cine *Substitution*

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Selective *cine* Substitution of 1-Arylethenyl Acetates with Arylboron Reagents and a Diene/Rhodium Catalyst**

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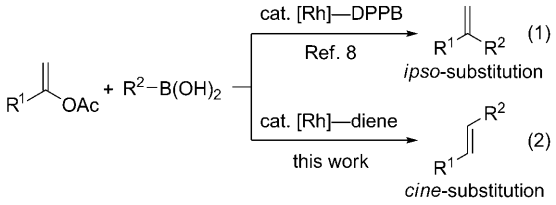
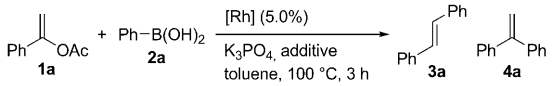
Nucleophilic substitution is a fundamental reaction in organic synthesis. In the reaction, the nucleophile normally attacks on the carbon atom bonded to a leaving group. However, the attack sometimes occurs at the adjacent position and forms a *cine*-substitution product.[1] Most of the reported *cine* substitutions have been observed in the reactions of electrophilic aromatic compounds with nucleophiles.[2] The unusual regioselectivity has been rare in the reaction of alkenyl electrophiles. Only alkenyl sulfones,[3] tosylates,[4,5] and phosphates[5,6] were known to react with organometals on the β-carbon atoms of the leaving group through transition-metal catalysis.[7] Recently, we reported that a phosphine/rhodium complex promoted the coupling of 1-phenylethenyl acetate with an arylboronic acid to exclusively produce the *ipso*-substitution product, 1,1-diarylethene [Eq. (1)].[8,9] During the course of the study, the *cine* substitution was observed when the reaction was conducted in the absence of the phosphine ligand. Herein, we report a rhodium-catalyzed *cine* substitution of alkenyl acetates with arylboronic acids [Eq. (2)]. The unusual regiochemistry was caused by the chelation of a diene ligand to the rhodium catalyst.



In our previous study,[8] the reaction of 1-phenylethenyl acetate (**1a**) with phenylboronic acid (**2a**) was attempted in the presence of a [{RhCl(cod)}$_2$]/dppb catalyst, which produced the typical cross-coupling product **4a** exclusively (Table 1, entry 1). To our surprise, the *cine* substitution proceeded selectively in the absence of the bidentate bisphosphine (Table 1, entry 2). When the cod ligand was replaced by norborna-2,5-diene,[10] cyclooctene, or ethylene, no formation of the *cine*-substitution product, stilbene (**3a**), was observed (Table 1, entries 3–5). These observations suggest that the coordination of cod to rhodium is crucial for the *cine* substitution. Indeed, [{RhCl(ethylene)$_2$}$_2$] preferentially catalyzed the *cine*-substitution reaction in the presence of cod (Table 1, entry 6).[11] As compared to the diene ligand, the anionic ligand or counteranion on the rhodium atom did not affect the regioselectivity (Table 1, entries 7 and 9). The yield of **3a** improved remarkably by the addition of *tert*-amyl alcohol or diisopropylamine (Table 1, entries 10 and 11).[12] The addition of cod brought about further enhancement of the production of **3a** when diisopropylamine was chosen as the additive (Table 1, entry 13). Furthermore, potassium phosphate was indispensable for successful *cine* substitution (Table 1, entry 14). The catalyst loading could be reduced to 3 mol% under the optimized conditions (Table 2, entry 1). The *cine*-substitution product **3a** was isolated in 75% yield.

