# **ORGANOMETALLICS**

# $Pd(\eta^{3}-1-PhC_{3}H_{4})(\eta^{5}-C_{5}H_{5})$ , an Unusually Effective Catalyst Precursor for Heck–Mizoroki and Sonogashira Cross-Coupling Reactions Catalyzed by Bis-Phosphine Palladium(0) Compounds

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**Supporting Information** 

**ABSTRACT:** The compound  $Pd(\eta^{3}-1-PhC_{3}H_{4})(\eta^{5}-C_{5}H_{5})$  reacts essentially quantitatively with a variety of phosphines L to form cross-coupling catalysts of the type  $PdL_{2}$  and has recently been shown to be a much more effective catalyst precursor for Suzuki–Miyaura cross-coupling Pt reactions in comparison to more commonly utilized precursors such as  $Pd(PPh_{3})_{4}$ ,  $Pd_{2}(dba)_{3}$ ,



and  $Pd(OAc)_2$ , which do not effectively generate two-coordinate species  $PdL_2$ . This advantage is expected to apply also to e.g. Heck-Mizoroki and Sonogashira cross-coupling reactions, both of which are generally believed to be catalyzed by species of the type  $PdL_2$ . Therefore, comparisons of the efficacies of catalyst systems based on  $Pd(\eta^3-1-PhC_3H_4)(\eta^5-C_5H_5)$ ,  $Pd(PPh_3)_4$ ,  $Pd_2(dba)_3$ , and  $Pd(OAc)_2$  are made utilizing the conventional coupling reactions of aryl halides with methyl acrylate and styrene for Heck–Mizoroki coupling and with phenylacetylene for Sonogashira coupling. As anticipated, catalyst systems based on  $Pd(\eta^3-1-PhC_3H_4)(\eta^5-C_5H_5)$  are found to be significantly more active.

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<sub>2</sub> (L = phosphine ligand).<sup>1</sup> Of these, the Heck-Mizoroki (eq 1)<sup>2</sup> and Sonogashira (eq 2)<sup>3</sup> cross-coupling reactions are of particular importance for the formation of  $C(sp^2)-C(sp^2)$ and  $C(sp^2)-C(sp)$  bonds, respectively.

$$ArX + CH_2 = CHAr' \rightarrow ArCH = CHAr'$$
(1)

$$ArX + RC \equiv CH \rightarrow RC \equiv CAr$$
(2)

The basic catalytic cycles are shown in Scheme 1, although many variations, some controversial, on these general



mechanistic themes have been proposed. In addition, a variety of cocatalysts have been utilized but their general applicability is not always clear. Therefore, for clarity, their potential roles are not reflected in Scheme 1.

Unfortunately, the catalytically active PdL<sub>2</sub> species are both air-sensitive and highly reactive, with the result that they are rarely used directly in practice. Instead, a majority of palladiumcatalyzed cross-coupling studies have utilized much more easily manipulated catalyst precursors such as  $Pd(PPh_3)_4$  (I),  $Pd_2(dba)_3$  (II; dba = dibenzylideneacetone),  $PdCl_2$  (III), and/or  $Pd(OAc)_2$  (IV), the last three in the presence of added ligand.<sup>1-3</sup> However, as we have recently commented,<sup>4a</sup> these precursors actually produce not the desired, oft presumed  $PdL_{2}$ , but rather the more sterically hindered three-coordinate Pd(0)complexes  $PdL_2L'$ , where  $L' = PPh_3$  (I), dba (II),  $Cl^-$  (III),  $OAc^{-}$  (IV). Furthermore, although catalytically active Pd(0)systems can be formed by reacting III and IV with many tertiary phosphines,<sup>1-4a</sup> there is little evidence in the literature that reductions of the palladium(II) precursors are ever effected either rapidly or completely with the majority of phosphines utilized.

The question arises then, if one particular palladium-based cross-coupling catalyst system is found to be more effective than another, does the difference arise because one phosphine is intrinsically superior, as seems generally thought? Conversely, does the difference arise because one type of three-coordinate Pd(0) species is inherently more reactive than another or, simply, because the Pd(II) precursor used is reduced more effectively by one phosphine than by another? These questions

Received: November 10, 2012 Published: December 24, 2012 seem, by and large, not to have been answered, and it follows that a significant number of the cross-coupling studies reported may not have made optimal use of the palladium added. The result could be unnecessarily high reaction temperatures or unnecessarily long reaction times and/or yields lower than would be possible if specifically  $PdL_2$  were used. In addition, it follows that conclusions based on comparative studies involving different precursors may not always be valid.

