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Pd(η^3-1-PhC$_3$H$_4$)(η^5-C$_5$H$_5$), an Unusually Effective Catalyst Precursor for Suzuki–Miyaura Cross-Coupling Reactions Catalyzed by Bis-Phosphine Palladium(0) Compounds

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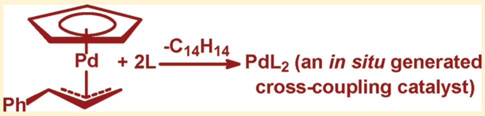
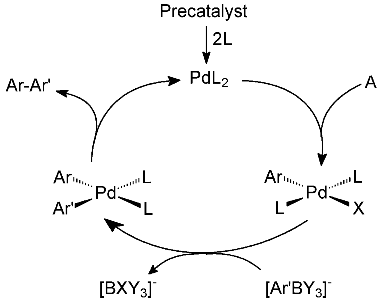


ABSTRACT: It has previously been shown that the easily handled, heat- and air-stable compound Pd(η^3-1-PhC$_3$H$_4$)(η^5-C$_5$H$_5$) (**Vb**) reacts rapidly with a wide variety of tertiary phosphines L to produce near-quantitative yields of the corresponding Pd(0) compounds PdL$_2$, which are widely believed to be the active species in many often-used cross-coupling catalyst systems based on Pd(PPh$_3$)$_4$ (**I**), Pd$_2$(dba)$_3$ (**II**), PdCl$_2$ (**III**), and Pd(OAc)$_2$ (**IV**). However, catalyst precursors **I**–**IV** are in fact known to preferentially generate sterically hindered, three-coordinate Pd(0) species rather than two-coordinate PdL$_2$, and thus **Vb** is hypothetically expected to be a better catalyst precursor for e.g. Suzuki–Miyaura cross-coupling reactions. Utilizing the conventional Suzuki–Miyaura cross-coupling reaction of phenylboronic acid with bromoanisole, comparisons are made of the efficacies of catalyst systems based on **Vb** with those based on compounds **I**–**IV** (L = the representative phosphines PPh$_3$, PCy$_3$, PBu$^t_3$). As anticipated, catalysts generated from **Vb** are significantly more competent and, as a bonus, **Vb** makes palladium(0) complexes PdL$_2$ available under rigorously anhydrous conditions.

A wide variety of palladium-catalyzed carbon–carbon bond forming methodologies are available through reactions catalyzed by Pd(0) compounds believed to be of the type PdL$_2$ (L = phosphine ligand),[1] with Suzuki–Miyaura cross-coupling reactions having particular significance in the synthesis of biaryl derivatives.[1a,h] In the general case, the aryl halide ArX (X = Cl, Br, I) reacts catalytically with the arylborate species [Ar′BY$_3$]$^-$ (Y = halide, alkoxide, etc.) to form the coupled product Ar–Ar′. The most widely accepted catalytic cycle (Scheme 1) typically involves oxidative addition of ArX to a bis-phosphine palladium(0) compound PdL$_2$ (L = tertiary phosphines) followed by transmetalation and reductive elimination steps, a process which has been studied both experimentally[2] and computationally.[3]

Scheme 1



Although specific catalytically active compounds such as Pd(PCy$_3$)$_2$ and Pd(PBu$^t_3$)$_2$ have long been available[4a] and a general route to compounds of this type has recently been reported,[4b] Pd(0) compounds are in fact air-sensitive and preformed catalysts of the type PdL$_2$ are rarely used.[5] Instead, the vast majority of palladium-catalyzed cross-coupling studies utilize the much more easily manipulated, commercially available catalyst precursors Pd(PPh$_3$)$_4$ (**I**), Pd$_2$(dba)$_3$ (**II**; dba = PhCH=CHCOCH=CHPh), PdCl$_2$ (**III**), and/or Pd(OAc)$_2$ (**IV**), the last three in association with added L.[5] Unfortunately, while **I** and **II** contain the metal already in the 0 oxidation state, **I** exists in solution primarily as the tris-phosphine complex Pd(PPh$_3$)$_3$[6] while **II** reacts with phosphines to form species of the type Pd(dba)L$_2$.[7] In neither case are the desired PdL$_2$ species formed, but rather sterically hindered, less active three-coordinate complexes and thus optimal catalytic activities may not be achieved.

