Transition-Metal-Free Suzuki–Miyaura Coupling Reaction of Arylpropargylic Bromides with Aryl- and Alkenylboronic Acids

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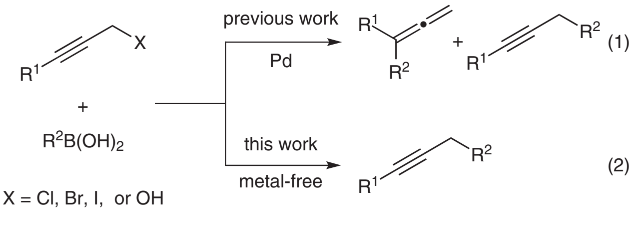
Abstract: In the absence of transition-metal catalyst, Suzuki–Miyaura coupling reaction between aryl- and alkenylboronic acids and arylpropargylic bromides proceeded to give the corresponding acetylenic products selectively.

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

The transition-metal-catalyzed cross-coupling reaction of organo halides or alcohols with organoboronic acids is among the most useful carbon–carbon bond-forming reactions.[1] The palladium-catalyzed cross-coupling reaction of propargylic halides or alcohols with organoboronic acids generally gives a mixture of allenic and propargylic products (Scheme 1, eq. 1).[2–4] To the best of our knowledge, there is only one example of selective propargylation of organoboronic acid, in which 2-methylphenylboronic acid was coupled with 3-trimethylsilyl-2-propyn-1-ol to give [3-(2-methoxyphenyl)prop-1-yn-1-yl]trimethylsilane.[2]

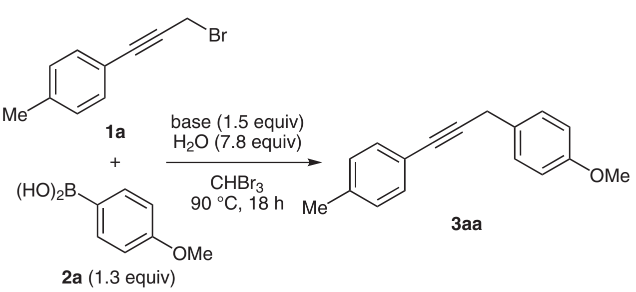


Scheme 1 Two types of the Suzuki–Miyaura coupling reaction of propargylic halides or alcohols

Recently, we[5] and the Scrivanti group[6] independently reported that a cross-coupling reaction between arylboronic acids and allylic bromides proceeded well without the use of a transition-metal catalyst to give the allylated products. Herein, we wish to report that a similar metal-catalyst-free reaction of arylpropargylic bromides with aryl- and alkenylboronic acids proceeded well to give propargylic products selectively (Scheme 1, eq. 2).

In our first investigation for the metal-catalyst-free propargylation, 1-(3-bromoprop-1-yn-1-yl)-4-methylbenzene (**1a**) was treated with 4-methoxyphenylboronic acid (**2a**, 1.3 equiv) and Cs_2CO_3 (1.5 equiv) in CH_2Cl_2 at 90 °C for 18 hours. We were pleased to find that the reaction proceeded to give 1-methoxy-4-[3-(*p*-tolyl)prop-2-yn-1-yl]benzene (**3aa**), albeit in low yield, in which no allenyl-type product was formed (Table 1, entry 1). The addition of H_2O (7.8 equiv) improved the yield of **2a** to 74% (Table 1, entry 2). We then surveyed the solvents and bases. While the reaction using $CHCl_3$ as a solvent afforded **3aa** in a 47% yield (Table 1, entry 3), significant improvement of the yield was achieved by using $CHBr_3$ as a solvent (84% yield, Table 1, entry 4). Switching the solvent from $CHBr_3$ to BTF (benzotrifluoride) and *t*-BuOH at 90 °C gave **3aa** in 66% and 51% yields, respectively (Table 1, entries 5 and 6). The reaction using K_2CO_3 and KF in $CHBr_3$ afforded **3aa** in 69% and 42% yields, respectively (Table 1, entries 7 and 8).

