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A Highly Efficient, Practical, and General Route for the Synthesis of $(R_3P)_2Pd(0)$: Structural Evidence on the Reduction Mechanism of Pd(II) to Pd(0)

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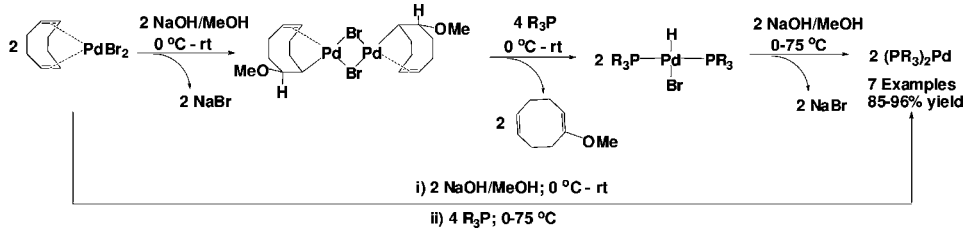
ABSTRACT



A highly efficient, practical, and general method was developed to synthesize a family of $(R_3P)_2Pd(0)$ complexes, using a stoichiometric amount of phosphine ligands and readily available Pd(II) precursors. The stepwise pathway of reducing Pd(II) to Pd(0) was established by isolating two key intermediates. Both $[t\text{-}Bu_2(4\text{-}Me_2NC_6H_4)P]_2Pd$ and $(t\text{-}Bu_2NpP)_2Pd$ are new compounds. Preliminary studies on $[t\text{-}Bu_2(4\text{-}Me_2NC_6H_4)P]_2Pd$ have indicated that it is a very active catalyst (84−95% isolated yield) in the Cu-free Sonogashira coupling involving aryl and heteroaryl chlorides at 0.5 mol % catalyst loading.

Over the past two decades, the palladium-catalyzed cross-coupling technology has emerged as one of the most powerful tools in organic synthesis, in both academia and industry.[1] Although both Pd(II) and Pd(0) complexes can facilitate the cross-coupling catalysis, it is well established that $L_nPd(0)$ (n = number of ligands) is the active species in the catalytic cycle.[1] However, the mechanism involving the reduction of $L_2Pd(II)$ to $L_2Pd(0)$ is not yet well understood, when $L_2Pd(II)X_2$ based precatalysts are used.[2] Due to practical and safety reasons, there is an increasing interest in using preformed $(R_3P)_2Pd(0)$ catalysts for cross-coupling reactions.[1b] To the best of our knowledge, there are not many examples of preformed $(R_3P)_2Pd(0)$ catalysts available commercially today. A few methods have been reported in the literature, which either lack generality or employ tedious isolation techniques.[3−5] For instance, the method employing $Pd(\eta_3\text{-}C_3H_5)(\eta_5\text{-}C_5H_5)$[3] as a precursor is not very practical, as it is not only unstable but also highly volatile,[4] while the route involving $Pd_2(dba)_3$[5] always requires recrystallization, with the use of a large amount of solvent under cryogenic conditions (e.g., purification of $(o\text{-}tol_3P)_2Pd$

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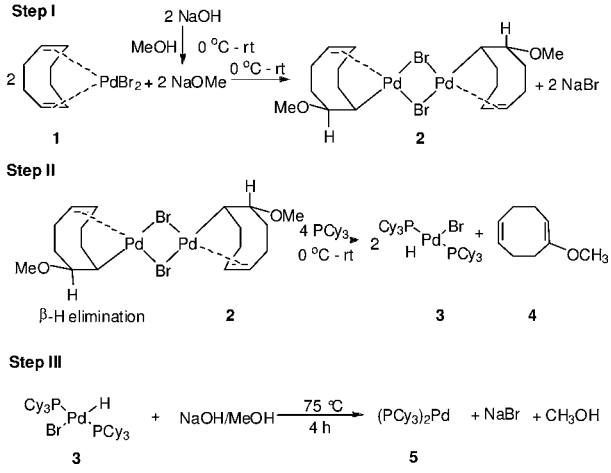
is very tedious). More recently, Pd(η_3-1-PhC$_3$H$_4$)(η_5-C$_5$H$_5$) has been reported[4] as a new precursor to generate L$_2$Pd(0) in situ, although its utility to synthesize the preformed catalysts has not been demonstrated.

