# A Highly Effective (Triphenyl phosphite)palladium Catalyst for a Cross−Coupling Reaction of Allylic Alcohols with Organoboronic Acids

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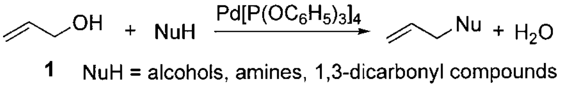
**Keywords:** Allylation / Boranes / C−C coupling / Green chemistry / Palladium

The cross coupling reaction of aryl and vinyl boronic acids and allylic alcohols proceeded smoothly in toluene or dioxane in the presence of a (triphenyl phosphite)palladium catalyst to give the corresponding allylbenzene derivatives and 1,4-dienes. Neither cocatalysts for promoting C–O bond cleavage of allylic alcohols nor bases for activation of organoboron reagents are required for promoting the coupling process.

## Introduction

Metal-catalyzed cross-coupling reactions between organic halides and organometallic reagents have been developed as a versatile and efficient tool for formation of carbon−carbon bonds in organic synthesis.[1] The palladium-catalyzed reaction with organoboron compounds (Suzuki−Miyaura coupling) has emerged as being advantageous in light of its low toxicity, operational simplicity, and broad functional group tolerance.[2] Recent marked progress in ligand design allows for the utilization of a variety of electrophilic substrates including less reactive aryl chlorides.[3] However, the use of stoichiometric amounts of a base or an activator for boron reagents with relatively poor nucleophilicity has generally been required for efficient Suzuki−Miyaura coupling reactions.[4]

We have recently developed a highly effective Pd catalyst that has a $P(OC_6H_5)_3$ ligand for dehydrative substitution of allylic alcohols with O-, N-, and C-nucleophiles; the $Pd-P(OC_6H_5)_3$ catalyst facilitated the C−O bond cleavage to generate a Pd−OH intermediate without additional promoters thus leading to a greener allylic alkylation, free from salt wastes [Equation (1)].[5−7] In this allylation, the Pd−OH species generated from the oxidative addition of allylic alcohols presumably has sufficient basicity to deprotonate the nucleophiles, liberating water. We utilize the potential basicity of the possible intermediate, the Pd−OH species, in the Suzuki−Miyaura coupling reaction and found that the $Pd-P(OC_6H_5)_3$ catalyst system efficiently promotes the cross-coupling reaction of allylic alcohols with organoboron reagents. The Pd−OH species possibly activates the boron center to facilitate transmetallation.[8−10]



(1)

## Results and Discussion

The reaction of allyl alcohol (**1**) (2.5 mmol) and phenylboronic acid (3.0 mmol) in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ ($1.25 \times 10^{-2}$ mmol/Pd, S/C = 200) was carried out in dioxane at 80 °C [Equation (2)]. As listed in Table 1, control of the molar ratio of Pd to $P(OC_6H_5)_3$ ligand is crucial for optimal catalyst performance. The use of an equimolar amount of the ligand with respect to Pd provided the desired allylbenzene (**2**) in 71% yield after 1 h (Entry 2), whereas no coupling product was obtained in the absence of $P(OC_6H_5)_3$ (Entry 1).[11] An increase in the P/Pd ratio resulted in a significant loss in the yield of coupled product, along with the formation of diallyl ether through dehydrative allylation of **1** as observed in our previous paper.[5] Other phenylboranes (Entries 6 and 7) gave satisfactory results except for the reaction with a catecholborane derivative (Entry 8). The choice of solvent proved to be crucial for determining the outcome of the reaction. The use of toluene gave a satisfactory result, the yield reaching 81% after a 1-h reaction, while polar solvents, acetonitrile, and DMF led to no conversion possibly because of their strong coordination ability. Dioxane can be used when boronic acids that have a poor solubility in toluene are employed for this reaction.

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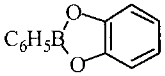
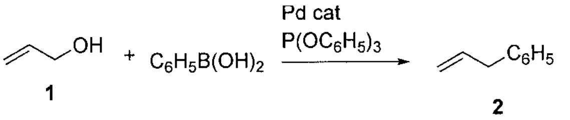
Table 1. Cross-coupling of **1** with phenylborane derivatives

| Run | $C_6H_5BR_2$ | P/Pd | Yield of **2**[c] [%] |
|---|---|---|---|
| 1 | $C_6H_5B(OH)_2$ | 0 | 0 |
| 2 | $C_6H_5B(OH)_2$ | 1 | 88 /71[d] |
| 3 | $C_6H_5B(OH)_2$ | 2 | 39[d] |
| 4 | $C_6H_5B(OH)_2$ | 3 | 2[d] |
| 5 | $C_6H_5B(OH)_2$ | 4 | 2[d] |
| 6 | $(C_6H_5)_3B$ | 1 | 91 |
| 7 | $C_6H_5$–9–BBN | 1 | 90 |
| 8 |  | 1 | 58 |

[a] Reaction conditions: **1** (2.5 mmol), boron reagent (3.0 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ ($1.25 \times 10^{-2}$ mmol/Pd), and $P(OC_6H_5)_3$ ($0-5.0 \times 10^{-2}$ mmol) at 80 °C for 6 h in dioxane (2.5 mL) under argon. [b] 9-BBN = 9-borabicyclo[3,3,1]nonane. [c] Determined by GC. [d] Reactions conducted for 1 h.



