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A Journal of
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Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201701450

Link to VoR: http://dx.doi.org/10.1002/ejoc.201701450

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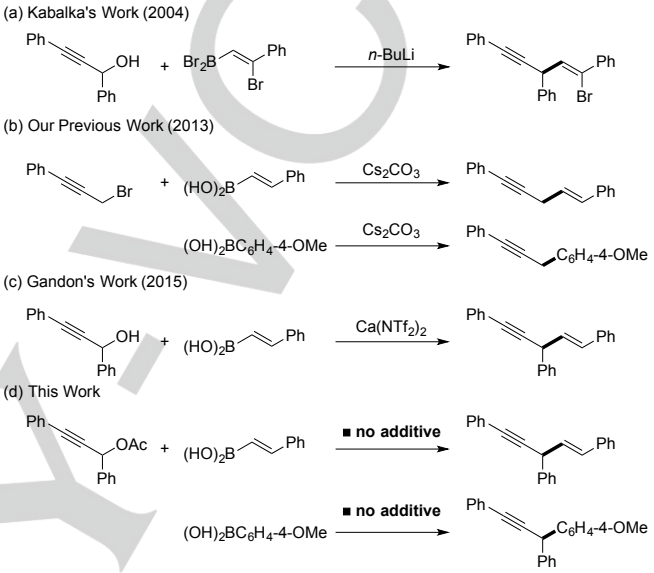
Transition-Metal-Catalyst-Free Cross-Coupling Reaction of Secondary Propargylic Acetates with Alkenyl- and Arylboronic Acids

Mitsuhiro Ueda,*[a] Daiki Nakakoji,[a] Takahiro Morisaki,[a] and Ilhyong Ryu[a]

Abstract: A cross-coupling reaction between secondary propargylic acetates and alkenylboronic acids proceeded to give 1,4-enynes in good yields without adding transition metal catalyst and base. This simple protocol was also applicable to arylboronic acids, which gave 3-arylated alkynes in good yields. The observed induction period suggested that the reaction of propargylic acetates and organoboronic acids was affected by the *in-situ* generated AcOH as a catalyst, which was confirmed by a separate experiment.

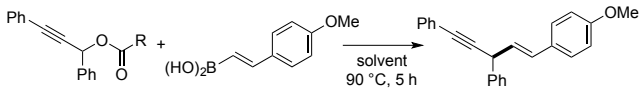
Propargylic alcohol esters, which are easy to synthesize from terminal acetylenes and aldehydes, serve as useful coupling partners for organoboronic acids.[1] For example, the Pd-catalyzed propargylation of arylboronic acids[2] and vinylboronic acids[3] was reported thus far to give acetylenic products. In recent times, efforts have been directed to develop transition-metal-free reactions. Nearly two decades ago, Kabalka and co-workers reported that the cross-coupling reaction of secondary propargylic alcohols with alkenylboron dihalides proceeded to give acetylenic products under catalyst-free conditions (Scheme 1-a).[4] In this reaction, a stoichiometric amount of *n*-BuLi is used as a base to prepare (halovinyl)(propargyloxy)boron halides working as a key intermediate. In 2013, we reported the transition-metal-free cross-coupling reaction of alkenylboronic acids and arylboronic acids with propargylic bromides in the presence of Cs_2CO_3 as a base (Scheme 1-b).[5,6] Recently Gandon and co-workers found that the cross-coupling reaction of propargylic alcohols with alkenylboronic acids proceeds efficiently by using $Ca(NTf_2)_2$ as a catalyst (Scheme 1-c).[7,8,9] Herein, we report that the cross-coupling reaction of propargylic acetates with alkenylboronic acids proceeds spontaneously to give 1,4-enynes in good yields (Scheme 1-d). We also report that, when arylboronic acids are used instead of alkenylboronic acids, 3-aryl-substituted alkynes are obtained in good yields.



Scheme 1. Transition-Metal-Free Cross-Coupling Reaction of Propargylic Alcohol Derivatives with Alkenyl- and Arylboron Reagents.

When 1,3-diphenylprop-2-yn-1-yl acetate (**1a**) was treated with (*E*)-(4-methoxystyryl)boronic acid (**2a**) in dioxane at 90 °C for 5 h, the cross-coupling reaction took place to give the enyne **3a** in 18% yield (Table1, entry 1). Switching the solvent from dioxane to DMF, toluene, and BTF did not give any products (entries 2–4). To our delight, the use of 1,2-dichloroethane (1,2-DCE) as a solvent dramatically improved the yield (78%, entry 5). The addition of a base such as K_2CO_3 resulted in no reaction (entry 6). While benzoate **1b** was also applicable to the present reaction (entry 7), the reaction of the corresponding methyl carbonate **1c** with **2a** was sluggish, giving **3a** in 11% yield (entry 8). Alkenylboronic acid esters **4a** and **4b**, and fluoroborate anion **4c** did not participate in the present cross-coupling reaction (Scheme 2).

