

# Palladium-Catalyzed γ-Selective and Stereospecific AllyI–Aryl Coupling between Allylic Acetates and Arylboronic Acids

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Transition metal catalyzed allylic substitution reactions with carbon nucleophiles are powerful C–C bond formation methods because of their broad substrate scopes under mild reaction conditions.<sup>1</sup> Characteristic among them are Cu-catalyzed allylic substitutions, which have excellent  $\gamma$ -regioselectivity. However, these reactions are only possible with strongly nucleophilic organometallic reagents such as Grignard or organozinc reagents.<sup>2</sup> Also, the reaction of sp<sup>2</sup>-carbon nucleophiles such as aryl or alkenylmetal reagents have not been well exploited due to the poor nucleophilicity of these reagents.<sup>3</sup>

Herein, we report a new Pd-catalyzed allylic substitution methodology, which allows for the reaction of allylic acetates with arylboronic acids with high  $\gamma$ -selectivity and E/Z-selectivity. The reaction of optically active allylic acetates having an  $\alpha$ -stereogenic center took place with excellent  $\alpha$ -to- $\gamma$  chirality transfer with *syn*-selectivity and gave the corresponding optically active allyl—aryl coupling products with a stereogenic center at the benzylic position.<sup>4–8</sup>

The reaction of allylic acetate **1a** with phenylboronic acid (1.5 equiv) in the presence of Pd(OAc)<sub>2</sub> (10 mol %), 1,10-phenanthroline (12 mol %) and AgSbF<sub>6</sub> (10 mol %) in 1,2-dichloroethane at 60 °C for 6 h afforded allyl–aryl coupling product **2a** in 80% isolated yield (91% convn of **1a**) with complete regio- (**2a/2a'** 100:0) and *E/Z*- (>20:1) selectivities (Scheme 1).<sup>9,10</sup> Conversely, the reaction of **1a'** afforded **2a'**, an isomer of **2a** with regard to the  $\alpha/\gamma$ -regioselectivity, with complete regio- (**2a/2a'** 0:100) and *E/Z*- (>20:1) selectivities. Notably, the Pd-catalyzed allylic substitution can be performed even under air without affecting the product yield and selectivities.

#### Scheme 1



In contrast, the reaction without 1,10-phenanthroline afforded a complex mixture with no allyl-aryl coupling product (100% convn). While 2,2'-bipyridyl was as effective as 1,10-phenanthroline (80% yield), other diamines that we tested were less effective under otherwise identical conditions. Phosphine ligands inhibited the reaction completely, giving only a trace of biphenyl. The catalytic reaction even proceeded without AgSbF<sub>6</sub> but with a significantly reduced yield (54%).

The Pd-catalyzed allyl—aryl coupling can be applied to various combinations of allylic acetates (1) and arylboronic acids (Table 1).<sup>10,11</sup> The reactions afforded the  $\gamma$ -substitution products **2** exclusively (entries 3–13) or predominantly (entries 1 and 2), irrespective of the substitution patterns of the allylic acetates. Moreover, the reactions took place with complete *E*-selectivity (not applicable for **1h**, entry 13). The

reaction tolerates a variety of functional groups in both 1 and arylboronic acids; MeO,  $CF_3$ , chloride, ketone, aldehyde, ester, and silyl ether functionalities can be present in the substrates (entries 2–8).

**Table 1.** Palladium-Catalyzed Reaction of Allylic Acetates with Arylboronic  $\operatorname{Acids}^a$ 

entry	allylic	boronic acid	product <sup>b</sup>	yield	$\gamma/\alpha^d$
	acetate			(%)	
1 <i>°</i>	Ph 1a	Me B(OH)2	Ph 2ab-ag	26	93:7
2	1a	MeO-B(OH) <sub>2</sub>	2ac	76	93:7
3	1a	F <sub>3</sub> CB(OH) <sub>2</sub>	2ad	82	>99:1
4	1a		2ae	80	>99:1
5	1a	Me B(OH) <sub>2</sub>	2af	81	>99:1
6 <sup>e</sup>	1a	H-K-B(OH) <sub>P</sub>	2ag	71	>99:1
7	t-Bu ↓0 1b	OAc PhB(OH) <sub>2</sub>	t-Bu → O Ph 2b	. 72	>99:1
8	TIPSO	OAc PhB(OH) <sub>2</sub>		68	>99:1
9/	Ph 1d	PhB(OH) <sub>2</sub>	Ph 2d Ph	84	>99:1
10	Ph 1e	° PhB(OH) <sub>2</sub>	Ph 2e	70	>99:1
11°	OAc 1f	PhB(OII) <sub>2</sub>	2f	39	>99:1
12	⊖Ac ↓ 1g	PhB(OII) <sub>2</sub>	Ph 2g	76	>99:1
13/		PhB(OH) <sub>2</sub>	2h Ph	75	>99:1

<sup>*a*</sup> Conditions: Pd(OAc)<sub>2</sub> (10 mol %), 1,10-phenanthroline (12 mol %), AgSbF<sub>6</sub> (10 mol %), **1** (0.50 mmol), arylboronic acid (0.75 mmol), 1,2-dichloroethane (3.0 mL), 60 °C, 12 h. <sup>*b*</sup> Isomeric ratios: E/Z > 20:1. See ref 10. <sup>*c*</sup> Isolated yield. <sup>*d*</sup> Determined by <sup>1</sup>H NMR. <sup>*e*</sup> Unreacted allylic acetate (1) was detected in the crude material by <sup>1</sup>H NMR analysis (entry 1, 40%; entry 6, 14%; entry 11, 15%). <sup>*f*</sup> Conditions: Pd(OAc)<sub>2</sub> (5 mol %), 1,10-phenanthroline (10 mol %), AgSbF<sub>6</sub> (10 mol %), **1** (0.50 mmol), PhB(OH)<sub>2</sub> (1.0 mmol), THF (3.0 mL), 60 °C, 12 h.

