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# Sulfonamidoquinoline/Palladium(II)-Dimer Complex As a Catalyst Precursor for Palladium-Catalyzed γ-Selective and Stereospecific Allyl–Aryl Coupling Reaction between Allylic Acetates and Arylboronic Acids

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*Dedicated to Professor Eiichi Nakamura on the occasion of his 60th birthday*

Transition-metal-catalyzed allylic substitution reactions with carbon nucleophiles are powerful carbon–carbon bond-formation methods because of their broad substrate scope under mild reaction conditions. For example, Tsuji–Trost allylic substitution involving a (π-allyl)metal intermediate has made impressive progress in this regard.[1] However, the allylic substitution of unsymmetrically substituted allylic substrates occurs competitively at the α- and γ-positions owing to formation of a (π-allyl)metal intermediate: the regioselectivity is highly dependent on the substitution pattern of the allylic substrates. Therefore, most previous studies in this area have focused on cases in which the allylic system is either located at the terminus of a molecule or is highly unsymmetric because of electronic and/or steric substituent effects.

To address the issue of regiochemical control in the allylic substitution reaction, we recently developed a new palladium-catalyzed allylic substitution methodology: coupling reactions between acyclic (*E*)-allylic acetates and arylboronic acids in the presence of a palladium catalyst prepared from $Pd(OAc)_2$, 1,10-phenanthroline, and $AgSbF_6$ (1:1.2:1) proceeded with excellent γ-selectivity to afford allyl–aryl coupling products with an *E* configuration.[2–8] From mechanistic studies, we knew that a (σ-aryl)palladium(II) intermediate with a vacant site was initially generated by a transmetalation reaction between an arylboronic acid and the cationic mono(acetoxo)palladium(II) complex, itself prepared from the phenanthroline-ligated $Pd(OAc)_2$ complex and $AgSbF_6$; subsequent steps involved the addition of the (σ-aryl)palladium(II) intermediate across the C–C double bond of the allylic acetate followed by *syn*-β-acyloxy elimination, with the assistance of intramolecular coordination of the acyloxy group to the cationic palladium center.[2b] However, the allyl–aryl coupling reaction with the $Pd(OAc)_2$/phenanthroline/$AgSbF_6$ catalytic system required relatively high catalyst loading to obtain reasonable product yields, presumably owing to low catalytic activity and short catalyst lifetime, as catalyst decomposition competed with the formation of the coupling products. This observation prompted us to investigate the nature of the reaction in more detail and to look for more-robust and effective catalyst systems.

Herein, we report that a new palladium(II)-dimer catalyst system involving anionic sulfonamidoquinoline ligands is effective for the γ-selective and stereospecific allyl–aryl coupling reaction between acyclic (*E*)-allylic acetates and arylboronic acids. Although the catalytic performance of the new system was only comparable to the previous one, this system takes advantage of the anionic nature of the supporting nitrogen ligand in avoiding the use of a silver salt as a co-catalyst. A mechanistic model is also proposed based on a monomeric, uncharged palladium center; this catalytic cycle is consistent with the previously reported one which contained a cationic palladium center. Our studies revealed that the cationic nature of the palladium center of a (σ-alkyl)palladium(II) complex is not a prerequisite for the predominance of *syn*-β-acetoxy elimination over β-hydride elimination.[8–11]

In designing a robust catalyst system, we reasoned that replacing the neutral nitrogen donors and one acetoxo ligand in the $Pd(OAc)_2$/phenanthroline system with a monoanionic *N*,*N*-bidentate ligand would afford a vacant coordination site on the palladium center without the need for a silver salt: in the previous $Pd(OAc)_2$/phenanthroline/$AgSbF_6$ system,[2] a vacant site was provided by abstracting one of the acetoxo ligands from the palladium center through the metathesis with $AgSbF_6$.

