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Palladium-catalyzed coupling reaction of propargylic oxiranes with arylboronic acids in aqueous media

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Abstract—A novel type of coupling reaction has been developed by the palladium-catalyzed reaction of propargylic oxiranes with arylboronic acids, in which *anti*-substituted 4-aryl-2,3-allenols were produced in a highly diastereoselective manner. A chiral-substituted allene has been synthesized from the reaction of a chiral propargylic oxirane without loss of the chirality.

The functionalized allenes are versatile building blocks for organic synthesis because of the inherent reactivity for their axially chiral backbones.[1] Furthermore, a large number of natural products containing an allene moiety have been isolated, and most of these have axial chirality.[2] Extensive studies for the synthesis of allenes have been undertaken from these reasons,[1] and S_N2'-type reactions of propargylic oxiranes are one of the most successful procedures to afford 2,3-allenols.[3] Propargylic oxiranes generally reacted with organocopper,[4] magnesium[5] and metal hydride[6] to produce the substituted 2,3-allenols in moderate to high diastereoselectivity. It is also known that palladium complexes catalyze the reactions of propargylic oxiranes with organozinc,[7] stannane[8] and carbon monooxide[9] yielding the corresponding 2,3-allenols. These reactions are normally required to be carried out under anhydrous conditions, and some of the organometallic reagents are unstable, expensive and toxic. Organoboronic acids are widely used reagents in organic synthesis because of their stability, commercial availability and nontoxicity. However, to the best of our knowledge, there are no examples about the reaction of propargylic oxiranes with organoboronic acids.

Herein, we describe a novel type of coupling reaction of propargylic oxiranes with arylboronic acids by palladium catalyst. The reactions can be carried out in aqueous media to produce the aryl-substituted 2,3-allenols with high *anti*-diastereoselectivity.

The initial reactions were carried out using phenyl-substituted propargylic oxirane **1a**[10] and 2-methylphenylboronic acid (**2a**).[11] When a mixture of **1a** and **2a** were subjected to the reaction with 10 mol% $Pd(PPh_3)_4$ in dioxane at 80 °C for 2 h, the aryl-substituted 2,3-allenol **3aa** having *anti*-geometry was obtained in 81% yield (Table 1, entry 1). The stereochemistry of **3aa** was determined unambiguously by NOESY correlation of dihydrofuran **4aa**, which was produced from the reaction of **3aa** with $AgNO_3^5$ (Scheme 1). The similar result was obtained by using $Pd_2(dba)_3{\cdot}CHCl_3$ with $P(o\text{-Tol})_3$ (entry 2), but poor results were obtained in the presence of bidentate phosphine ligands (entries 3–5). It was found that the yields of **3aa** were increased in the presence of water (entries 6–8), and the product was produced in 92% yield when the reaction was employed in dioxane–H_2O (2:1) (entry 7). Since the obtained 2,3-allenol had all *anti*-geometry in any conditions, it was ascertained that this addition reaction proceeds in a high diastereoselective manner.

A series of substituted arylboronic acids **2b–f** were then subjected to the reaction. The corresponding products **3ab** and **ac** were obtained in good yields by the reactions of **1a** with 2- and 4-methoxyphenylboronic acids (**2b** and **c**) (Table 2, entries 1 and 2). 1-Naphthalene- and phenylboronic acids (**2d** and **e**) were also efficiently transformed to the coupled products **3ad** and **ae** (entries

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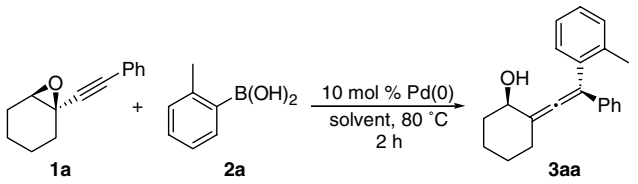
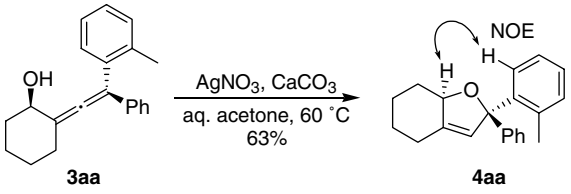
Table 1. Palladium-catalyzed coupling of propargylic oxirane **1a** with 2-methylphenylboronic acid (**2a**)