Table 1 also shows that the efficiency of the reaction is sensitive to the steric demand of the arylboronic acids and the  $\gamma$ -substituent of **1**, but substantial steric bulk is tolerated at the  $\alpha$ -position. For instance, the reaction of **1a** with *o*-tolylboronic acid is much slower than that with phenylboronic acid and gave the coupling product **2ab** in only 26% yield (entry 1). Furthermore, as the  $\gamma$ -substituent became bulkier (H < Me < Et < *i*-Bu), the product yield decreased (Scheme 1 and Table 1, entries 9–11). On the other hand, allylic acetates **1g** and **1h**, bearing a bulky isopropyl group and two methyl groups, respectively, at the  $\alpha$ -position were efficiently coupled with phenylboronic acid (entries 12 and 13).

The reaction of (*S*)-(*E*)-**1g** (97% ee), which has  $\alpha$ -*i*-Pr and  $\gamma$ -Me substituents, with phenylboronic acid in the presence of Pd(OAc)<sub>2</sub>, 1,10-phenanthroline, and AgSbF<sub>6</sub> gave (*R*)-(*E*)-**2g** with 97% ee, showing that the allyl–aryl coupling with  $\alpha$ -chiral allylic acetates took place with excellent  $\alpha$ -to- $\gamma$  chirality transfer with *syn*-selectivity (Scheme 2).<sup>10</sup> The reaction of (*S*)-(*E*)-**1i** (97% ee), which has  $\alpha$ -Bu and  $\gamma$ -Me substituents, with phenylboronic acid gave (*R*)-(*E*)-**2i** with 97% ee, suggesting that the efficiency of the chirality transfer is not significantly influenced by the steric demand of the  $\alpha$ -substituent. On the other hand, the reaction of (*S*)-(*E*)-**1j** (97% ee), which has  $\alpha$ -Hex and  $\gamma$ -Et groups, afforded (*S*)-(*E*)-**2j** (89% ee) with slightly decreased enantiomeric purity.

#### Scheme 2



A possible mechanism for the Pd-catalyzed reaction is proposed in Scheme 3. First, the reaction of 1,10-phenanthroline-ligated Pd(OAc)<sub>2</sub> and AgSbF<sub>6</sub> forms the cationic palladium(II) complex **A**. The catalytic cycle is initiated by transmetalation between **A** and an arylboronic acid to form the ( $\sigma$ -aryl)palladium(II) intermediate **B**.<sup>12</sup> Subsequently, **B** forms  $\pi$ -complex **C** with allylic acetate **1**. Then, the  $\pi$ -complex **C** undergoes the regioselective C–C double bond insertion into the aryl–Pd bond with the assistance of intramolecular coordination of the carbonyl oxygen of the acetoxy group to the cationic Pd center, forming metallacyclic alkylpalladium(II) **D**. Finally,  $\beta$ -acetoxy elimination, rather than  $\beta$ -hydride elimination, from **D** affords coupling product **2** and regenerates **A**.<sup>13</sup>

## Scheme 3. Proposed Mechanism



**Scheme 4.** Proposed Mechanism for the Pd-Catalyzed Allyl–Aryl Coupling with (S)-(E)-1i and PhB(OH)<sub>2</sub>



The stereochemical outcome observed in the reaction of the chiral allylic acetate (*S*)-(*E*)-**1i** can be rationalized by considering the  $A^{1.3}$ -strain in the substrate during the coordination-assisted insertion (**C'** to **D'**) and the *syn-β*-acetoxy elimination (from **D'**) as shown in Scheme 4.<sup>14</sup>

In summary, we have established an air-tolerable, Pd-catalyzed  $\gamma$ -selective and stereospecific substitution reaction between allylic acetates and arylboronic acids, which gives allyl-aryl coupling

products with a stereogenic center at the benzylic position. Exploration of the reaction mechanism and development of more advanced catalyst systems and enantioselective reactions with a chiral catalyst are ongoing in our laboratory.

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**Supporting Information Available:** Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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- (10) For Schemes 1 and 2 and Table 1, the crude materials after removal of the catalyst and boron compounds consisted of the coupling product (2), biaryl, unreacted allylic acetate (1), and/or unidentified compounds. The Mizoroki–Heck-type product was not detected. The isolated products were contaminated with traces of unidentified materials (0.1-5%). The isolated yields for the reaction of 1f,g,h,i in Table 1 and Scheme 2 may be reduced by the evaporation of the products.
- (11) The reaction of terminal alkenes 1d and 1h were carried out with THF solvent (Table 1, entries 9 and 13). The use of THF suppressed the formation of unidentified side products.
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- (14) Since  $\pi$ -complex C (C') is a normal 16-electron square planar complex, the acetoxy group of C (C') should be uncoordinated. Although both diastereomeric  $\pi$ -complexes may form, the description of equilibrium with the nonproductive diastereomer is omitted in Scheme 4.

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