Table 1: Optimization of the rhodium catalyst for *cine* substitution of 1-phenylethenyl acetate (**1a**) with phenylboronic acid (**2a**).[a]



Entry	[Rh]	Additive[b]	Yield of **3a** [%][c]	Yield of **4a** [%][c]
1	[{RhCl(cod)}$_2$]	dppb (5)	<1	14
2	[{RhCl(cod)}$_2$]	–	26	4
3	[{RhCl(nbd)}$_2$]	–	<1	19
4	[{RhCl(coe)$_2$}$_2$]	–	<1	3
5	[{RhCl(C_2H_4)$_2$}$_2$]	–	<1	3
6	[{RhCl(C_2H_4)$_2$}$_2$]	cod (10)	18	<1
7	[Rh(cod)$_2$]BF_4	–	38	1
8	[Rh(nbd)$_2$]SbF_6	–	<1	4
9	[{Rh(OAc)(cod)}$_2$]	–	42	5
10	[{Rh(OAc)(cod)}$_2$]	*t*AmOH (100)	80	8
11	[{Rh(OAc)(cod)}$_2$]	*i*Pr$_2$NH (100)	62	13
12	[{Rh(OAc)(cod)}$_2$]	cod (10), *t*AmOH (100)	69 (75)[d]	5 (6)[d]
13	[{Rh(OAc)(cod)}$_2$]	cod (10), *i*Pr$_2$NH (100)	71 (85)[d]	5 (5)[d]
14[e]	[{Rh(OAc)(cod)}$_2$]	cod (10), *i*Pr$_2$NH (100)	8	<1

[a] Reactions were conducted in toluene (1.0 mL) for 3 h. The ratio of **1a** (0.20 mmol)/**2a**/K_3PO_4/[Rh] was 100:150:300:5.0. [b] The amount of each additive (mol% to **1a**) was indicated in parentheses. [c] GC yield (average of two runs). [d] GC yields after 24 h are indicated in the parentheses. [e] The reaction was conducted without K_3PO_4. dppb = 1,4-bis(diphenylphosphino)butane, cod = cycloocta-1,5-diene, nbd = norborna-2,5-diene, coe = cyclooctene, *t*Am = 1,1-dimethylpropyl.

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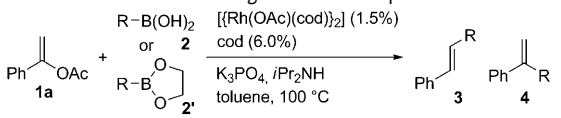
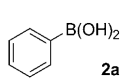
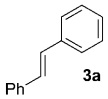
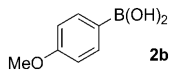
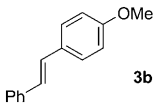
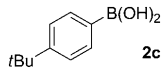
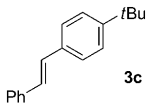
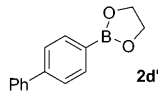
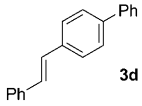
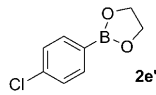
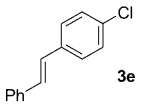
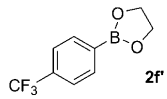
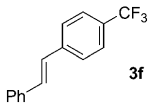
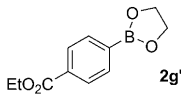
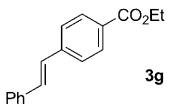
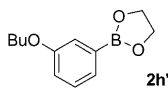
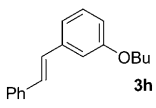
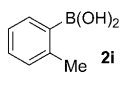
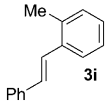
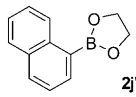
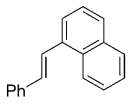
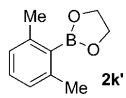
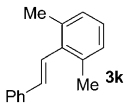
Table 2: Reactions of **1a** with organoboron compounds **2** or **2′**.[a]



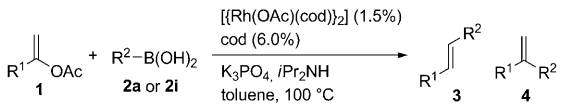
Entry	Substrate **2** or **2′**	*t* [h]	**3**/**4**[b]	Product **3**	Yield [%][c]
1	 **2a**	48	93:7	 **3a**	75
2	 **2b**	24	94:6	 **3b**	70
3	 **2c**	24	83:17	 **3c**	67
4	 **2d′**	48	90:10[d]	 **3d**	81
5	 **2e′**	72	85:15	 **3e**	71
6	 **2f′**	72	89:11	 **3f**	68
7	 **2g′**	72	93:7	 **3g**	71
8	 **2h′**	72	92:8	 **3h**	73
9	 **2i**	24	>99:1	 **3i**	96
10	 **2j′**	48	>99:1	 **3j**	85
11	 **2k′**	72	43:57	 **3k**	24[e]