A simple, quantitative, unequivocal route for the synthesis of catalysts  $PdL_2$  has therefore been desirable for some time, and to this end we have previously advocated the use of the compound  $Pd(\eta^3-1-PhC_3H_4)(\eta^5-C_5H_5)$  (V), which reacts rapidly with a large number of phosphines L to form the compounds  $PdL_2$  (eq 3).<sup>4</sup> Compound V is easily synthesized and is stable to heat and in air (even in solution for hours); it is thus very "user friendly".

$$Pd + 2L \longrightarrow PdL_2 + C_{14}H_{14}$$
(3)

As part of an investigation to test the hypothesis that V is superior to the commonly used catalyst precursors I-IV in its ability to form  $PdL_2$  and hence generate catalytically active solutions for cross-coupling reactions, we have previously compared V with I-IV as catalyst precursors for the Suzuki– Miyaura cross-coupling reaction.<sup>4a</sup> We confirmed that combinations of V with the representative phosphines  $PPh_3$ ,  $PCy_3$ , and  $PBu_3^t$  do indeed 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 V generates catalytically active species  $PdL_2$  quickly and quantitatively while, in contrast, the others do not for various reasons.<sup>4</sup>

Since our initial disclosure of the merits of utilizing V for synthesis of palladium(0) compounds,<sup>4b</sup> others have also demonstrated its utility. Thus, Bauer et al. found V to be useful for the high-yield synthesis of a heteroleptic (phosphine)(NHC)Pd<sup>0</sup> compound, Pd(PCy<sub>3</sub>)(*N*,*N'*-bis(*tert*butyl)-imidazol-2-ylidene);<sup>5a</sup> other precursors resulted in the formation of mixtures. Similarly, Saget et al. found V to be "the best" precursor for the synthesis of palladium(0) complexes containing a series of new electron-rich phosphines, used as catalysts for enantioselective  $C(sp^3)$ –H functionalization.<sup>5b</sup> Finally, and in a direct comparison, Hanthorn et al. demonstrated that the V/XPhos catalyst system is much more effective for a series of Buchwald–Hartwig amination reactions than is the more conventional II/XPhos catalyst system.<sup>5c,d</sup>

As an extension of our previous work<sup>4a</sup> and to assess further the general efficacy of V, we now report preliminary findings of an investigation in which we compare the effectiveness of V with those I, II, III, and/or IV for Heck–Mizoroki and Sonogashira cross-coupling reactions (eqs 1 and 2). To begin, we selected the representative Heck–Mizoroki cross-coupling reaction of chlorobenzene with methyl acrylate to form *trans*methyl cinnamate (eq 4).

PhCl + CH<sub>2</sub>=CHCO<sub>2</sub>Me → *trans*-PhCH=CHCO<sub>2</sub>Me
$$(4)$$

We utilized PBu<sup>t</sup><sub>3</sub>, as we had previously found this ligand to be particularly effective for Suzuki–Miyaura cross-coupling reactions;<sup>4a</sup> in addition, the II/PBu<sup>t</sup><sub>3</sub> catalyst system is known to be relatively effective for Heck–Mizoroki cross-coupling reactions.<sup>6</sup> Shown in Figure 1 are reaction profiles for the



**Figure 1.** Reaction profile showing the conversion to methyl cinnamate from the cross-coupling of chlorobenzene and methyl acrylate utilizing (a)  $\mathbf{V} + 2PBu_{3}^{t}$  (b)  $\mathbf{II} + 4PBu_{3}^{t}$  and (c)  $\mathbf{IV} + 3PBu_{3}^{t}$ .

formation of methyl cinnamate using V, II, and IV, each activated with the appropriate amount of  $PBu_{3}^{t}$ , at 95 °C; see the Supporting Information for experimental details.

As can be seen, catalyst efficacies vary in the order  $V/PBu_3^t > II/PBu_3^t \gg IV/PBu_3^t$ , as found previously for Suzuki–Miyaura coupling by the same catalyst systems.<sup>4a</sup> We note also that the conversion data obtained utilizing the II/PBu\_3^t catalyst system are in reasonable agreement, given that reaction conditions are not precisely identical, with previous work involving the same substrates and the II/PBu\_3^t catalyst system.<sup>6</sup> A complementary cross-coupling study involving bromobenzene was carried out in DMF at 80 °C, and again V was by far the most superior catalyst precursor, giving ~90% conversion within 45 min, while catalysts based on II and IV resulted in <5% conversion. As before, we attribute the higher activity of the V/PBu\_3^t)<sub>2</sub>, is formed in much higher yields employing V.