Table 1. Optimization of the Reaction Conditions.[a]



1 **2a** (1.5 equiv) **3a**

Entry	Solvent	R	Yield (%)[b]
1	dioxane	Me (**1a**)	18

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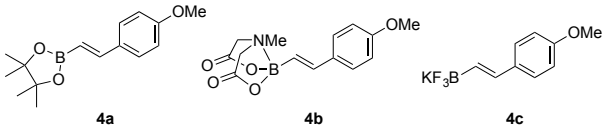
2	DMF	Me (**1a**)	0
3	toluene	Me (**1a**)	0
4	BTF[c]	Me (**1a**)	0
5	1,2-DCE	Me (**1a**)	78
6[d]	1,2-DCE	Me (**1a**)	0
7	1,2-DCE	Ph (**1b**)	73
8	1,2-DCE	OMe (**1c**)	11

[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.75 mmol), solvent (0.33 mL), 90 °C, 5 h. [b] Isolated yield of **3a**. [c] BTF: Benzotrifluoride. [d] Used K_2CO_3 (1 equiv).



4a **4b** **4c**

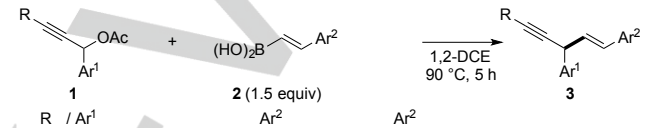
Scheme 2. No Reactions with Alkenylboronic Esters and Borate Derivatives **2h**-**2j**.

Having the optimal conditions of entry 5 in hand, we next explored the scope of the coupling reaction of propargylic acetates with vinylboronic acids **2a** (Table 2). The reaction of 1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-yl acetate (**1b**) with **2a** gave the corresponding 1,3-enyne **3b** in 78% yield (Table 2). The regio-isomeric substrates, 1-(2-methoxyphenyl)-3-phenylprop-2-yn-1-yl acetate (**1c**) and 1-(3-methoxyphenyl)-3-phenylprop-2-yn-1-yl acetate (**1d**) showed a comparable reactivity with **1b** (**3c**: 70%, **3d**: 73%). 1-(Naphthalen-1-yl)-3-phenylprop-2-yn-1-yl acetate (**1e**) reacted with **2a** to give **3e** in 80% yield. The reaction of (*E*)-alkenylboronic acids **2b**-**2f** with **1a** proceeded well to give **3f**-**3j** in good yields (74%-82%). The reaction of (*E*)-2-[4-(trifluoromethyl)phenyl]vinylboronic acid (**2g**) with **1a** was sluggish and gave a 39% yield of **3k**. An alkyl-substituted acetylene, such as 1-phenylhept-2-yn-1-yl acetate (**1f**), was also applicable albeit in a modest yield (**3l**: 58%).[10]

Since the catalyst-free cross-coupling of secondary propargylic derivatives with arylboronic acids is yet to be reported, we then examined arylboronic acids under similar conditions, which also proved to work well (Table 3).[11] For example, the reaction of **1a** with **5a** proceeded to give (3-(4-methoxyphenyl)prop-1-yne-1,3-diyl)dibenzene (**6a**) in good yield (81%). In the reaction with **5a**, propargylic acetates **1b** having an electron-rich phenyl group showed a comparable reactivity with **1a** (**6b**: 78%). On the other hand, the reaction of propargylic acetate **1c** having a 2- methoxyphenyl group was sluggish and gave the corresponding product **6c** in moderate yield (47%). Propargylic acetate **1d**, which has a 3-methoxyphenyl group, also served well as a coupling partner. Indeed, the reaction of **1d** with **5a** gave the desired coupling product **6d** in 68% yield. Propargylic acetate **1i** reacted with **5a** to give **6e** in an 82% yield. In the cases of propargylic acetates **1g** and **1h** having an electron-deficient phenyl group, the addition of 10 mol % of AcOH was required to obtain good yields of the coupling products **6f** and **6g** (vide infra). Aliphatic alkyne and terminal alkyne, such as 1-phenylhept-2-yn-1-yl acetate (**1f**) and 1-phenylprop-2-yn-1yl acetate (**1j**), were also examined. The reaction of **1f** and **1j** with **5a** led to the corresponding coupling products, **6h** and **6i**, in good yields. On the other hand, phenylboronic acid and electron-deficient arylboronic acids, such as 4-nitrophenylboronic acid, did not participate in the reaction.