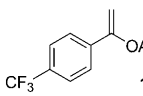
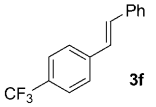
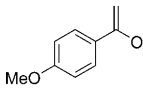
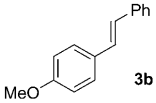
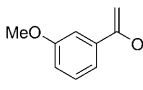
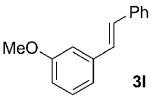
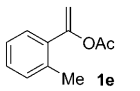
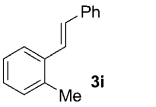
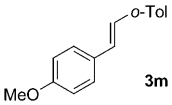
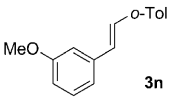
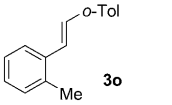
[a] Reactions were conducted in toluene (2.0 mL). The ratio of **1** (0.5 mmol)/**2**/K_3PO_4/iPr_2NH/[{Rh(OAc)(cod)}$_2$]/cod was 100:150:300:100:1.5:6.0. [b] Determined by the ^{1}H NMR analysis of the reaction mixture. [c] Yield of isolated **3**. [d] Determined by GC analysis. [e] Compound **4k** was isolated in 58% yield.

The optimized catalyst system allowed a variety of arylboronic acids to react with alkenyl acetate **1a**, thus selectively yielding the desired *cine*-substitution products **3** (Table 2). The production of **3** was scarcely affected by the electronic property of the *para* or *meta* substituent on the aromatic ring of **2** (Table 2, entries 2–8). Electron-deficient arylboronic acids caused the decomposition of **1a** to acetophenone,[13] but the undesirable reaction was successfully suppressed by using ethylene glycol ester **2′** in the place of **2**. Steric hindrance from the *ortho* substituent of **2i** would be favorable for the *cine* substitution (Table 2, entry 9). As with **2i**, 1-naphthylboronic ester **2j′** afforded **3j** in high yield with no *ipso* substitution (Table 2, entry 10). However, the use of more-congested substrate **2k′** resulted in disturbing the *cine* substitution, giving **4k** preferentially (Table 2, entry 11).

The regioselectivity of the reaction of **1** with **2** was strongly influenced by both the electronic and steric properties of the substituent on the aromatic ring of **1** (Table 3). The electron-deficient substrate **1b** was converted into the desired stilbene **3f** with complete regioselectivity (Table 3, entry 1), whilst the electron-donating methoxy group of **1c** induced the undesired *ipso*-substitution (Table 3, entry 2). The reaction of **1d**, which has the methoxy substituent at the *meta*-position, afforded comparable regioselectivity to that of **1a** (Table 3, entry 3). The *ortho* substituent in **1e** hampered the *cine* substitution (Table 3, entry 4). The ratio of **3** to **4** in the reactions of **1c** and **1d** was raised by using **2i** as the nucleophilic substrate (Table 3, entries 5 and 6). These observations

Table 3: Reaction of 1-arylethenyl acetates **1** with **2a** or **2i**.[a]



Entry	Substrate **1**	**2**	*t* [h]	**3**/**4**[b]	Product **3**	Yield [%][c]
1	 **1b**	**2a**	48	>99:1	 **3f**	91
2	 **1c**	**2a**	48	64:36	 **3b**	45
3	 **1d**	**2a**	48	85:15	 **3l**	69
4	 **1e**	**2a**	48	57:43	 **3i**	39
5	**1c**	**2i**	24	95:5	 **3m**	90
6	**1d**	**2i**	24	>99:1	 **3n**	73
7	**1e**	**2i**	72	66:34	 **3o**	30

[a] Reactions were conducted in toluene (2.0 mL). The ratio of **1**(0.5 mmol)/**2**/K_3PO_4/iPr_2NH/[{Rh(OAc)(cod)}$_2$]/cod was 100:150:300:100:1.5:6.0. [b] Determined by ^{1}H NMR analysis of the reaction mixture. [c] Yield of isolated **3**.

suggest that the regiochemistry was controlled by the steric hindrance of R^2 as well as by the electronic property of R^1.