Impetus for widespread use of the Pd(II) catalyst precursors **III** and **IV**[5] is found in seminal research by Amatore and Jutand,[8] who have shown that treatment of e.g. **IV** with 3 equiv of triarylphosphines L results in the formation of catalytically active Pd(0) complexes [Pd(OAc)L$_2$]$^-$ in addition to oxidized phosphorus byproducts. Similarly, reduction of the analogous halo compounds PdX$_2$L$_2$ (X = Cl, Br, I) results in formation of the Pd(0) complexes [PdXL$_2$]$^-$.[8d] Therefore, as with catalyst precursors **I** and **II**, the major palladium species derived from reduction of Pd(II) precursors are not the often presumed catalytically active compounds PdL$_2$ but, again, three-coordinate species.[8k] Complicating the issue, there is to our knowledge no evidence that reductions of Pd(II) precursors are ever effected either rapidly or completely in the majority of catalyst systems employed in cross-coupling studies.[1,9a,b] It is also not generally known if "poor" phosphine-based catalyst systems are intrinsically inferior (in the context of the catalytic cycle, as is frequently assumed) or, trivially, because the

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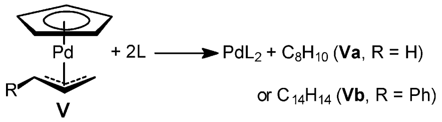
phosphines involved are just poor reducing agents for Pd(II) salts.

The intrinsic complexities involved in cross-coupling chemistry and arising from these problems have long been recognized, and the relevant mechanistic literature has been referred to as a "morass, with an endless list of hypothesized or claimed true catalytic species".[1i] Other authors call attention to more practical problems arising from the aforementioned uncertainties, such as the extensive screening and optimization procedures which are found to be necessary in many of the studies reported in the literature.[10]

In this vein, and assuming also that the two-coordinate species PdL_2 are generally more active than are the sterically hindered three-coordinate derivatives, it seems quite possible that a significant number of cross-coupling studies have not made optimal use of the palladium added. The result could be unnecessarily high reaction temperatures, unnecessarily long reaction times, and/or yields lower than would be possible if specifically PdL_2 were used. Also, of course, where reduction of Pd(II) by a phosphine actually does occur to some extent, utilization of one-third of an expensive and/or difficult to prepare phosphine as a reducing agent is clearly wasteful and undesirable.

To make possible the more effective use of both palladium and phosphine in the generation of catalysts PdL_2, we and others have described the use of the compounds $Pd(\eta^3\text{-}C_3H_5)(\eta^5\text{-}C_5H_5)$ (**Va**, R = H), which react rapidly and quantitatively with phosphines L to form the compounds PdL_2 as in eq 1.[4a]



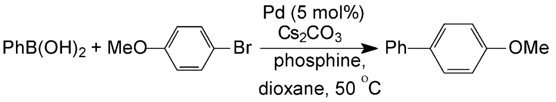
(1)

Unfortunately, **Va** decomposes on storage at room temperature[4a] and therefore, in spite of its potential advantages, is not a practical catalyst precursor.[4c] As an alternative, we have shown that the easily synthesized air- and heat-stable analogue $Pd(\eta^3\text{-}1\text{-}PhC_3H_4)(\eta^5\text{-}C_5H_5)$ (**Vb**, R = Ph) also reacts readily with phosphines L as in eq 1 (L = a variety of mono- and bidentate phosphines), forming the compounds PdL_2 quickly and efficiently.[11] Compound **Vb** should therefore be a very useful catalyst precursor for the generation of PdL_2 and appears to be a potentially very useful cross-coupling catalyst precursor because it makes rapid, quantitative, and economical use of both the palladium and the phosphine.

To test the hypothesis that **Vb** might be significantly superior to **I**−**IV** in its ability to form PdL_2 and hence generate catalytically active species, we have carried out an investigation in which we compare **Vb** with compounds **I**−**IV** as catalyst precursors for a representative, conventional Suzuki−Miyaura cross-coupling reaction. We now report our findings, *noting that our intention has not been to develop new catalysts per se but rather to investigate the potentially greater competence of* ***Vb*** *relative to* ***I***−***IV****, the catalyst precursors most commonly utilized.* We ultimately come to the conclusion that **Vb** is to be preferred over the alternatives because it generates the desired catalytically active species PdL_2 quickly and more efficiently.

