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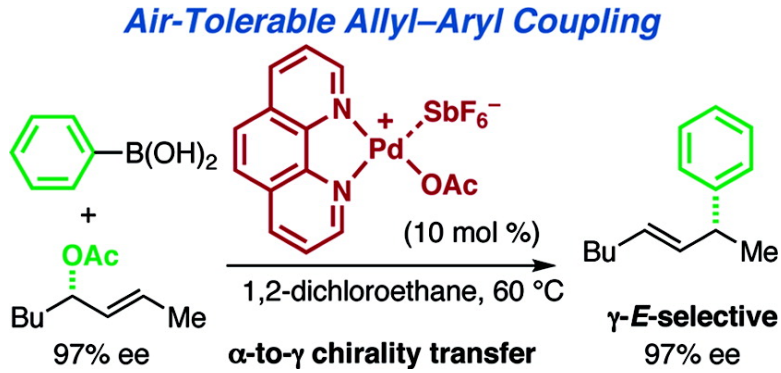


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# Palladium-Catalyzed γ-Selective and Stereospecific Allyl−Aryl Coupling between Allylic Acetates and Arylboronic Acids

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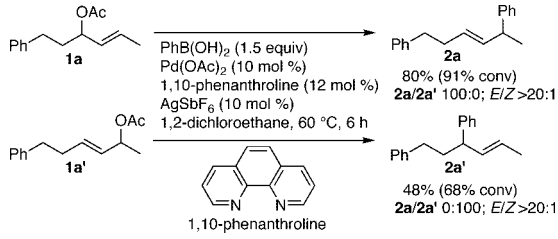
Transition metal catalyzed allylic substitution reactions with carbon nucleophiles are powerful C−C bond formation methods because of their broad substrate scopes under mild reaction conditions.[1] Characteristic among them are Cu-catalyzed allylic substitutions, which have excellent γ-regioselectivity.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

Herein, we report a new Pd-catalyzed allylic substitution methodology, which allows for the reaction of allylic acetates with arylboronic acids with high γ-selectivity and *E*/*Z*-selectivity. The reaction of optically active allylic acetates having an α-stereogenic center took place with excellent α-to-γ chirality transfer with *syn*-selectivity and gave the corresponding optically active allyl−aryl coupling products with a stereogenic center at the benzylic position.[4−8]

The reaction of allylic acetate **1a** with phenylboronic acid (1.5 equiv) in the presence of $Pd(OAc)_2$ (10 mol %), 1,10-phenanthroline (12 mol %) and $AgSbF_6$ (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).[9,10] Conversely, the reaction of **1a′** afforded **2a′**, an isomer of **2a** with regard to the α/γ-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.

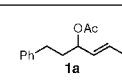
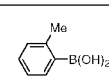
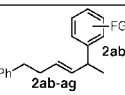
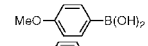
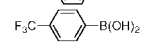
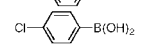
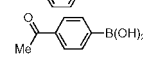
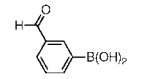
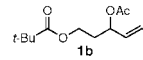
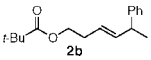
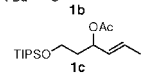
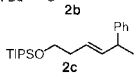
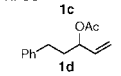
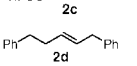
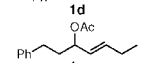
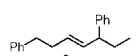
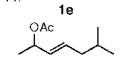
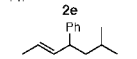
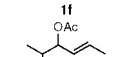
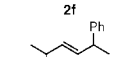
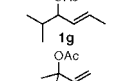
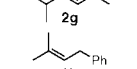
***Scheme 1***




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 $AgSbF_6$ 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).[10,11] The reactions afforded the γ-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 Acids[a]

| entry | allylic acetate | boronic acid | product[b] | yield[c] (%) | γ/α[d] |
|---|---|---|---|---|---|
| 1[e] |  **1a** |  |  **2ab** **2ab-ag** | 26 | 93:7 |
| 2 | **1a** |  | **2ac** | 76 | 93:7 |
| 3 | **1a** |  | **2ad** | 82 | >99:1 |
| 4 | **1a** |  | **2ae** | 80 | >99:1 |
| 5 | **1a** |  | **2af** | 81 | >99:1 |
| 6[e] | **1a** |  | **2ag** | 71 | >99:1 |
| 7 |  **1b** | $PhB(OH)_2$ |  **2b** | 72 | >99:1 |
| 8 |  **1c** | $PhB(OH)_2$ |  **2c** | 68 | >99:1 |
| 9[f] |  **1d** | $PhB(OH)_2$ |  **2d** | 84 | >99:1 |
| 10 |  **1e** | $PhB(OH)_2$ |  **2e** | 70 | >99:1 |
| 11[e] |  **1f** | $PhB(OH)_2$ |  **2f** | 39 | >99:1 |
| 12 |  **1g** | $PhB(OH)_2$ |  **2g** | 76 | >99:1 |
| 13[f] |  **1h** | $PhB(OH)_2$ |  **2h** | 75 | >99:1 |