1a **2a** **3aa**

Entry	Palladium catalyst	Solvent	Yield (%)
1	$Pd(PPh_3)_4$	Dioxane	81
2[a]	$Pd_2(dba)_3{\cdot}CHCl_3$, P(*o*-Tol)$_3$	Dioxane	73
3[b]	$Pd_2(dba)_3{\cdot}CHCl_3$, dppe	Dioxane	16
4[b]	$Pd_2(dba)_3{\cdot}CHCl_3$, dppp	Dioxane	38
5[b]	$Pd_2(dba)_3{\cdot}CHCl_3$, dppf	Dioxane	42
6	$Pd(PPh_3)_4$	Dioxane–H_2O = 9:1	91
7	$Pd(PPh_3)_4$	Dioxane–H_2O = 2:1	92
8	$Pd(PPh_3)_4$	Dioxane–H_2O = 1:2	61

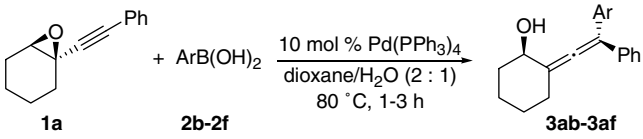
[a] 5 mol% palladium and 40 mol% ligand were used.
[b] 5 mol% palladium and 20 mol% ligand were used.



3aa **4aa**

Scheme 1.

Table 2. Palladium-catalyzed coupling of propargylic oxirane **1a** with arylboronic acids **2b–f**



1a **2b-2f** **3ab-3af**

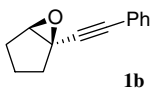
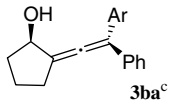
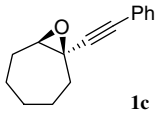
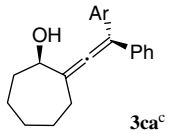
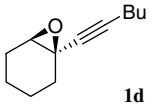
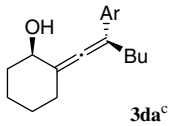
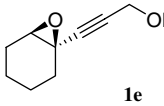
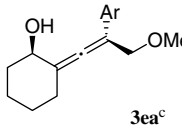
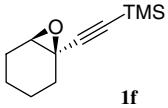
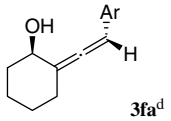
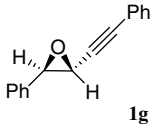
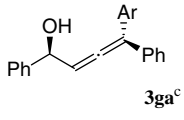
Entry	Boronic acid	Product[a]	Yield (%)
1	2-Methoxyphenylboronic acid (**2b**)	**3ab**[a]	77
2	4-Methoxyphenylboronic acid (**2c**)	**3ac**[a]	81
3	1-Naphthaleneboronic acid (**2d**)	**3ad**[a]	86
4	Phenylboronic acid (**2e**)	**3ae**[a]	55
5	3-Nitrophenylboronic acid (**2f**)	**3af**[b]	38

[a] The stereochemistry of each product was tentatively assigned by comparison of its NMR spectra with **3aa** and **af**.
[b] The stereochemistry was determined unambiguously by NOESY correlation of dihydrofuran **4af**, which was produced from the reaction of **3af** with $AgNO_3$ and $CaCO_3$.

3 and 4). When 3-nitrophenylboronic acid (**2f**) having an electron-withdrawing group was subjected to the reaction, the yield of the resulting product **3af** was slightly lowered (entry 5).