■ RESULTS AND DISCUSSION

We report herein an investigation of the effectiveness of **Vb** compared with those of the commonly used catalyst precursors **I**−**IV** for a representative Suzuki−Miyaura cross-coupling reaction. To this end we utilized as a basis of comparison the representative reaction of phenylboronic acid with 4-bromoanisole (eq 2), the 4-bromoanisole chosen to distinguish between the desired product 4-methoxybiphenyl and the homocoupling coupling product biphenyl. In addition, bromoanisole is a more difficult coupling partner than is the analogous bromobenzene and should better distinguish subtle differences in efficacies of the various precursors.



(2)

Shown in Figure 1 are reaction profiles for the formation of 4-methoxy-1,1′-biphenyl using various catalyst precursors with PPh_3 as ligand L. Each reaction was carried out several times under the conditions shown with periodic sampling and monitoring by GC of both the 4-methoxy-1,1′-biphenyl and the bromoanisole starting material. In general, there was good mass balance between reactant and product.

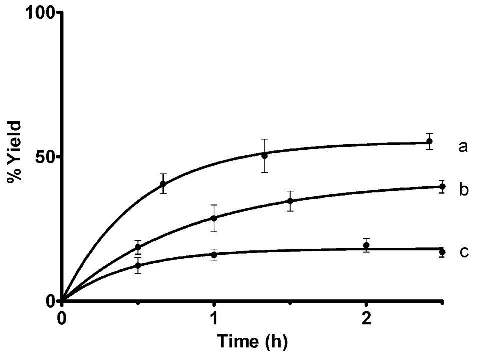


Figure 1. Yield of 4-methoxy-1,1′-biphenyl from the cross-coupling of phenylboronic acid and 4-bromoanisole catalyzed by 5 mol % Pd catalyst systems utilizing (a) **Vb** + $2PPh_3$, (b) $Pd(PPh_3)_4$, and (c) $Pd(OAc)_2 + 3PPh_3$, all in dioxane containing 1 equiv of Cs_2CO_3 at 50 °C.

As can be seen, the $Pd(OAc)_2$-based catalyst system was clearly very ineffective, possibly because of sluggish reduction of Pd(II) under these conditions; we note that reports of applications of this commonly used catalyst precursor generally involve higher temperatures and longer reaction times.[12] Water is also frequently added to reaction mixtures,[1] in the apparent belief that it is required for reduction to occur, although it has been shown that the rate-determining step in the formation of Pd(0) species from e.g. $Pd(OAc)_2(PPh_3)_2$ is an inner-sphere reduction and that the role of water is to convert the oxidized phosphorus species to $O{=}PPh_3$.[8b,c,e,f,h] Nonetheless, we repeated the reaction shown in Figure 1c, utilizing 20% aqueous dioxane; as anticipated on the basis of the literature,[8b,c,e,f,h] we obtained a reaction profile essentially identical with that shown in Figure 1c. Thus, the intrinsic efficacy of the **IVb**/PPh_3 system was not underestimated when working under anhydrous conditions.

The other frequently used catalyst precursor, $Pd(PPh_3)_4$, exhibited somewhat greater activity, but **Vb** was clearly the most effective of the three, exhibiting a higher initial rate and producing a higher yield of product over the course of the experiment. The observation that the reaction rate leveled off well before 100% conversion will be discussed below. Note that use of **Vb** alone, without added phosphine, was ineffective.

Figure 2 shows the reaction profile of the same coupling reaction, but with PPh_3 substituted by the bulkier PCy_3, which has been shown elsewhere to be an effective ligand for Suzuki—Miyaura coupling reactions.[13]

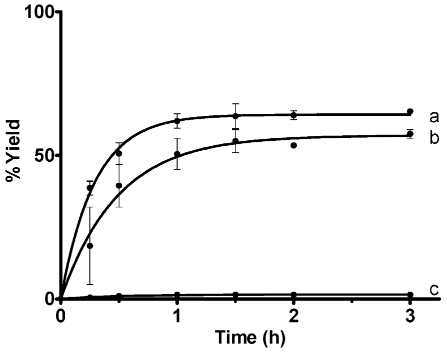


Figure 2. Yield of 4-methoxy-1,1′-biphenyl from the cross-coupling of phenylboronic acid and 4-bromoanisole catalyzed by 5 mol % Pd catalyst systems utilizing (a) **Vb** + $2PCy_3$, (b) $^1/_2Pd_2(dba)_3$ + $2PCy_3$, and (c) $Pd(OAc)_2$ + $3PCy_3$, all in dioxane containing 1 equiv of Cs_2CO_3 at 50 °C.