[a] Conditions: $Pd(OAc)_2$ (10 mol %), 1,10-phenanthroline (12 mol %), $AgSbF_6$ (10 mol %), **1** (0.50 mmol), arylboronic acid (0.75 mmol), 1,2-dichloroethane (3.0 mL), 60 °C, 12 h. [b] Isomeric ratios: *E*/*Z* > 20:1. See ref 10. [c] Isolated yield. [d] Determined by $^1H$ NMR. [e] Unreacted allylic acetate (**1**) was detected in the crude material by $^1H$ NMR analysis (entry 1, 40%; entry 6, 14%; entry 11, 15%). [f] Conditions: $Pd(OAc)_2$ (5 mol %), 1,10-phenanthroline (10 mol %), $AgSbF_6$ (10 mol %), **1** (0.50 mmol), $PhB(OH)_2$ (1.0 mmol), THF (3.0 mL), 60 °C, 12 h.

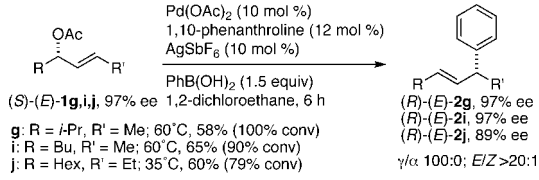
Table 1 also shows that the efficiency of the reaction is sensitive to the steric demand of the arylboronic acids and the γ-substituent of **1**, but substantial steric bulk is tolerated at the α-position. For instance, the reaction of **1a** with *o*-tolylboronic acid is much slower than that with phenylboronic acid and gave the coupling product **2ab** in only 26% yield (entry 1). Furthermore, as the γ-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 α-position were efficiently coupled with phenylboronic acid (entries 12 and 13).



10.1021/ja808673n CCC: $40.75 

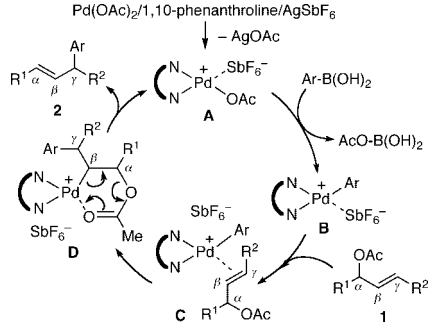
The reaction of (*S*)-(*E*)-**1g** (97% ee), which has α-*i*-Pr and γ-Me substituents, with phenylboronic acid in the presence of $Pd(OAc)_2$, 1,10-phenanthroline, and $AgSbF_6$ gave (*R*)-(*E*)-**2g** with 97% ee, showing that the allyl−aryl coupling with α-chiral allylic acetates took place with excellent α-to-γ chirality transfer with *syn*-selectivity (Scheme 2).[10] The reaction of (*S*)-(*E*)-**1i** (97% ee), which has α-Bu and γ-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 α-substituent. On the other hand, the reaction of (*S*)-(*E*)-**1j** (97% ee), which has α-Hex and γ-Et groups, afforded (*S*)-(*E*)-**2j** (89% ee) with slightly decreased enantiomeric purity.

***Scheme 2***

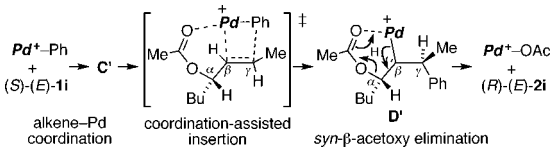



A possible mechanism for the Pd-catalyzed reaction is proposed in Scheme 3. First, the reaction of 1,10-phenanthroline-ligated $Pd(OAc)_2$ and $AgSbF_6$ forms the cationic palladium(II) complex **A**. The catalytic cycle is initiated by transmetalation between **A** and an arylboronic acid to form the (σ-aryl)palladium(II) intermediate **B**.[12] Subsequently, **B** forms π-complex **C** with allylic acetate **1**. Then, the π-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, β-acetoxy elimination, rather than β-hydride elimination, from **D** affords coupling product **2** and regenerates **A**.[13]

***Scheme 3.*** Proposed Mechanism




***Scheme 4.*** Proposed Mechanism for the Pd-Catalyzed Allyl−Aryl Coupling with (*S*)-(*E*)-**1i** and $PhB(OH)_2$




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.[14]

In summary, we have established an air-tolerable, Pd-catalyzed γ-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.