Table 1 Screening of Reaction Conditions for the Transition-Metal-Free Suzuki–Miyaura Coupling Reaction of 1-(3-Bromoprop-1-yn-1-yl)-4-methylbenzene (**1a**) with 4-Methoxyphenylboronic Acid (**2a**)[a]



Entry	Base	Solvent	Yield of **3aa** (%)[b]
1[c]	Cs_2CO_3	CH_2Cl_2	32
2	Cs_2CO_3	CH_2Cl_2	74
3	Cs_2CO_3	$CHCl_3$	47
4	Cs_2CO_3	$CHBr_3$	84 (81)[d]
5	Cs_2CO_3	BTF	66
6	Cs_2CO_3	*t*-BuOH	51
7	K_2CO_3	$CHBr_3$	69
8	KF	$CHBr_3$	42

[a] Reaction conditions: **1a** (1.0 equiv), **2a** (1.3 equiv), base (1.5 equiv), H_2O (7.8 equiv), solvent (1.5 M for **1a**), 90 °C (bath temp), 18 h.
[b] NMR yield. Tetrachloroethane was used as an internal standard.
[c] The reaction was carried out without H_2O.
[d] Isolated yield by silica gel chromatography.

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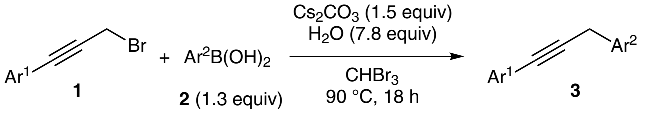
With the optimized reaction conditions (Table 1, entry 4) in hand, the scope of the regioselective Suzuki–Miyaura coupling reaction with respect to various organoboronic acids and propargylic bromides was investigated (Table 2).[7] The reaction of 3,4-dimethoxyphenylboronic acid (**2b**) and 4-benzyloxyphenylboronic acid (**2c**) with **1a** gave the corresponding internal acetylenes **3ab** and **3ac** in 62% and 51%, respectively (Table 2, entries 2 and 3). On the other hand, the reaction of 4-fluorophenylboronic acid (**2d**) with **1a** was very sluggish to give **3ad** in 13% yield (Table 2, entry 4). The cross-coupling reaction of *trans*-2-(4-methylphenyl)vinylboronic acid (**2e**) with **1a** also proceeded to give the expected 1,4-enyne **3ae** in a 43% yield (Table 2, entry 5).

Table 2 Transition-Metal-Free Suzuki–Miyaura Coupling Reaction of Propargylic Bromides **1** with Organoboronic Acids **2**[a]



