IR (neat): 3031, 1454, 1231 cm^{-1}. HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{22}H_{20}O$: 300.1514; found: 300.1512.