We found, as is shown, that the $PCy_3/Pd(OAc)_2$ system gave only trace amounts of product, suggesting that PCy_3 is a poor reducing agent under these conditions. As with catalysts based on PPh_3, water is frequently (but not always) added to PCy_3-based catalysts,[13] although the possible role(s) of water with ligands L other than triarylphosphines have not been ascertained with certainty. Water has been reported to be necessary for the reduction of $Pd(OAc)_2$ by the bidentate phosphine binap,[14a] but a subsequent investigation involving reduction by another bidentate phosphine, dppp, revealed that intramolecular reduction by coordinated dppp occurs, as with PPh_3, but that the redox reaction is reversible. The water serves merely to shift the equilibrated reaction to completion.[8g] Water is apparently not required in reactions involving $Pd(OAc)_2$ activation by $PBu^n{}_3$,[14b,c] PMe_2Ph,[8c] and $PMePh_2$,[8c] but we nonetheless carried out a cross-coupling reaction as in Figure 2c but utilizing 20% aqueous dioxane. Only a 4% yield of coupled product was obtained, and thus again the added water had no effect on the yield of the cross-coupling reaction.

Catalyst precursors $Pd_2(dba)_3$ and **Vb** resulted ultimately in higher, comparable conversions, but use of the latter resulted in a higher initial rate of coupling and is certainly more effective at short reaction times. As with the PPh_3 system, the reactions did not go to completion.

We next employed the sterically demanding, normally very effective $PBu^t{}_3$ (Figure 3),[13a−d,g] to further our comparison of **Vb** with conventional palladium catalyst precursors.

As was found with the $Pd(OAc)_2/PPh_3$ and $Pd(OAc)_2/PCy_3$ systems, the palladium(II)-based catalyst systems $Pd(OAc)_2/PBu^t{}_3$ and $PdCl_2/PBu^t{}_3$ exhibited low efficacies, although in this case the use of aqueous dioxane with $Pd(OAc)_2$ resulted in a higher conversion (48%) after 2.5 h (not shown). Interestingly, a ^{31}P NMR investigation of the $Pd(OAc)_2/PBu^t{}_3$ reaction mixture indicated that one of the major palladium species in solution was a cyclometalated complex of the type reported previously (δ −9.04)[9c] and discussed above. The ^{31}P NMR spectrum also exhibited resonances at δ 65.5 (s), 62.2 (s), and 51.7 (w), possibly indicating the presence of free $PBu^t{}_3$[4a] and $[Pd(C_6H_4OMe)(\mu\text{-Br})(PBu^t{}_3)]_2$, the product of oxidative addition of bromoanisole to $Pd(PBu^t{}_3)_2$;[13g] there was no evidence for $Pd(PBu^t{}_3)_2$ (δ 84.7).[4a]

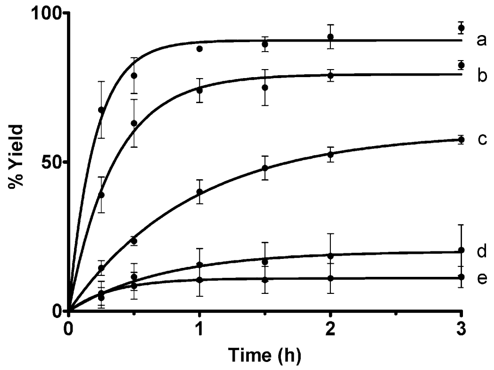


Figure 3. Yield of 4-methoxy-1,1′-biphenyl from the cross-coupling of phenylboronic acid and 4-bromoanisole catalyzed by 5 mol % Pd catalyst systems utilizing (a) **Vb** + $2PBu^t{}_3$, (b) $Pd_2(dba)_3$ + $4PBu^t{}_3$, (c) $[PdCl(\eta^3\text{-}C_3H_5)]_2$ + $4PBu^t{}_3$, (d) $PdCl_2$ + $3PBu^t{}_3$, and (e) $Pd(OAc)_2$ + $3PBu^t{}_3$, all in dioxane containing 1 equiv of Cs_2CO_3 at 50 °C.