(2)

The markedly beneficial effect of the $P(OC_6H_5)_3$ ligand on catalyst activity was observed by comparing with other ligands. Triphenylarsane and tris(2-furyl)phosphane, which are known to be efficient ligands for Stille coupling,[12] gave lower yields of 53% and 20%, respectively (Entries 2 and 3 in Table 2). Little or no reaction took place in the case of other phosphorus ligands including triphenylphosphane under the reaction conditions described in Table 2 (Entries 4−9). Recently, a closely related coupling reaction of allylic alcohols with boronic acids by using a $(PPh_3)Pd$ catalyst was reported independently by Tsukamoto et al.; however, higher catalyst loadings (S/C =20) with $PPh_3$ and longer reaction times were required for the coupling.[13,14]

Table 2. Ligand effects on the formation of **2**

| Entry[a] | Ligand[b] | Yield of **2**[c] [%] |
|---|---|---|
| 1 | $P(OC_6H_5)_3$ | 81 |
| 2 | $As(C_6H_5)_3$ | 53 |
| 3 | P(2-furyl)$_3$ | 20 |
| 4 | $P(C_6H_5)_3$ | 9 |
| 5 | $P(OC_2H_5)_3$ | 5 |
| 6 | $P(C_6H_{11})_3$ | 0 |
| 7 | $P(^nC_4H_9)_3$ | 0 |
| 8 | DPPB[d] | 0 |
| 9 | $P[N(C_2H_5)_2]_3$ | 0 |

[a] Reaction conditions: **1** (2.5 mmol), phenylboronic acid (3.0 mmol), and $Pd_2(dba)_3 \cdot CHCl_3$ ($5.0 \times 10^{-3}$ mmol/Pd) at 80 °C for 1 h in toluene (2.5 mL) under argon. [b] P (or As)/Pd = 1. [c] Determined by GC. [d] DPPB = 1,4-bis(diphenylphosphanyl)butane.

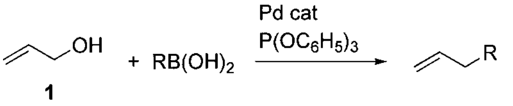
A variety of ring-substituted boronic acids can be converted into the coupling products with **1** by using $Pd-P(OC_6H_5)$ (P/Pd = 1) in toluene or dioxane, as shown in Table 3 [Equation (3)]. The reaction between arylboronic acids that have 4-methyl, 4-methoxy, and 4-vinyl groups and **1** gave the allylbenzene derivatives in good to excellent yields (Entries 1−3), while the coupling with congested 2-methylphenylboronic acid gave the product in a slightly lower yield, and the reaction with the more sterically demanding (2,6-dimethylphenyl)boronic acid provided unsatisfactory results even under forced conditions (Entries 5 and 6). At a higher reaction temperature (100 °C) and with a higher concentration of the catalyst (S/C = 100), the reaction of boronic acids bearing electron-deficient groups proceeded smoothly to give the desired product in reasonably high yields as shown in Table 3 (Entries 7−13). It should be noted that the reaction tolerated the carbon−chlorine

Table 3. Cross-coupling of **1** with various organoboronic acids

| Entry[a] | R | S/C | Temp. [°C] | Solvent | Time [h] | Yield[b] [%] |
|---|---|---|---|---|---|---|
| 1 | $4-CH_3C_6H_4$ | 500 | 80 | toluene | 2 | 89 |
| 2 | $4-CH_3OC_6H_4$ | 500 | 80 | dioxane | 2 | 89 |
| 3 | 4-vinylphenyl | 500 | 80 | toluene | 2 | 92 |
| 4 | 2-naphthyl | 500 | 80 | dioxane | 2 | (79) |
| 5 | $2-CH_3C_6H_4$ | 500 | 80 | toluene | 2 | 84 |
| 6 | $2,6-(CH_3)_2C_6H_3$ | 50 | 80 | toluene | 7 | 19 |
| 7 | $4-FC_6H_4$ | 100 | 100 | dioxane | 3 | 95 |
| 8 | $4-ClC_6H_4$ | 500 | 100 | dioxane | 3 | 72 |
| 9 | $4-BrC_6H_4$ | 100 | 100 | dioxane | 3 | (82) |
| 10 | $4-IC_6H_4$ | 100 | 100 | dioxane | 3 | 0 |
| 11 | $4-CHOC_6H_4$ | 100 | 100 | dioxane | 3 | (89) |
| 12 | $4-CH_3COC_6H_4$ | 100 | 100 | dioxane | 3 | (100) |
| 13 | $4-CF_3C_6H_4$ | 100 | 100 | dioxane | 3 | 85 |