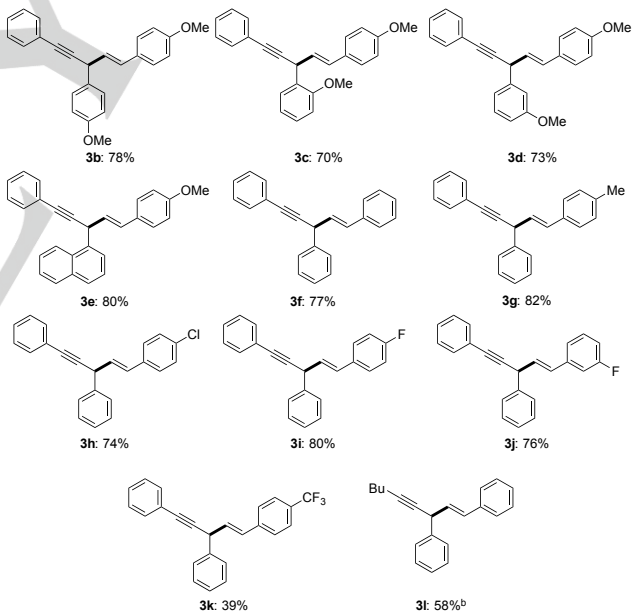
The reaction of some other electron-rich arylboronic acids **5b**-**5d** with **1a** proceeded well to give **6j**-**6l** in good yields (78%-82%). The reaction of 2-methoxy-5-methylphenylboronic acid (**5e**) with **1a** gave **6m** in 78% yield. The reaction of 5-chloro-2-methoxyphenylboronic acid (**5f**) gave the corresponding product **6n** in moderate yield due to the slow reaction (55%). 2-Furylboronic acid (**5g**) tolerated the reaction conditions and formed the corresponding coupling product **6o** in an 80% yield.

Table 2. Substrate Scope of Coupling Reaction of Secondary Propargylic Acetates **1** with Styrylboronic Acid **2**.[a]



1 **2** (1.5 equiv) **3**

R / Ar[1]	Ar[2]	Ar[2]
1b : Ph / 4-MeO-C_6H_4	**2a** : 4-MeO-C_6H_4	**2f** : 3-F-C_6H_4
1c : Ph / 2-MeO-C_6H_4	**2b** : Ph	**2g** : 4-CF_3-C_6H_4
1d : Ph / 3-MeO-C_6H_4	**2c** : 4-Me-C_6H_4	
1e : Ph / 1-Naphthyl	**2d** : 4-Cl-C_6H_4	
1f : Bu / Ph	**2e** : 4-F-C_6H_4	



3b: 78% **3c**: 70% **3d**: 73%

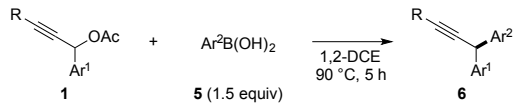
3e: 80% **3f**: 77% **3g**: 82%

3h: 74% **3i**: 80% **3j**: 76%

3k: 39% **3l**: 58%[b]

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), 1,2-dichloroethane (0.33 mL), 90 °C, 5 h. [b] Reaction time: 24 h.

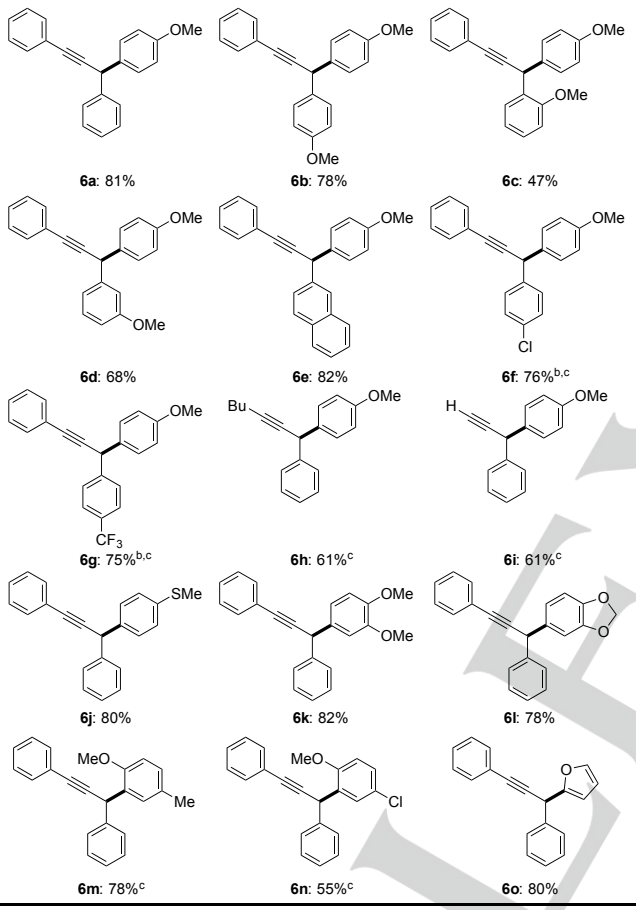
Table 3. Substrate Scope of Coupling Reaction of Secondary Propargylic Acetates **1** with Arylboronic Acid **5**.[a]