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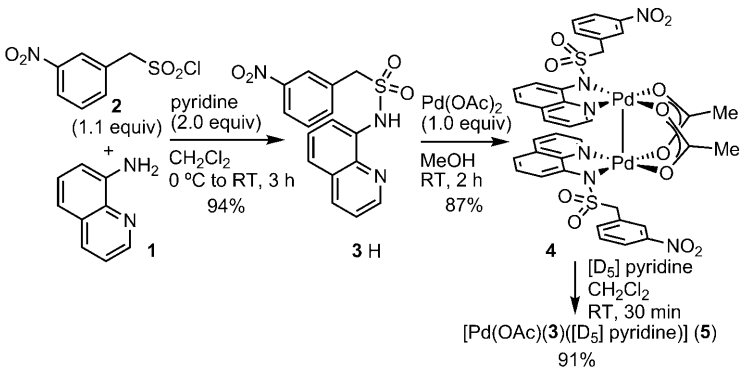
For a monoanionic *N*,*N*-bidentate-ligand precursor, we focused on sulfonamide quinolines.[12] Our initial ligand screen indicated that the substituent on the sulfonyl group had a significant effect on the reaction, with *meta*-nitrobenzylsulfonamide quinoline *meta*-nitrobenzylsulfonamidoquinoline (**3**H) being identified as the optimum one (see the Supporting Information). Sulfonamidoquinoline **3**H was prepared by reacting 8-aminoquinoline **1** with *meta*-nitrobenzylsulfonyl chloride **2** in the presence of pyridine in dichloromethane (Scheme 1). Then, **3**H was treated with $Pd(OAc)_2$ in methanol at room temperature for 2 hours. After filtration of the mixture, the precipitate was collected and $[\{Pd(\mu\text{-}OAc)(\mathbf{3})\}_2]$ (**4**) was obtained in 87% yield as an orange solid. The palladium(II) dimer **4** is stable against oxidative and hydrolytic decomposition in air. The molecular structure was determined by X-ray diffraction analysis (Figure 1).[13] The dimer adopts a "clamshell" shape in which the acetoxo ligands are perpendicular to the plane containing the palladium atoms and sulfonamidoquinoline ligands; the palladium atoms are in close proximity to one another, with a distance of 2.85 Å.




Scheme 1. Synthesis of palladium(II) dimer **4.** **3**H is the protonated form of the ligand in **5**.

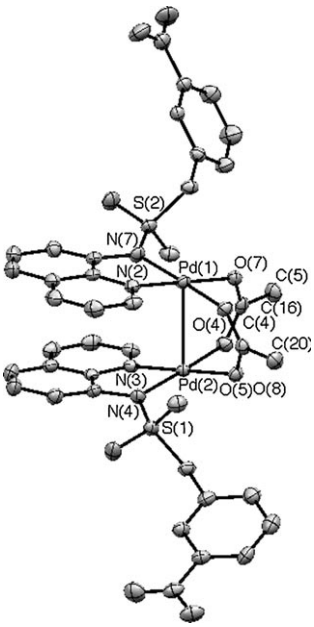
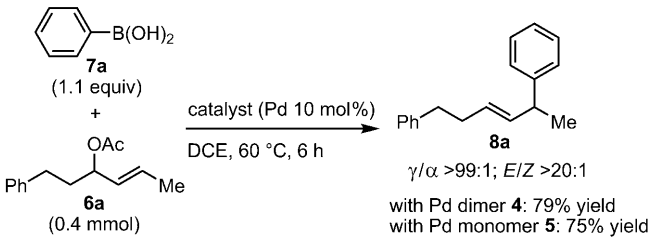



Figure 1. The molecular structure of palladium(II) dimer **4** determined by X-ray diffraction analysis of $[\{Pd(\mu\text{-}OAc)(\mathbf{3})\}_2]\cdot CHCl_3$. A chloroform molecule and hydrogen atoms are omitted for clarity.

The reaction of **4** with 3.0 equivalents of $[D_5]$pyridine in dichloromethane at room temperature for 30 minutes gave the monomeric palladium(II) complex [Pd(OAc)(**3**)($[D_5]$pyridine)] (**5**) in 91% yield after filtration and concentration (Scheme 1). The coordination geometry of **7** has not yet been determined.

The reaction of allylic acetate **6a** with phenylboronic acid (**7a**, 1.1 equiv) in the presence of the palladium(II) dimer **4** (10 mol% Pd) in 1,2-dichloroethane (DCE) at 60 °C for 6 hours afforded the isolated allyl-aryl coupling product **8a** in 79% yield (100% conversion of **6a**) with excellent regio- [$\gamma/\alpha$ (**8a**/**8d**) > 99:1] and *E*/*Z*- (>20:1) selectivities (Scheme 2). As was the case with the previous catalytic system, the catalytic reaction could be performed in air and in undried solvent without affecting the product yield and selectivities.