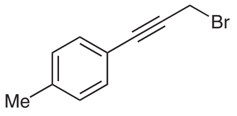
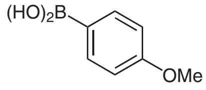
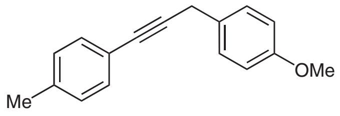
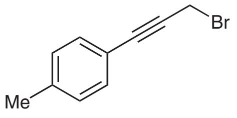
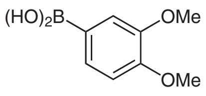
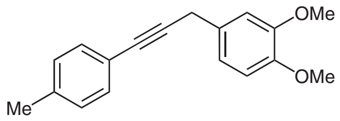
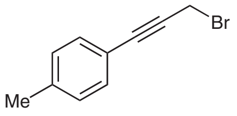
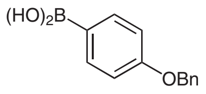
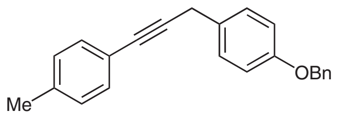
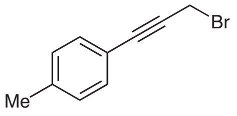
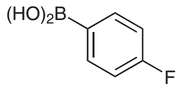
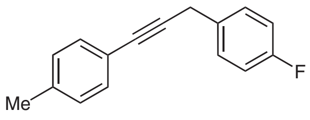
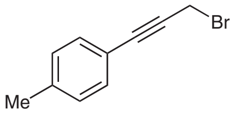
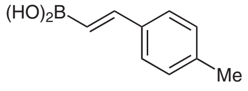
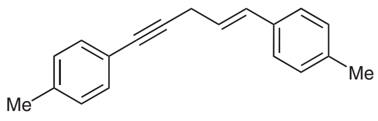
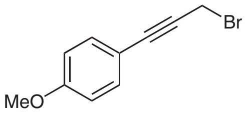
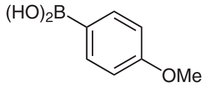
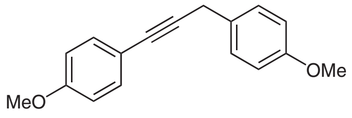
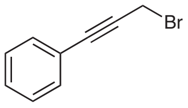
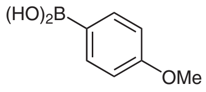
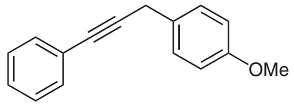
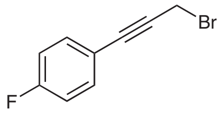
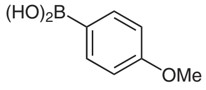
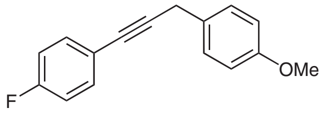
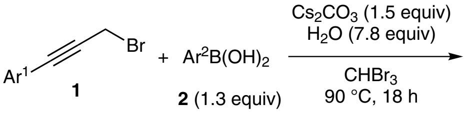
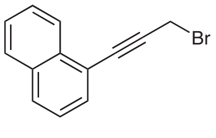
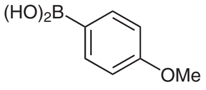
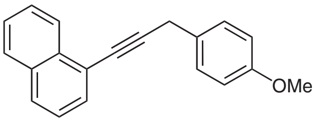
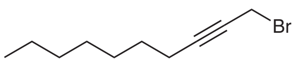
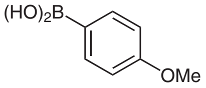
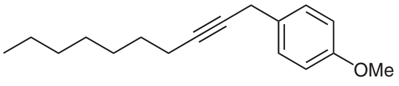
Entry	Propargylic bromide **1**	Organoboronic acid **2**	Product **3**	Yield (%)[b]
1	 **1a**	 **2a**	 **3aa**	81
2	 **1a**	 **2b**	 **3ab**	62
3	 **1a**	 **2c**	 **3ac**	51
4	 **1a**	 **2d**	 **3ad**	13
5	 **1a**	 **2e**	 **3ae**	43
6	 **1b**	 **2a**	 **3ba**	71
7	 **1c**	 **2a**	 **3ca**	58
8	 **1d**	 **2a**	 **3da**	62

Table 2 Transition-Metal-Free Suzuki–Miyaura Coupling Reaction of Propargylic Bromides **1** with Organoboronic Acids **2**[a] (continued)

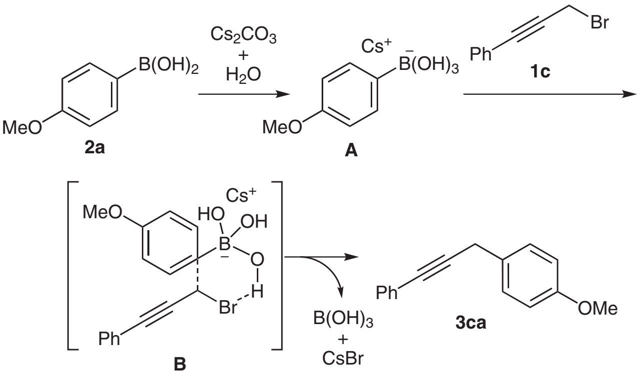


Entry	Propargylic bromide **1**	Organoboronic acid **2**	Product **3**	Yield (%)[b]
9	 **1e**	 **2a**	 **3ea**	64
10	 **1f**	 **2a**	 **3fa**	0

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.3 equiv), Cs_2CO_3 (1.5 equiv), H_2O (7.8 equiv), $CHBr_3$ (1.5 M for **1**), 90 °C, 18 h.
[b] Isolated yield of **3**.

While the transition-metal-free reaction of some other arylpropargylic bromides **1b**–**e** with **2a** proceeded well to give **3ba**–**ea** in good yields (Table 2, entries 6–9), aliphatic propargylic bromide **1f** did not react give the coupling product (Table 2, entry 10).