To investigate the mechanism of the catalytic *cine* substitution, we attempted the reaction using the deuterium-labeled substrate [D_2]-**1a** (> 99% D) (Scheme 1). The reaction of [D_2]-**1a** with phenylboronic acid **2a** afforded the *cine*-substitution product [D_2]-**3a** with 63% deuteration at its alkene moiety. When the reaction was stopped after 3 hours, 91% of [D_2]-**1a** had been consumed and the alkene moiety of the recovered starting material retained 60% deuteration.[14] This observation indicates that the incorporation of a hydrogen atom into the *cine*-substitution product was partly caused by the deuterium–hydrogen exchange, which took place before the catalytic cycle of the *cine* substitution. Furthermore, [D_2]-**3f** (43% D^α, 80% D^β) was obtained from the reaction of **2f** with [D_2]-**1a**, in which one of the deuterium atoms at the β position migrated onto the α position during the catalytic process. The results of these deuterium-labeled experiments suggest that the 1-arylethenyl esters **1** undergo the *cine* substitution through the pathway as shown in Scheme 2. The diene-ligated (acetato)rhodium(I) **A** reacts with organoboron **2** to form (aryl)rhodium **B**. The transmetalation might take precedence over the oxidative addition of **1** to **A**, because the coordination of cod to the rhodium center accelerates the formation of **B**.[15] The *syn* addition of **B** to alkenyl acetate **1** takes place, and then forms (alkyl)rhodium **C** preferentially. The regiochemistry in the addition would be governed synergistically by the electronic property of R^1 and the steric repulsion between R^1 and R^2. Electron-withdrawing R^1 is advantageous to the selective formation of **C**, because it enhances the electrophilicity of the β-carbon atom in **1**. The β-hydride elimination from **C** and the successive re-insertion of the carbon–carbon double bond to the (hydrido)rhodium in **D** with reverse direction generates the intermediate **E**, which yields the *cine*-substitution product **3** through β-oxygen elimination. The undesired *ipso*-substitution might proceed through the insertion of **1** into the carbon–rhodium bond in **B** with opposite regiochemistry, thus leading to the formation of **F**. Alternatively, the side-product **4** might be formed through a typical cross-coupling mechanism.[8,16]

In summary, the selective *cine* substitution of 1-aryl ethenyl acetates **1** with arylboronic acids **2** was found to proceed in the presence of a cod-ligated rhodium catalyst. The chelation of the diene to rhodium is crucial for the unusual regiochemistry. The catalytic reaction reported here is the first successful *cine* substitution of alkenyl acetates.

Scheme 1. Deuterium-labeled experiments.

Scheme 2. A possible pathway of the catalytic *cine* substitution.

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[13] The uses of the electron-deficient arylboronic acids, **2d**, **2e**, and **2f**, instead of their corresponding arylboronate, afforded the *cine*-substitution products **3d**, **3e**, and **3f** in 25%, 21%, and 19% yield, respectively. The use of electron-deficient arylboronic acid **2g** did not afford any *cine*-substitution product (**3g**).
[14] The reaction produced [D_2]-**3a** and [D_2]-**4a** in a 92:8 molar ratio. The *cine*-substitution product (67% D) was isolated in 70% yield.
[15] The kinetic studies of the rhodium-catalyzed 1,4-addition of phenylboronic acid to the enone indicated that the reaction between (hydroxo)rhodium(I) and the organoboron compound is the rate-determining step in the catalytic reaction and that the use of a diene ligand in place of bisphosphine causes the acceleration of the transmetalation step. See: a) A. Kina, H. Iwamura, T. Hayashi, *J. Am. Chem. Soc.* **2006**, *128*, 3904; b) A. Kina, Y. Yasuhara, T. Nishimura, H. Iwamura, T. Hayashi, *Chem. Asian J.* **2006**, *1*, 707; c) W.-L. Duan, H. Iwamura, R. Shintani, T. Hayashi, *J. Am. Chem. Soc.* **2007**, *129*, 2130.
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