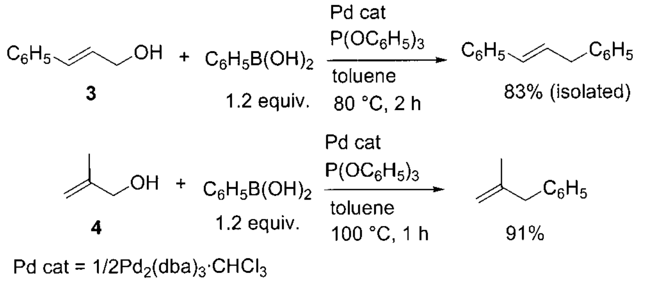
[a] Reaction conditions: **1** (2.5 mmol) and $RB(OH)_2$ (3.0 mmol), under argon. P/Pd = 1. [b] Determined by $^1H$ NMR spectroscopy. Isolated yields are in parenthesis.

and carbon−bromine bonds in the arylboronic acids under the reaction conditions. However, 4-iodophenylboronic acid gave neither the corresponding substituted allylbenzene nor diallyl ether formed by dehydrative allylation of **1**, possibly because facile oxidative addition of the carbon−iodine bond to a Pd$^0$ intermediate consequently prevented C−O bond activation of **1** (Entry 10).

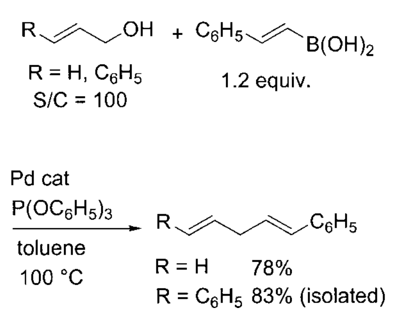


(3)

Substituted allylic alcohols can successfully be used for the Suzuki−Miyaura coupling by using the Pd−P(OC$_6$H$_5$)$_3$ catalyst system. Cinnamyl alcohol (**3**) and 2-methallyl alcohol (**4**) reacted smoothly with phenylboronic acid to give the desired products in good to excellent yields (Scheme 1). The reaction of crotyl alcohol (**5**) with the phenylborane reagent provided a mixture of phenylbutenes (**7** and **8**). As shown in Scheme 2, products **7** and **8** were obtained in comparable ratios from the reaction of the regioisomeric substrate, 1-methyl-2-propen-1-ol (**6**), and this implies that the products from **5** and **6** may be derived from an identical η$^3$-allylpalladium intermediate. The catalyst system based on the P(OC$_6$H$_5$)$_3$ ligand was also effective for the formation of 1,4-dienes when styrylboronic acid was used as a coupling partner. A single stereoisomer was obtained from the reaction of **1** or **3** [Equation (4)].

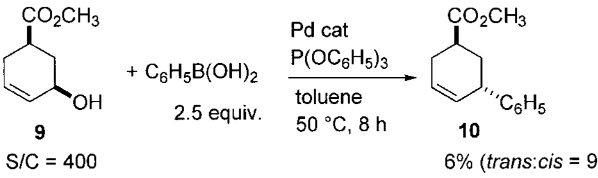


Scheme 1. Suzuki−Miyaura coupling of substituted allylic alcohols by the Pd−P(OC$_6$H$_5$)$_3$ catalyst



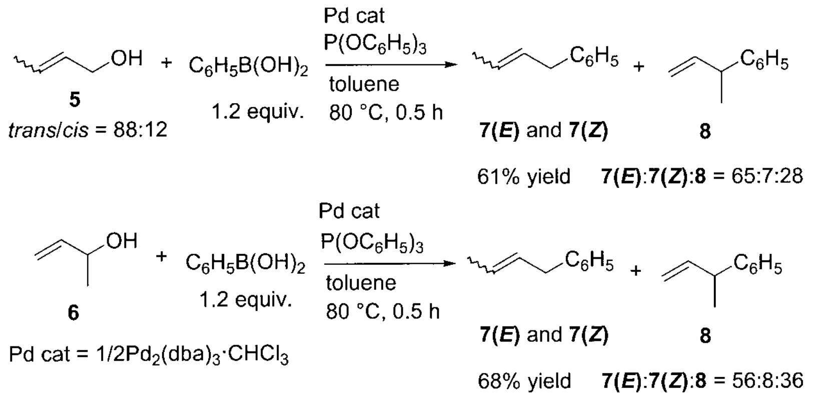
(4)