Although the mechanistic details of this reaction remain to be elucidated, an ionic substitution mechanism including an *ipso* attack of organoboronic acid is proposed in Scheme 2. As a first step, **2a** was converted into a borate anion **A** by H_2O and Cs_2CO_3. The borate anion **A** could then react with **1c** through a six-membered transition state **B** to give the cross-coupling product **3ca** with the liberation of boronic acid.[8,9]



Scheme 2 Plausible mechanism for the formation of **3ca**

In summary, we have developed a regioselective Suzuki–Miyaura coupling reaction of arylpropargylic bromides with aryl- and alkenylboronic acids to give aryl benzyl and aryl allyl substituted alkynes, which does not require a transition-metal catalyst. This work achieved regioselective propargylation at the carbon attached to the bromine of propargylic bromides, which is complementary to the palladium-catalyzed Suzuki–Miyaura reaction.

Acknowledgment

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References and Notes

(1) For recent reviews, see: (a) Suzuki, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 6722. (b) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417. (c) Heravi, M. M.; Hashemi, E. *Tetrahedron* **2012**, *68*, 9145. (d) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062.

(2) Yoshida, M.; Gotou, T.; Ihara, M. *Tetrahedron Lett.* **2004**, *45*, 5573.

(3) We tested the Suzuki–Miyaura cross-coupling reaction of (3-bromoprop-1-yn-1-yl)benzene (**1c**) with phenylboronic acid by using $Pd(PPh_3)_4$ (1 mol%) and Cs_2CO_3 in toluene at 90 °C for 3 h. As the result, propargylic compound (36% yield) and allenic compound (14% yield) were obtained.

(4) (a) Moriya, T.; Miyaura, N.; Suzuki, A. *Synlett* **1994**, 149. (b) Yoshida, M.; Ueda, H.; Ihara, M. *Tetrahedron Lett.* **2005**, *46*, 6705. (c) Molander, G. A.; Sommers, E. M.; Baker, S. R. *J. Org. Chem.* **2006**, *71*, 1563. (d) Miura, T.; Shimada, M.; Mendoza, P.; Deutsch, C.; Krause, N.; Murakami, M. *J. Org. Chem.* **2009**, *74*, 6050.

(5) Ueda, M.; Nishimura, K.; Kashima, R.; Ryu, I. *Synlett* **2012**, *23*, 1085.

(6) Scrivanti, A.; Beghetto, V.; Bertoldini, M.; Matteoli, U. *Eur. J. Org. Chem.* **2012**, 264.

(7) **Typical Procedure for a Metal-Catalyst-Free Suzuki–Miyaura Cross-Coupling Reaction of Propargylic Bromides with Aryl- and Alkenylboronic Acids**
A mixture of 1-(3-bromoprop-1-yn-1-yl)naphthalene (**1e**, 0.5 mmol), 4-methoxyphenylboronic acid (**2a**, 0.65 mmol, 1.3 equiv), Cs_2CO_3 (0.75 mmol, 1.5 equiv), and H_2O (7.8 equiv) in $CHBr_3$ (0.33 mL, 1.5 M for **1e**) was stirred at 90 °C. After 18 h, 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 in vacuo, and the resulting residue

was purified by column chromatography on silica gel (hexane–EtOAc, 100:1) to give 1-[3-(4-methoxy)-phenylprop-1-yn-1-yl]naphthalene (**3ea**) as a yellow liquid (87.4 mg, 64%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.82 (s, 3 H), 3.94 (s, 2 H), 6.91 (d, J = 8.7 Hz, 2 H), 7.41 (m, 3 H), 7.53 (m, 2 H), 7.67 (d, J = 6.9 Hz, 1 H), 7.80 (d, J = 8.3 Hz, 1 H), 7.84 (d, J = 7.4 Hz, 1 H), 8.35 (d, J = 8.3 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.2, 55.2, 80.4, 93.0, 114.0, 121.4, 125.2, 126.2, 126.5, 128.2, 128.8, 128.9, 130.2, 133.1, 133.5, 158.4. IR (neat): 3058, 2223, 1248, 1034 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{20}H_{16}O$: 272.1201; found: 272.1200.

(8) The reaction of isolated sodium trihydroxy(4-methoxyphenyl)borate (1.3 equiv) with **1c** gave the corresponding product **3ca** in 41% yield under the same conditions as shown in Table 2 without base.

(9) Methyl ester of **2a** did not work as a substrate. This result clarifies the significance of a six-membered transition state **B** to give the corresponding acetylenic products selectively.