Herein, we report a general route to various L$_2$Pd(0) catalysts in nearly quantitative yield on scale, specifically with sterically bulky, electron rich phosphines such as *t*-Bu$_3$P, Cy$_3$P, *o*-tol$_3$P, *t*-Bu$_2$PhP, *t*-Bu$_2$(4-Me$_2$NC$_6$H$_4$)P, (C$_5$H$_4$FeC$_5$Ph$_5$)(*t*-Bu)$_2$P (Q-Phos), and *t*-Bu$_2$NpP (Np = neopentyl).[6] This method uses readily available, inexpensive air-stable precursors (diene)PdBr$_2$ with a stoichiometric amount of phosphine ligand, in the presence of a Brønsted base (e.g., alkali hydroxides) in a protic solvent. In addition, this study also provides mechanistic insights into the reduction of Pd(II) to Pd(0) without the use of excess phosphine as a reducing agent.[2a]

Although the method that we have developed is applicable to synthesize a variety of L$_n$Pd(0) compounds, we chose (Cy$_3$P)$_2$Pd (**5**) as a model complex to understand the mechanism clearly, as its reaction rate was moderate enough to allow us to isolate the key intermediates, **2** and **3**. In the overall process (COD)PdBr$_2$ (**1**) was treated with NaOH in MeOH, and was subsequently reacted with Cy$_3$P to produce (Cy$_3$P)$_2$Pd (**5**).

Scheme 1. Stepwise Pathway To Form (Cy$_3$P)$_2$Pd (**5**)



Step I of Scheme 1 shows the reaction of (COD)PdBr$_2$ with NaOH in MeOH solution to form a dimeric Pd complex, **2**.[7] The molecular structure of organopalladium dimer **2** (Figure 1) reveals the oxypalladation of the COD via the nucleophilic attack of the MeO$^-$ anion at one of its double bonds. The C1−C2 bond length of 1.373 Å is typical of a C=C double bond, while the C5−C6 distance (1.512 Å) indicates clearly a C−C single bond. The Pd−C6 distance is 2.062 Å, typical of a Pd−C σ bond.

Step II is a stoichiometric reaction of **2** with Cy$_3$P (4 equiv) to form **3** and the oxidized byproduct, 1-methoxycycloocta-1,5-diene (**4**), and its minor isomer through β-hydride elimination.[8] Although the chloride analogues of **2**[9] and **3**[10] have been reported previously via a similar route, the poor solubility of the NaCl byproduct makes it impractical to isolate and purify the final L$_2$Pd(0) complexes by using the chloride analogue of the Pd precursor. Recently hydridopalladium halide complexes have been receiving much attention in mechanistic studies.[11] For example, (*t*-Bu$_3$P)$_2$Pd(H)(Cl), an analogue of **3**, has been identified as a key intermediate in the catalytic cycle of the Heck reaction[11b] and (*t*-Bu$_3$P)$_2$Pd(H)(Br) was proposed in the autocatalytic oxidative addition of PhBr to (*t*-Bu$_3$P)$_2$Pd(0),[11c] by Fu and Hartwig, respectively. The crystal structure of **3** is shown in Figure 2.

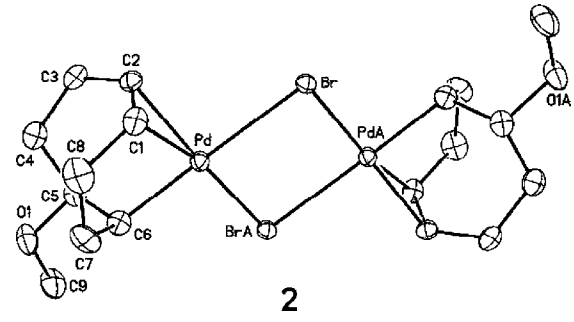


Figure 1. Molecular structure of **2**.[12]

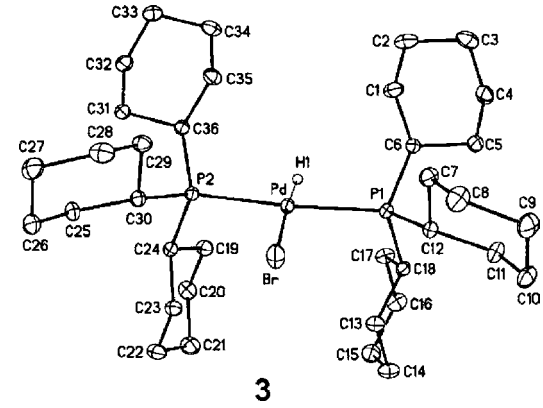


Figure 2. Molecular structure of **3**.[13]