The catalyst systems based on $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and $Pd_2(dba)_3$ exhibited somewhat better activities, but the use of **Vb** resulted clearly in a higher initial rate of coupling and higher conversions over all time periods. Near-quantitative conversion to 4-methoxybiphenyl was achieved within 1 h using **Vb**.

Reason for Decreases in Rates: Catalyst Deactivation?

As indicated in Figures 1−3, the profiles of those reactions which were not essentially completed within 1 h tended to level off after about 1 h. In an effort to determine whether this behavior was a result of catalyst deactivation or of side reactions involving the phenylboronic acid, we carried out an experiment involving the **Vb**/PPh_3 catalyst system, analogous to that shown in Figure 1. After about 2 h, at which point cross-coupling had definitely ceased, an additional 1 equiv of phenylboronic acid was added to the reaction mixture. As is shown in Figure 4, cross-coupling began anew and thus the problem clearly did not involve catalyst deactivation.

Interestingly, however, addition of a 2- or 3-fold molar excess of phenylboronic acid at the beginning of a reaction of the type shown in Figure 4 resulted in essentially quantitative yield of cross-coupling product within 1 h. This finding is rather surprising, as it means that the **Vb**/PPh_3 catalyst system may be

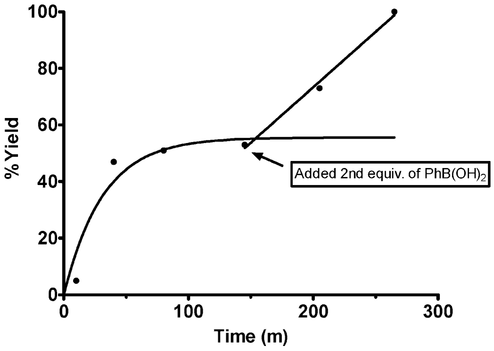
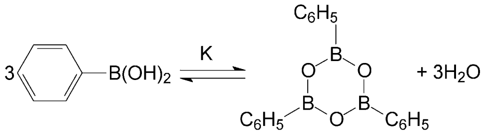


Figure 4. Yield of 4-methoxy-1,1′-biphenyl from the cross-coupling of phenylboronic acid and 4-bromoanisole catalyzed by 5 mol % **Vb** and 2 equiv of PPh_3; another 1 equiv of phenylboronic acid was added after 3 h.

comparable in activity to the **Vb**/PBu$^t_3$ catalyst system if one of the reactants is present in excess.

In any case, these results indicate that the originally added phenylboronic acid was for some reason no longer available for cross-coupling after about 1 h and we briefly investigated possible mode(s) of deterioration to less active species. Moreno-Mañas et al. have identified several side reactions of phenylboronic acid which can occur during Suzuki–Miyaura cross-coupling reactions,[15a] including protodeboronation to give benzene, homocoupling to give biphenyl, hydroxylation to give phenol, and dehydration on heating to give phenylboroxine (Scheme 2).

Scheme 2



In general, our GC studies did not reveal the presence of benzene as a byproduct and yields of biphenyl and phenol were too low (~5%) to account for the discrepancies. Phenylboroxine has been reported to exhibit relatively low cross-coupling activity in other systems,[16,17a] and we found that it is indeed much less effective than is phenylboronic acid in its ability to cross-couple with bromoanisole. Phenylboroxine is also likely to be formed[15b] at the temperature used in our cross-coupling experiments, and at one point we considered the possibility that dehydration of the phenylboronic acid was the reason for the lowering of activity. This hypothesis was dispelled, of course, when we found (see above) that water has no effect on the efficacy of the $Pd(OAc)_2/PPh_3$ system. Thus, added water enhances neither the reduction of $Pd(OAc)_2$ nor the concentration of active phenyl-boron species.