A possible mechanism for the formation of allylbenzene from **1** and phenylboronic acid is outlined in Scheme 3. According to previous results from the stoichiometric reaction of **1** with Pd$^0$, we predicted that an η$^3$-allyl(hydroxo)palladium complex **A** would be generated by oxidative addition of the alcohol.[15,16] The subsequent transmetallation of phenylboronic acids affords allyl(phenyl)palladium species **B**, the Pd−OH species might interact with the organoboron reagents to accelerate the reaction. The coupling products, allylbenzenes, are obtained by reductive elimination from intermediate **B**. In the step from **A** to **B**, excess ligand molecules would block an available coordination site for the incoming phenyl group. Indeed, a decrease in the catalyst activity was observed when excess P(OC$_6$H$_5$)$_3$ ligand or coordinating polar solvents were added, as mentioned above.



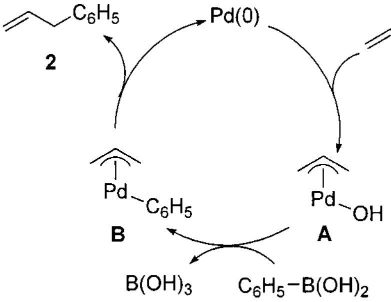
(5)

The stereochemical course of the coupling process was investigated at an early stage of the reaction of the cyclohexenol derivative (**9**) (*cis*/*trans* = 99%). To suppress the stereochemical scrambling of the η$^3$-allylpalladium intermediates,[17] the reaction of **9** with phenylboronic acid was performed at 50 °C and with a low catalyst loading (S/C =



Scheme 2. Stereochemical results of the cross-coupling of **5** or **6** with phenylboronic acid

400). The product, *trans*-**10**, was found to have 92% stereoisomeric purity at 6% conversion by $^1$H NMR spectroscopy [Equation (5)], and this implies that the reaction may proceed through the widely accepted mechanism involving oxidative addition to Pd$^0$ with inversion of configuration, and subsequent transmetallation and reductive elimination steps with retention of stereochemistry.[18]



Scheme 3. Possible mechanism of Suzuki−Miyaura coupling of allylic alcohol with phenylboronic acid

## Conclusion

In summary, we have demonstrated a facile C−C bond forming reaction by using allylic alcohols catalyzed by the Pd−P(OC$_6$H$_5$)$_3$ system. The present process requires neither cocatalysts for promoting C−O bond cleavage of allylic alcohols nor bases for activation of organoboron reagents. Although allylic compounds have generally been considered to be inert for cross-coupling reactions relative to aryl and alkenyl substrates,[9,19] the present catalyst system is characterized by high activity (S/C = 100−500) and high functional group tolerance as well as operational simplicity. Further studies on the reaction mechanism and other applications will be forthcoming.

## Experimental Section

**Typical Procedure for the Coupling Reactions:** P(OC$_6$H$_5$)$_3$ (1.3 μL, $5.0 \times 10^{-3}$ mmol) and **1** (0.17 mL, 2.5 mmol) was added successively to a mixture of Pd$_2$(dba)$_3$·CHCl$_3$ (2.6 mg, $5.0 \times 10^{-3}$ mmol/Pd) and 2-naphthylboronic acid (516.0 mg, 3.0 mmol) in dioxane (3.0 mL) under argon. After stirring at 80 °C for 2 h, the reaction mixture was cooled to room temperature, poured into diethyl ether, and washed with brine. The organic layer was dried with MgSO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel to afford 2-allylnaphthalene with a yield of 79% (334 mg). $^1$H NMR (300.04 MHz, CDCl$_3$): $\delta$ = 3.55−3.57 (d, $^3J_{\rm H,H}$ = 6.6 Hz, 2 H, CH$_2$), 5.06−5.12 (m, 1 H, terminal CH$_2$), 5.14−5.18 (ddt, $^3J_{\rm H,H}$ = 9.0, $^3J_{\rm H,H}$ = 1.7, $^4J_{\rm H,H}$ = 1.7 Hz, 1 H), 6.00−6.13 (m, 1 H, terminal CH$_2$), 7.32−7.50 (m, 4 H, arene), 7.77−7.86 (m, 3 H, arene) ppm. $^{13}$C NMR (75.45 MHz, CDCl$_3$): $\delta$ = 40.3, 116.1, 125.3, 125.9, 126.7, 127.4, 127.5, 127.6, 127.9, 132.1, 133.6, 137.3, 137.5 ppm. EIMS: $m/z$ = 169 [M$^+$].

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