1 **5** (1.5 equiv) **6**

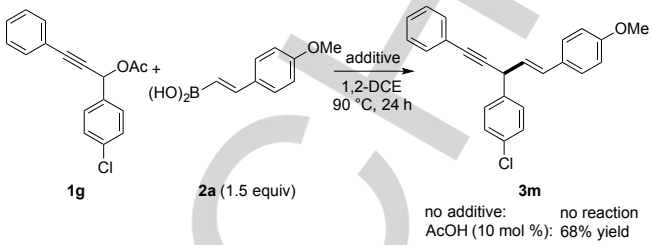
R / Ar1
1a : Ph / Ph
1b : Ph / 4-MeO-C_6H_4
1c : Ph / 2-MeO-C_6H_4
1d : Ph / 3-MeO-C_6H_4
1f : Bu / Ph
1g : Ph / 4-Cl-C_6H_4
1h : Ph / 4-CF_3-C_6H_4
1i : Ph / 2-Naphthyl
1j : H / Ph

Ar2
5a : 4-MeO-C_6H_4
5b : 4-MeS-C_6H_4
5c : 3,4-$(MeO)_2$-C_6H_3
5d : 3,4-(CH_2O_2)-C_6H_3
5e : 2-MeO-5-Me-C_6H_3
5f : 2-MeO-5-Cl-C_6H_3
5g : 2-furanyl

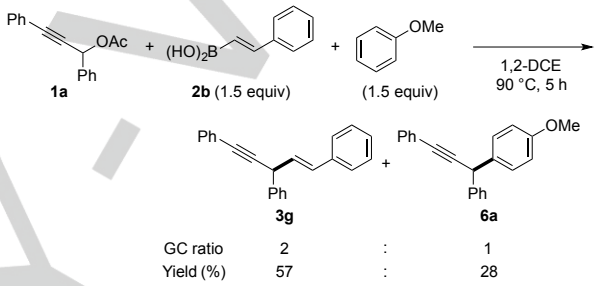


[a] Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), 1,2-dichloroethane (0.33 mL), 90 °C, 5 h. [b] 10 mol % of AcOH was added. [c] Reaction time: 24 h.

To get some insights into the mechanism of the present catalyst-free reaction, we carried out a time course study of the reaction of **2b** with **1a** and found that there is an induction period of the order of a few hours, and the addition of AcOH dramatically shortened the period. Since the reaction of propargylic acetate, having the 4-chlorophenyl moiety **1g**, with **2a** did not proceed, we tested the addition of AcOH. Thus, when 10 mol % of AcOH was added in the reaction of **1g** with **2a**, the desired product **3m** was obtained in 68% yield (Scheme 3).[12] These results rigorously suggest that the reaction of propargylic acetates and organoboronic acids would be initiated by *in-situ* generated AcOH.[13,14] We then examined the cross-over experiment of **2b** and anisole, which gave a 2 : 1 mixture of **3g** and **6a**. These results suggest the intermediacy of propargylic cations in the present coupling reaction (Scheme 4). The fact that an aromatic substituent at the propargylic position was indispensable is rationalized by the formation of the cation intermediates.

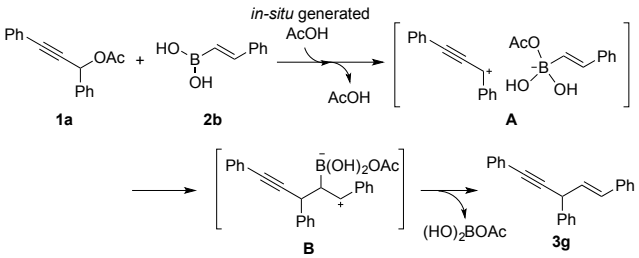


Scheme 3. Reaction of Propargylic Acetate Having 4-Chlorophenyl Moiety **1g** with **2a**.



Scheme 4. Control Experiment.