However, we note that there is a strong sense in the literature that unexpectedly facile dehydration of phenylboronic acid can result in the presence of phenylboroxine impurities,[18] presumed to decrease reactivity; water is therefore frequently added to commercial phenylboronic acid reaction mixtures in an attempt to convert any phenylboroxine present to phenylboronic acid.[17] To the contrary, however, Tokunaga et al. have provided an alternative scenario. They find that the exchange process shown in Scheme 2 occurs sufficiently slowly on the NMR time scale that the ^{1}H chemical shifts of phenyboronic acid and phenylboroxine are readily distinguishable.[19a] Using the NMR data, *K* for the equilibrium shown was determined in $CDCl_3$ and found to be such that a solution of phenyboronic acid over a range of temperatures actually contains about 75% or more of the phenyl-boron moieties present as phenylboroxine. Therefore, and as we have confirmed,[19b] examination of a high-quality sample of phenylboronic acid by ^{1}H NMR spectroscopy in an anhydrous NMR solvent reveals the presence of a very large proportion of phenylboroxine, suggesting incorrectly that the sample is badly contaminated (and probably leading to the aforementioned attempts to suppress dehydration of phenylboronic acid by adding water). Added water is not required to "restore" the dehydrated phenylboronic acid, as the equilibrium of Scheme 2 shifts to the left as phenylboronic acid is consumed via e.g. transmetalation.

That said, it seemed clear that the phenylboronic acid present in our reaction mixtures must be deteriorating in some way, and we obtained ^{1}H NMR spectra of a typical reaction mixture containing phenylboronic acid and cesium carbonate in dioxane. Although phenyboronic acid and phenylboroxine were present in the expected proportions in a freshly prepared solution, addition of cesium carbonate resulted in the ^{1}H resonances of both being quickly replaced by resonances of at least six new phenyl-containing compounds (*o*-H doublets at δ 7.47, 7.67, 7.73, 7.83, 7.89, 7.98). Brief heating to 50 °C followed by cooling to 25 °C revealed the presence of additional unidentifiable resonances, and we terminated the investigation, since it seemed very unlikely that we would be able to identify many of the new compounds.

■ SUMMARY AND CONCLUSIONS

Our results clearly confirm our hypothesis that combinations of **Vb** with various representative phosphines would generate catalyst solutions which are much more active than catalyst systems obtained using combinations of catalyst precursors **I–IV** with the same phosphines. The reason almost certainly lies in the fact that **Vb** generates catalytically active species PdL_2 quickly and quantitatively while the others do not, in part at least for the reasons discussed above. A second advantage of the use of **Vb** is that the Pd(0) products PdL_2 are formed under rigorously anhydrous conditions. The potential benefits of carrying out cross-coupling chemistry in the absence of water have been noted previously.[20]

The potential problems associated with use of catalyst precursors **I–IV** are discussed above and have been recognized by others but there seems previously to have been little recognition of this fact and **I–IV** all continue to be used frequently.[5] However, while our study shows that $Pd_2(dba)_3$ can be effective for Suzuki–Miyaura cross-coupling reactions,[21] catalyst systems based on reduction of palladium(II) are unreliable and, in the absence of experiments explicitly demonstrating the actual formation in high yields of the anticipated palladium(0) compounds, should not be utilized when comparing e.g. the effectiveness of various phosphine ligands in cross-coupling reactions involving boronic acids.

Our results have also provided the first evidence available, to our knowledge, for the negative consequences of phenylboronic acid degradation during the course of Suzuki–Miyaura cross-coupling reactions. Our reaction profiles also provide information on the time scale over which this side reaction is a factor affecting yields of cross-coupled products. Most publications in the area of catalytic cross-coupling reactions report isolated yields, obtained on termination of reactions after arbitrary periods of time.[1] In such studies, little distinction can be made between catalytic reactions which are still proceeding at the point of termination and those whose rates have decreased to zero before the point of termination. Indeed, the advantages of reactions which are completed within a relatively short time span, well before the point of termination, likewise remain unappreciated. Thus use of isolated yields in comparisons of various ligand systems can also be misleading.