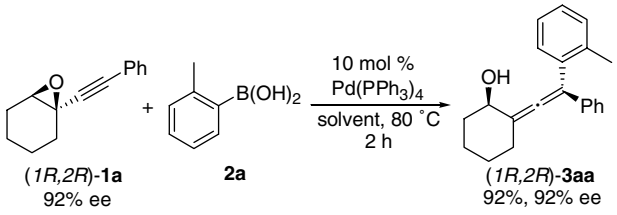
Results of reactions of various propargylic oxiranes **1b–g** with 2-methylphenylboronic acid (**2a**) are summarized in Table 3. When the reactions of substrates **1b** and **c** possessing a five- and a seven-membered ring were carried out, the coupled 2,3-allenols **3ba** and **ca** were obtained in 64% and 83% yields, respectively (entries 1 and 2). Substrates **1d** and **e**, having a butyl and a methoxymethyl group at the terminal position, were uneventfully reacted with **2a** to afford the corresponding products **3da** and **3ea** in good yields (entries 3 and 4). When TMS-substituted propargylic oxirane **1f** was subjected to the reaction, the desilylated 2,3-allenol **3fa** was predominantly produced (entry 5). The reaction of acyclic substrate **1g** also uneventfully proceeded to yield the corresponding coupled product **3ga** in moderate yield (entry 6).

Table 3. Reactions of various propargylic oxiranes **1b–g** with 2-methylphenylboronic acid (**2a**)[a]

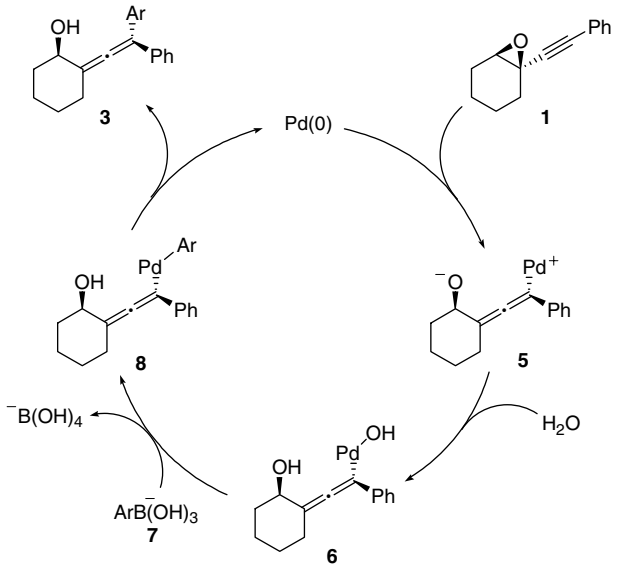
Entry	Substrate	Product[b]	Yield (%)
1	 **1b**	 **3ba**[c]	64
2	 **1c**	 **3ca**[c]	83
3	 **1d**	 **3da**[c]	77
4	 **1e**	 **3ea**[c]	85
5	 **1f**	 **3fa**[d]	43
6	 **1g**	 **3ga**[c]	50

[a] Reactions were carried not with 2-methylphenylboronic acid (**2a**) in the presence of 10 mol% $Pd(PPh_3)_4$ in dioxane–H_2O (2:1) at 80 °C.
[b] Ar = 2-methylphenyl.
[c] The stereochemistry of each product was tentatively assigned by comparison of its NMR spectra with **3aa**, **af** and **fa**.
[d] The stereochemistry was determined unambiguously by NOESY correlation of dihydrofuran **4fa**, which was produced from the reaction of **3fa** with $AgNO_3$ and $CaCO_3$.

We further attempted the reaction of enantiomerically enriched propargylic oxirane (1*R*,2*R*)-**1a** (Scheme 2). When (1*R*,2*R*)-**1a**[12] (92% ee) was reacted with 2-methylphenylboronic acid (**2a**), the corresponding chiral coupled product (1*R*,2*R*)-**3aa**[13] was provided in 92% yield. The enantiomeric excess of (1*R*,2*R*)-**3aa** was determined as 92%, and the result showed that the reaction proceeded with complete transferring chirality.



Scheme 2.



Scheme 3.