Scheme 2. Palladium-catalyzed ally–aryl coupling

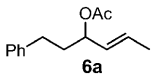
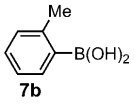
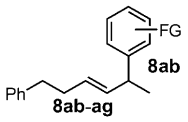
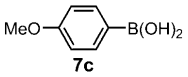
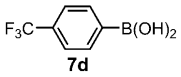
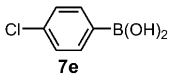
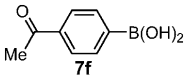
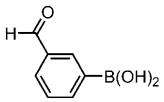
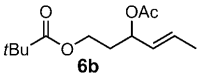
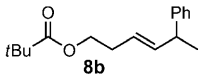
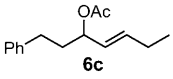
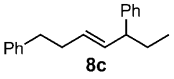
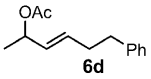
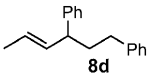
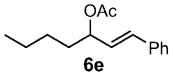
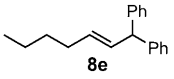
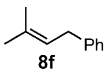
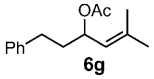
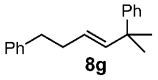
The monomeric palladium(II) complex (**5**) exhibited catalytic performance comparable with the dimer **4**: 75% yield with the excellent $\gamma/\alpha$- and *E*/*Z*-selectivities unchanged (Scheme 2). This result strongly suggests that the dimer **4** enters a catalytic cycle with its monomeric form.

The palladium(II) complex (**4**) was found to be applicable to various combinations of allylic acetates (**6**) and arylboronic acids (**7**; Table 1), affording the γ-substitution products (**8**) exclusively, irrespective of the substitution patterns of the allylic acetates. Moreover, the reactions took place with high *E*-selectivity, except for the reactions with **7b**, **7d**, **7f**, **7g** (Table 1, entries 1, 3, 5 and 6), and **6f** (not applicable; Table 1, entry 11). The reaction tolerates a variety of functional groups on both **6** and **7**; MeO, $CF_3$, chloro, ketone, aldehyde, ester, and silyl ether functionalities were tolerated successfully in the substrates (entries 2–7; Scheme 3).

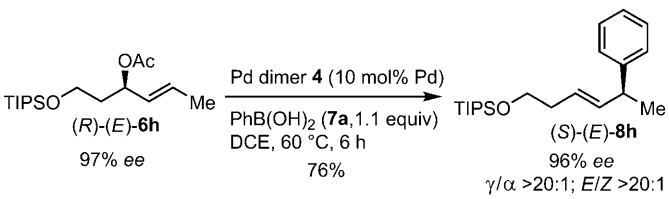
Table 1 also showed that the efficiency of the reaction was sensitive to the steric demands of the aryl group on **7** and the γ-substituent on **6**, although substantial steric bulk was tolerated successfully at the α-position of **7**. For instance, the reaction of **6a** with *ortho*-tolylboronic acid (**7b**) was less efficient than that with phenylboronic acid (**7a**), and gave the coupling product **8ab** in only 30% yield (Table 1, entry 1) and with a decreased *E*-selectivity (16:1). The

Table 1. Substrate Scope.[a]

| Entry | Allylic acetate | Boronic acid | Product[b] | Yield [%][c] | *E*/*Z*[d] |
|---|---|---|---|---|---|
| 1 |  **6a** |  **7b** |  **8ab-ag** | 30 | 16:1 |
| 2 | **6a** |  **7c** | **8ac** | 57 | >20:1 |
| 3 | **6a** |  **7d** | **8ad** | 70 | 6:1 |
| 4 | **6a** |  **7e** | **8ae** | 58 | >20:1 |
| 5 | **6a** |  **7f** | **8af** | 59 | 9:1 |
| 6[e] | **6a** |  **7g** | **8ag** | 68 | 7:1 |
| 7 |  **6b** | $PhB(OH)_2$ (**7a**) |  **8b** | 80 | >20:1 |
| 8 |  **6c** | $PhB(OH)_2$ (**7a**) |  **8c** | 67 | >20:1 |
| 9 |  **6d** | $PhB(OH)_2$ (**7a**) |  **8d** | 63 | >20:1 |
| 10 |  **6e** | $PhB(OH)_2$ (**7a**) |  **8e** | 45 | >20:1 |
| 11 |  **6f** | $PhB(OH)_2$ (**7a**) |  **8f** | 64 | -- |
| 12 |  **6g** | $PhB(OH)_2$ (**7a**) |  **8g** | 39 | >20:1 |

[a] Conditions: [Pd] dimer **4** (10 mol% Pd), **6** (0.4 mmol), **7** (0.44 mmol), 1,2-dichloroethane (2.4 mL), 60 °C, 6 h. [b] Isomeric ratios: γ/α > 20:1. Determined by $^1$H NMR spectroscopy. [c] Yield of isolated product. [d] Determined by $^1$H NMR spectroscopy. FG = functional group.