An analogous cross-coupling study of bromobenzene with styrene (eq 5) to form *trans*-stilbene gave similar results at 80

$$PhBr + CH_2 = CHPh \rightarrow trans-PhCH = CHPh$$
 (5)

°C, with V taking the reaction to near completion (96%) within 30 min while, over the same time frame, II achieved only 30% conversion (1.5 h to reach completion). In contrast, IV produced only trace amounts of *trans*-stilbene over 30 min: 10% after 24 h (see the Supporting Information, Figure S1). Note that 1,1-diphenylethylene was at most a minor side product (<5%) in all cases.

We have also begun an investigation of the Sonogashira cross-coupling reaction of bromobenzene and phenylacetylene to form diphenylacetylene (eq 6).<sup>3</sup>

$$PhBr + PhC \equiv CH \rightarrow PhC \equiv CPh$$
(6)

Since much of the Sonogashira cross-coupling literature involves palladium-based catalyst systems containing PPh<sub>3</sub>, including the precursors  $Pd(PPh_3)_4$  (I) and  $PdCl_2(PPh_3)_2$  (i.e., III + 2PPh<sub>3</sub>),<sup>3</sup> our investigation focused initially on comparisons of the catalyst precursors I, II, preformed

 $PdCl_2(PPh_3)_2$ , IV, and V with II, IV, and V at 50 °C, all activated with PPh<sub>3</sub>. The reaction profiles utilizing the various catalyst precursors are shown in Figure 2.



**Figure 2.** Yields of diphenylacetylene from the cross-coupling of phenylacetylene and bromobenzene catalyzed by 1 mol % Pd catalyst systems utilizing (a)  $V + 2PPh_3$ , (b)  $IV + 3PPh_3$ , (c)  $PdCl_2(PPh_3)_2$ , (d) I, and (e) II + 4PPh<sub>3</sub> at 50 °C.

As can be seen, the combination of V and PPh<sub>3</sub> resulted in near-quantitative formation of diphenylacetylene over ~24 h, while the other catalyst precursors were considerably less effective. Sonogashira cross-couplings are often carried out in the presence of Cu(I) salts as cocatalysts,<sup>3</sup> but utilization of the V/PPh<sub>3</sub> catalyst system induces high conversion in the absence of copper salts at mild temperatures.

We have also investigated briefly the effect of substituting PPh<sub>3</sub> by PBu<sup>t</sup><sub>3</sub>, which produces much more effective catalysts generally for Suzuki–Miyaura<sup>4a</sup> and Heck–Mizoroki<sup>7</sup> coupling reactions than does PPh<sub>3</sub>. Some improvement (>90% completion within ~12 h) in catalyst activity over the PPh<sub>3</sub> catalyst system was observed, as expected and consistent with results elsewhere for Sonogashira coupling (see the Supporting Information, Figure S2). Note also that the PBu<sup>t</sup><sub>3</sub> catalyst systems generated from the precursors II and IV were less effective, as anticipated. Interestingly, catalysis by the V/PBu<sup>t</sup><sub>3</sub> system at 100 °C resulted in essentially 100% conversion within 3 h, as did catalysis by the same system at 50 °C in the presence of 1 equiv of CuI. Essentially no homocoupled product, 1,4-diphenylbutadiyne, was formed in these reactions.

We continue our investigations of V as a uniquely efficient precursor for the generation of catalysts of the type  $PdL_2$  for cross-coupling reactions of various substrates with emphasis on more challenging substrates for Suzuki–Miyaura, Heck– Mizoroki, and Sonogashira reactions. Note that we are not claiming to have discovered the optimal *catalyst* for these crosscoupling reactions, only *an excellent procedure* for generating specifically catalysts of the type  $PdL_2$ , if these are what one wishes to employ. We are also investigating carbon– heteroatom coupling reactions and the use of copper(I) cocatalysts for Sonogashira cross-coupling reactions.

Our results clearly confirm our hypothesis that combinations of **V** with tertiary phosphines can generate catalyst solutions for Heck-Mizoroki and Sonogashira cross-coupling reactions which are much more active than analogous catalysts systems obtained using catalyst precursors **I**-**IV**. The results are consistent with previous findings for Suzuki-Miyaura crosscoupling reactions, and again the reason almost certainly lies in the fact that **V** generates catalytically active species  $PdL_2$  quickly and quantitatively while, in contrast, the others do not.

## ASSOCIATED CONTENT

#### **S** Supporting Information

Text and figures giving experimental procedures. This material is available free of charge via the Internet at http://pubs.acs. org..

#### AUTHOR INFORMATION

#### Notes

The authors declare no competing financial interest.

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