Consequently, a mechanism involving the propargylic cation is proposed (Scheme 5). As the first step, **1a** would react with **2b** to give the ion-pair **A** of propargylic cation and alkenylborate anion. This process was affected by the *in-situ* generated AcOH. The propargylic cation in ion-pair **A** would then react with the alkenylborate anion or **2b** to give the zwitterionic intermediate **B**. Finally, the desired product **3g** was obtained by deboration.



Scheme 5. Plausible Mechanism.

In summary, we have developed a simple protocol for cross-coupling reaction of propargylic acetates with alkenylboronic acids leading to 1,3-enynes, which does not use a transition metal catalyst and a base. The protocol has also been successfully extended to the reaction of propargylic acetates with arylboronic acids, which gave 3-aryl-substituted alkynes in good yields. Further studies regarding the detailed reaction mechanism and the application of using **2** and **6**, such as the synthesis of

functional molecules bearing π-conjugated skeletons,[15] are currently in progress.

Experimental Section

A magnetic stirring bar, styrylboronic acids (**2a**, 133.5 mg, 0.75 mmol), propargylic acetates (**1a**, 125.1 mg, 0.50 mmol), 1,2-dichloroethane (0.33 mL) were placed in a screw capped test tube. The test tube was purged with argon and sealed. The mixture was stirred at 90 °C for 5 h. After the reaction, solvent was removed under reduced pressure. The residue was purified by chromatography on silica-gel (hexane/ethyl acetate = 20/1) to give **3a** (126.2 mg, 78%).

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from the MEXT and the JSPS (26105752 for MU; 26248031 for IR).

Keywords: Transition-Metal-Catalyst-Free • Cross-Coupling • Secondary Propargylic Acetates • Alkenylboronic acid • Arylboronic acid

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[12] We also examined the reaction of **4a**-**4c** with **1a** in the presence of 10 mol % AcOH. As the results, the corresponding cross-coupling products were not obtained.

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[14] NMR studies: ^{1}H NMR (400 MHz, DMSO-d6): **2e** only; δ 6.05 (d, *J* = 18.4 Hz, 1H, -CH=C*H*-B), 7.14-7.26 (m, 3H, -Ph-F + -C*H*=CH-B), 7.52 (dd, J_{HH} = 8.8 Hz, J_{HF} = 5.6 Hz, 2H, -Ph-F), 7.79 (s, 2H, -B(O*H*)$_2$); **2e** + AcOH (1 equiv); δ 6.06 (d, *J* = 18.0 Hz, 1H, -CH=C*H*-B), 7.18 (dd, J_{HH} = J_{HF} = 8.8 Hz, 2H, -Ph-F), 7.24 (d, *J* = 18.4 Hz, 1H, -C*H*=CH-B), 7.52 (dd, J_{HH} = 8.8 Hz, J_{HF} = 5.6 Hz, 2H, -Ph-F), 7.79 (broad s, 2H, -B(O*H*)$_2$). ^{11}B NMR (128 MHz, DMSO-d6): **2e** only; δ 27.5; **2e** + AcOH (1 equiv); δ 27.4.
^{1}H NMR (400 MHz, DMSO-d6): AcOH only; δ 1.903 (s, 3H), 11.9 (broad s (10.6-13.0 ppm), 1H); AcOH + **2e** (1 equiv); δ 1.904 (s, 3H), 12.0 (broad s (11.5-12.3 ppm), 1H). These results might suggest the interaction of **2e** and AcOH (pKa 4.76/H_2O). In biochemistry, it is known that a protonated imidazole (pKa 6.95/H_2O) as an acid coordinates to hydroxyl group of alkylboronic acid: E. Tsilikounas, C. A. Kettner and W. W. Bachovchin, *Biochemistry*, **1992**, *31*, 12839.

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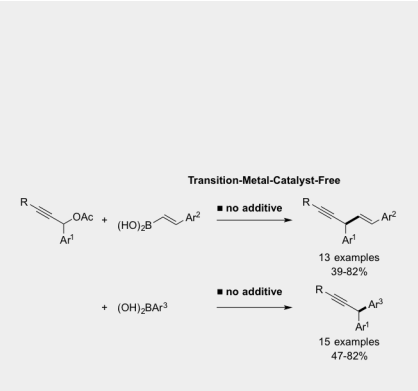
Layout 1:

COMMUNICATION

A cross-coupling reaction between secondary propargylic acetates and alkenylboronic acids proceeded to give 1,4-enynes in good yields without adding transition metal catalyst and base. This simple protocol was also applicable to arylboronic acids, which gave 3-arylated alkynes in good yields.



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