■ EXPERIMENTAL SECTION

General Procedures. All syntheses were carried out under a dry, deoxygenated argon or nitrogen atmosphere with standard Schlenk line techniques. Argon was deoxygenated by passage through a heated column of BASF copper catalyst and then dried by passing through a column of 4 A molecular sieves. Solvents were dried by the procedure described in the literature.[22] The authors state that H_2O levels of <5 ppm can be obtained for drying THF over appropriately activated molecular sieves for 72 h. Although we are using 1,4-dioxane as a solvent, one can assume similar levels of dryness are achieved. Phosphines were purchased from Strem Chemicals and all other compounds from Aldrich. Handling and storage of air-sensitive compounds (PBu^t_3, PCy_3) were carried out in an MBraun Labmaster glovebox. NMR spectra were recorded on Bruker 400 or 600 MHz spectrometers, with ^{1}H NMR data being referenced to TMS via the residual proton signals of the deuterated solvents, and GC experiments were carried out using a Varian 3900 GC equipped with a CP 8400 autosampler, a 0.32 mm Varian fused silica column, and an FID. The injector temperature was set at 250 °C, the initial column temperature at 140 °C, and the detector temperature at 250 °C. Hexadecane was added as an internal standard, and GraphPad Software Prism Version 3.02 was used for curve fitting.

Synthesis of $Pd(\eta^3\text{-}1\text{-}PhC_3H_4)(\eta^5\text{-}C_5H_5)$ (Vb).[23] THF was dried by passage through a column of activated alumina and was stored over 4 Å molecular sieves. A solution of NaCp in THF (2.0 M, Aldrich; 1.45 mL, 2.90 mmol of NaCp) was diluted by THF (20 mL) in a dropping funnel and added dropwise to a solution of $[Pd(\eta^3\text{-}1\text{-}PhC_3H_4)Cl]_2$ (0.601 g, 1.16 mmol) in THF (20 mL) at −78 °C. The resulting deep purple solution was stirred for 5 min, warmed to room temperature, and then placed in an ice bath. The solvent was removed from the cooled solution under reduced pressure, and the product was extracted using three 20 mL portions of hexanes. The filtrate was reduced under vacuum, yielding an oily purple solid. The solid was dissolved in a minimum of hexanes, and purple-red crystals were collected at −40 °C. Beautiful purple-red crystals can also be obtained by sublimation, but with some loss. Yield: 0.565 g, 84%. ^{1}H NMR (C_7D_8, 600 MHz): δ 2.16 (d, J = 10.5 Hz, 1H, H(3a)), 3.36 (d, J = 6.1 Hz, 1H, H(3s)), 3.84 (d, J = 9.8 Hz, 1H, H(1)), 5.14 (ddd, J = 10.5, 9.8, 6.1 Hz, 1H, H(2)), 5.63 (s, 5H, C_5H_5), 6.98−7.03 (m, 3H), 7.24−7.27 (m, 2H)).

General Experimental Methodologies for Determining Reaction Profiles: Formation of 4-Methoxy-1,1′-biphenyl.

Utilizing $Pd(\eta^3\text{-}1\text{-}PhC_3H_4)(\eta^5\text{-}C_5H_5)$ (Vb). Under an atmosphere of argon, **Vb** (0.072 g, 0.25 mmol) and a phosphine (0.5 mmol; PPh_3, PCy_3, PBu^t_3) were combined in 5 mL of dioxane and stirred at 25 °C for h. The resulting brown solution was added to a mixture of 4-bromoanisole (0.935 g, 5.0 mmol), phenylboronic acid (0.610 g, 5.0 mmol), and Cs_2CO_3 (3.258 g, 10 mmol) in 5 mL of dioxane, and the mixture was stirred at 50 °C for 3 h. Aliquots of 0.5 mL were removed at specified intervals, diluted with ∼10 mL of ethyl ether, filtered through a pad of Celite with 10−20 mL of ethyl ether, concentrated in vacuo to a solid, dissolved in 20 mL of toluene/hexadecane (0.0034 M), and analyzed by GC.

Utilizing $Pd(PPh_3)_4$. Under an atmosphere of argon, a solution of 4-bromoanisole (0.935 g, 5.0 mmol) in 5 mL of dioxane was added to a mixture of $Pd(PPh_3)_4$ (0.289 g, 0.25 mmol), phenylboronic acid (0.610 g, 5.0 mmol), and Cs_2CO_3 (3.258 g, 10 mmol) in 5 mL of dioxane, and the mixture was stirred at 50 °C for 3 h. Aliquots of 0.5 mL were removed at specified intervals, diluted with ∼10 mL of ethyl ether, filtered through a pad of Celite with 10−20 mL of ethyl ether, concentrated in vacuo to a solid, dissolved in 20 mL of toluene/hexadecane (0.0034 M), and analyzed by GC.