Scheme 3. Chirality transfer. TIPS = triisopropylsilyl.

methyl group at the γ-position of the allylic acetate (**6a**) could be replaced by an ethyl (Table 1, entry 8) or phenylethyl group (Table 1, entry 9) to give the coupling product in good yields. The cinnamyl acetate derivative **6e** also underwent the γ-selective coupling reaction, giving the *gem*-diarylalkane derivative **8e**, which contained an unconjugated alkenic substituent. Notably, even the γ,γ-disubstituted primary allylic acetate **6g** reacted exclusively at the γ-position to afford an all-carbon quaternary center albeit in a lower yield (Table 1, entry 12). On the other hand, allylic acetate **6f**, which contained two methyl groups at the α-position, was efficiently coupled with **7a** (Table 1, entry 11).

The allyl–aryl coupling with an α-chiral allylic acetate took place with excellent α-to-γ chirality transfer and *syn*-selectivity. The reaction of (*S*)-(*E*)-**6h** (97% *ee*) with phenylboronic acid in the presence of palladium(II) dimer **4** gave (*R*)-(*E*)-**8h** which was isolated in 76% yield and 96% *ee* (Scheme 3). This stereochemical outcome is the same as that of $Pd(OAc)_2$/phenanthroline/$AgSbF_6$ system.[2]

According to these experimental results, we proposed the mechanistic model as shown in Scheme 4. The palladium complex **4** enters into a catalytic cycle as its monomeric form **A**. The catalytic cycle is initiated by transmetalation

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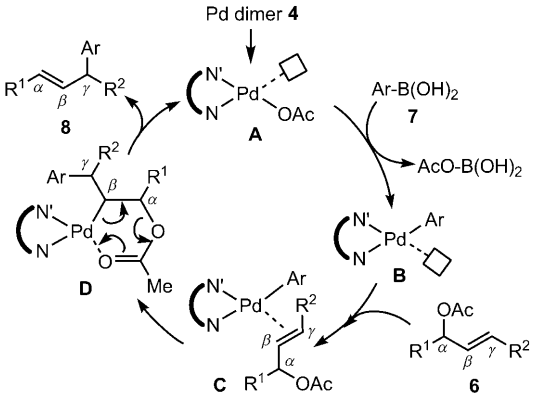


Scheme 4. A Proposed mechanistic model.

between an arylboronic acid (**7**) and **A**, which has a vacant coordination site. The resulting (σ-aryl)palladium(II) intermediate **B** forms π-complex **C** with an allylic acetate (**6**). The π-complex **C** then undergoes regioselective C–C-double-bond insertion into the aryl–palladium bond with the assistance of intramolecular coordination of the carbonyl oxygen of the acetoxy group to the palladium center, thus forming metallacyclic alkylpalladium(II) **D**. Finally, β-acetoxy elimination from **D**, rather than β-hydride elimination, affords coupling product **8** and regenerates **A**. Throughout the catalytic cycle the palladium center stays electronically neutral, in sharp contrast with the cationic character of the previous catalytic system [$Pd(OAc)_2$/phenanthroline/$AgSbF_6$].[2] This observation led to an important conclusion that having a cationic palladium center in the (σ-alkyl)palladium(II) complex is not necessary for the predominance of *syn*-β-acetoxy elimination over β-hydride elimination.[8–11]

In summary, the neutral palladium(II)-dimer complex with the anionic sulfonamidoquinoline ligands was successfully used in the γ-selective and stereospecific allyl-aryl coupling between allylic acetates and arylboronic acids. The use of the neutral palladium(II)-dimer complex did not require a silver salt as a co-catalyst. Furthermore, we found that *syn*-β-acetoxy elimination occurs predominantly over β-hydride elimination from (σ-alkyl)palladium(II) complexes with an uncharged palladium center.

## Experimental Section

**Typical Procedure for the Palladium(II)-Catalyzed Allyl–Aryl Coupling Reactions between Allylic Acetates and Arylboronic Acids**: The reaction of **6a** with phenylboronic acid (**7a**; Scheme 2) is representative. 1,2-Dichloroethane (2.4 mL) was added to [Pd] dimer **4** (20.3 mg, 0.02 mmol) and phenylboronic acid (**7a**) (53.6 mg, 0.44 mmol) and allylic acetate **6a** (87.3 mg, 0.40 mmol) were sequentially added at room temperature. The resulting mixture was heated at 60 °C for 6 h. After the mixture was cooled to room temperature, it was filtered through a short plug of silica gel and washed through with diethyl ether. The solvent was removed under reduced pressure and flash chromatography on silica gel (*n*-hexane) of the crude product provided the isolated **8a** (75.0 mg, 0.32 mmol) in 79 % yield.

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**Keywords:** allylic acetate · arylboronic acids · C–C coupling · palladium · regioselectivity

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