Plausible mechanism for the formation of aryl-substituted 2,3-allenols **3** is shown in Scheme 3. In the first step, regio- and stereoselective *anti*-S_N2' attack of palladium catalyst[14] on the propargylic oxirane **1** takes place to yield the twitter ionic allenylpalladium species **5**, which was further hydrated in the presence of H_2O to form the allenylpalladium hydroxide **6**.[15] Transmetallation of **6** with arylborate **7**,[16] derived from arylboronic acid **2** and H_2O, and then reductive elimination of palladium from the resulting intermediate **8** diastereoselectively produces *anti*-coupled 4-aryl-2,3-allenol **3**.

In conclusion, the effort described above has led to the discovery of a palladium-catalyzed coupling reaction occurring between propargylic oxiranes and arylboronic acids. The process can be carried out in aqueous conditions to yield *anti*-substituted 4-aryl-2,3-allenols in a highly diastereoselective manner. Furthermore, the chiral-substituted allene has been synthesized from the chiral propargylic oxirane without loss of the chirality. Continuing studies probing the scope and synthetic applications of this reaction are now in progress.

Acknowledgement

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10. Substrate **1** was easily prepared by the epoxidation of the corresponding known eneyne with *m*-CPBA in moderate to good yields.
11. Typical procedure: to a stirred solution of propargylic oxirane **1a** (45.0 mg, 0.227 mmol) in 1,4-dioxane (2.0 ml) and H_2O (1.0 ml) were added 2-methylphenylboronic acid (**2a**) (92.8 mg, 0.682 mmol) and $Pd(PPh_3)_4$ (26.3 mg, 22.7 μmol) at rt, and the stirring was continued for 1.5 h at 80 °C. After filtration of the reaction mixture using small amount of silica gel, the mass was extracted with AcOEt. The combined filtrates were washed with 10% aqueous NaOH and brine, and the residue upon workup was chromatographed on silica gel with hexane–AcOEt (90:10, v/v) as eluent to give the 4-aryl-2,3-allenol **3aa** (60.3 mg, 92%) as colourless crystals; mp 98–99 °C; IR (neat) 3342, 2933, 1948, 1595 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.15 (9H, m), 4.12–4.05 (1H, m), 2.62–2.55 (1H, m), 2.20 (3H, s), 2.24–2.05 (2H, m), 1.95–1.85 (1H, m), 1.92 (1H, s), 1.85–1.75 (1H, m), 1.62–1.38 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 137.3, 136.5, 136.5, 130.3, 130.2, 128.3, 127.5, 126.7, 126.5, 125.8, 111.5, 110.9, 69.6, 36.6, 30.1, 27.1, 23.9, 20.2; MS *m*/*z* 290 (M^+); HRMS *m*/*z* calcd for $C_{21}H_{22}O$: 290.1671 (M^+). Found: 290.1688.

12. Chiral substrate (1*R*,2*R*)-**1a** was prepared by the asymmetric epoxidation of the corresponding eneyne using Shi's fructose-derived chiral ketone with oxone; Wang, Z.-X.; Cao, G.-A.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7646.
13. Enantiomeric excess of the obtained (1*R*,2*R*)-**3aa** was determined by HPLC analysis (DAICEL CHIRALCEL AD).
14. It is known that chiral allenes can be synthesized from the palladium-catalyzed reaction of chiral propargylic compounds via stereoselective S_N2' attack of palladium catalyst: (a) Elsevier, C. J.; Stehouwer, P. M.; Westmijze, H.; Vermeer, P. *J. Org. Chem.* **1983**, *48*, 1103; (b) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1997**, *62*, 367; (c) Dixneuf, P.; Guyot, T.; Ness, M. D.; Roberts, S. M. *Chem. Commun.* **1997**, 2083; (d) Konno, T.; Tanikawa, M.; Ishihara, T.; Yamanaka, H. *Chem. Lett.* **2000**, 1360.
15. From the results that the reaction smoothly proceeded in the absence of water (Table 1, entries 1–5), the direct transmetallation of cationic allenylpalladium **5** to intermediate **8** would also be possible.
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