**Acknowledgment.** This work was supported by a MEXT program, Global COE grant (Project No. B01: Catalysis as the Basis for Innovation in Materials Science).

**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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(1) (a) Tsuji, J. *Acc. Chem. Res.* **1969**, *2*, 144–152. (b) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615–2649. (c) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422.

(2) Even for Cu-catalyzed systems, studies to date have focused largely on the reactions of primary allylic electrophiles that give terminal alkenes. For a review on enantioselective allyic substitutions catalyzed by chiral copper complexes, see: Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 4435–4439.

(3) For γ-selective allylic substitution reactions with stoichiometric arylcopper(I) reagents with excellent 1,3-chirality transfer, see: (a) Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111–2114. (b) Kiyotsuka, Y.; Acharya, H. P.; Katayama, Y.; Hyodo, T.; Kobayashi, Y. *Org. Lett.* **2008**, *10*, 1719–1722.

(4) For related studies from our group (Cu-catalyzed regioselective allylic and propargylic substitutions with diboron), see: (a) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034–16035. (b) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856–14857. (c) Ito, H.; Kosaka, Y.; Nonoyama, K.; Sasaki, Y.; Sawamura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7424–7427. (d) Ito, H.; Sasaki, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 15774−15775.

(5) Pd-catalyzed γ-selective allyl−aryl coupling between aryl iodides and allylic acetates has been reported. However, the reaction required harsh conditions (typically 180 °C) and is not stereoselective. See: Mariamphillai, B.; Herse, C.; Lautens, M. *Org. Lett.* **2005**, *7*, 4745–4747.

(6) Maddaford reported the Pd-catalyzed *C*-glycosidation of peracetylated glycals (γ-substitution of γ-alkoxy-substituted allylic acetates with *anti*-stereochemistry) with arylboronic acids. This reaction goes through a (π-allyl)palladium(II) intermediate. The regioselectivity is controlled by the electronic effect of the oxygen functionality and is limited to this specific substrate class. See: Ramanauth, J.; Poulin, O.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2013–2015.

(7) For Pd-catalyzed allyl−$sp^2$-carbon coupling between allyl alcohol derivatives and organoboron compound via a (π-allyl)palladium(II) intermediate, see: (a) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972–980. (b) Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron Lett.* **1990**, *31*, 7453–7456. (c) Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384–3388, See also ref 6.

(8) For Pd-catalyzed oxidative Mizoroki−Heck-type reactions of allylic acetates with arylboronic acids, see: (a) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076–15077. (b) Ruan, J.; Li, X.; Saidi, O.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 2424–2425.

(9) This result is in sharp contrast to the fact that the regioselectivity in the transition metal catalyzed allylic substitutions that involve a (π-allyl)metal intermediate is highly dependent on the substitution pattern of allylic substrates. For reviews on Pd-catalyzed allylic substitution reactions, see ref 1c. See also ref 7.

(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.

(12) For a mechanistic study on the formation of a (σ-aryl)palladium(II) intermediate by transmetalation with arylboronic acid and $Pd(OAc)_2$, see: Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346–2351.

(13) (a) Alkene products derived by β-hydride elimination from alkylpalladium intermediate **D** were not observed (see ref 10). This is contradictory with the reported results of the oxidative Mizoroki−Heck-type arylation of allylic esters with arylboronic acid. See ref 8. For Mizoroki−Heck-type arylation of allylic acetates with aryl iodides, see: (b) Pan, D.; Chen, A.; Su, Y.; Zhou, W.; Li, S.; Jia, W.; Xiao, J.; Liu, Q.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4729–4732.

(14) Since π-complex **C** (**C′**) is a normal 16-electron square planar complex, the acetoxy group of **C** (**C′**) should be uncoordinated. Although both diastereomeric π-complexes may form, the description of equilibrium with the nonproductive diastereomer is omitted in Scheme 4.

JA808673N