Utilizing $Pd(OAc)_2$. Under an atmosphere of argon, a solution of 4-bromoanisole (0.935 g, 5.0 mmol) and a phosphine (0.75 mmol; PPh_3, PCy_3, PBu^t_3) in 5 mL of dioxane was added to a mixture of $Pd(OAc)_2$ (0.056 g, 0.25 mmol), phenylboronic acid 0.610 g, 5.0 mmol), and Cs_2CO_3 (3.258 g, 10 mmol) in 5 mL of dioxane, and the mixture was stirred at 50 °C for 3 h. Aliquots of 0.5 mL were removed at specified intervals, diluted with ∼10 mL of ethyl ether, filtered through a pad of Celite with 10−20 mL of ethyl ether, concentrated in vacuo to a solid, dissolved in 20 mL of toluene/hexadecane (0.0034 M), and analyzed by GC.

Utilizing $Pd_2(dba)_3$. Under an atmosphere of argon, a solution of 4-bromoanisole (0.935 g, 5.0 mmol) and phosphine (0.5 mmol; PPh_3, PCy_3, PBu^t_3) in 5 mL of dioxane was added to a mixture of $Pd_2(dba)_3$ (0.114 g, 0.125 mmol), phenylboronic acid (0.610 g, 5.0 mmol), and Cs_2CO_3 (3.258 g, 10 mmol) in 5 mL of dioxane, and the mixture was stirred at 50 °C for 3 h. Aliquots of 0.5 mL were removed at specified intervals, diluted with ∼10 mL of ethyl ether, filtered through a pad of Celite with 10−20 mL of ethyl ether, concentrated in vacuo to a solid, dissolved in 20 mL of toluene/hexadecane (0.0034 M), and analyzed by GC.

Utilizing $[PdCl(\eta^3\text{-}C_3H_5)]_2$. Under an atmosphere of argon, a solution of 4-bromoanisole (0.935 g, 5.0 mmol) and phosphine (0.5 mmol of PBu^t_3) in 5 mL of dioxane was added to a mixture of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.0458 g, 0.125 mmol), phenylboronic acid (0.610 g, 5.0 mmol), and Cs_2CO_3 (3.258 g, 10 mmol) in 5 mL of dioxane, and the mixture was stirred at 50 °C for 3 h. Aliquots of 0.5 mL were removed at specified intervals, diluted with ∼10 mL of ethyl ether, filtered through a pad of Celite with 10−20 mL of ethyl ether, concentrated in vacuo to a solid, dissolved in 20 mL of toluene/hexadecane (0.0034 M), and analyzed by GC.

Utilizing $PdCl_2$. Under an atmosphere of argon, a solution of 4-bromoanisole (0.935 g, 5.0 mmol) and phosphine (0.5 mmol of PBu^t_3) in 5 mL of dioxane was added to a mixture of $PdCl_2$ (0.0443 g, 0.25 mmol), phenylboronic acid (0.610 g, 5.0 mmol), and Cs_2CO_3 (3.258 g, 10 mmol) in 5 mL of dioxane, and the mixture was stirred at 50 °C for 3 h. Aliquots of 0.5 mL were removed at specified intervals, diluted with ∼10 mL of ethyl ether, filtered through a pad of Celite with 10−20 mL of ethyl ether, concentrated in vacuo to a solid, dissolved in 20 mL of toluene/hexadecane (0.0034 M), and analyzed by GC.

■ AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

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(5) A search, using the keyword "Suzuki", of the 2010 issues of *Organic Letters* turned up 323 hits. These were sorted by relevance, and the first 80 were perused. Of these, about 50 described Pd(0)-catalyzed cross-coupling reactions and of these only 1 utilized a preformed catalyst, Pd(PBu$^t_3$)$_2$. Of the remaining hits, 26 (52%) utilized Pd(PPh$_3$)$_4$, 9 (18%) utilized Pd$_2$(dba)$_3$, 11 (22%) utilized Pd(OAc)$_2$, and 21 (42%) utilized preformed PdCl$_2$L$_2$ or a combination of PdCl$_2$ and L. Note that PdCl$_2$ reacts readily with e.g. PPh$_3$; see: Kalek, M.; Stawinski, J. *Organometallics* **2007**, *26*, 5840.

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