It is interesting to note that the P(1)−Pd−P(2) angle is 163.38° in **3**, while it is 180.00° in the analogous chloride, (Cy$_3$P)$_2$Pd(H)(Cl),[11b] presumably reflecting the steric bulkiness of Br vs Cl. The (R$_3$P)$_2$Pd(H)(X) complexes are the resting state of the catalytic Heck reaction and their reduction to (R$_3$P)$_2$Pd(0) is not only dependent on the steric bulk of

(6) These catalysts are now commercially available.

(7) Other hydroxide bases such as KOH, LiOH, and Bu$_4$NOH in conjunction with a protic solvent or alkoxide bases without protic solvents can be used.

(8) In addition to **4**, a minor isomer was also detected due to β-H elimination from the adjacent positions of the Pd−C6 bond in **2** (see the Supporting Information).

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the phosphine ligand and the choice of base, as Fu demonstrated,[11b] but it may also depend on the nature of the halide ligand originating from the aryl halide.

As shown in Step III, 1 equiv of base was required to abstract HBr from **3** to generate $(Cy_3P)_2Pd(0)$.

In the actual one-pot procedure, the total amount of base required for the overall process was dissolved in a protic solvent and added up front to **1** in toluene. Upon generation of **2**, the reaction mixture was heated directly to obtain $(Cy_3P)_2Pd(0)$ in toluene without the isolation of **3**. The process is very efficient, where additional MeOH was added in the final step to precipitate/crystallize the product, while dissolving the NaBr byproduct, thereby avoiding any recrystallization. At room temperature, the reaction stopped at compound **3** despite the use of excess base.

In the overall process, the methoxy group generated in situ was transferred to the cyclooctadiene ligand to form the oxidized byproduct **4**, while Pd(II) was reduced to Pd(0), via β-H elimination followed by a base-assisted reductive elimination of HBr. This method does not require the use of excess expensive phosphine as a sacrificing reducing agent, thereby making the whole process highly efficient and atom-economical.[14] The method outlined above has been applied to a family of $(R_3P)_2Pd(0)$ complexes, but not limited to $L_2Pd(0)$.[15]

We also observed that Step III is the rate determining step, where the reaction rate appears to depend on the steric bulk of the phosphine in the following order: t-$Bu_3P \sim o$-$tol_3P \sim t$-$Bu_2NpP > t$-$Bu_2PhP >$ Q-Phos $\sim t$-$Bu_2(4\text{-}Me_2NC_6H_4)P > Cy_3P$. For example, the reaction took place at 75 °C in the case of Cy_3P and at room temperature for t-Bu_2PhP, while with the bulky t-Bu_3P and o-tol_3P ligands, the reaction proceeded even at 0 °C (Table 1).[16]

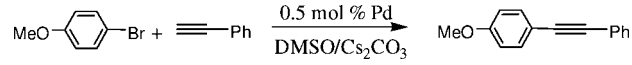
Table 1. Examples of $L_2Pd(0)$ Catalysts Synthesized

ligand (L)	temp (°C)	yield (%)[a]	^{31}P NMR (ppm)[b]
t-Bu_3P	0	95	86.5
t-Bu_2NpP	0	85	45.5
o-$tolyl_3P$	0	91	−7.3
t-Bu_2PhP	25	96	67.6
t-$Bu_2(4\text{-}Me_2C_6H_4)P$	60	85	64.5
Q-Phos	50	95	59.0
Cy_3P	75	85	39.2

[a] Isolated yields. [b] ^{31}P NMR chemical shifts of $L_2Pd(0)$ complexes.

Having developed a synthetic protocol for various $L_2Pd(0)$ complexes with the isolation of two new complexes, $[t$-$Bu_2(4\text{-}Me_2NC_6H_4)P]_2Pd$ and $(t$-$Bu_2NpP)_2Pd$, we decided to study their activities in catalysis. In this regard, we determined the X-ray crystal structure of $(t$-$Bu_2NpP)_2Pd$ catalyst and briefly studied its applications in the amination and α-arylation reactions with arylbromide and chloride substrates.[17] Of the known compounds, $(o$-$tol_3P)_2Pd$ was recently evaluated to be a very efficient precatalyst for amination/ammoniation of aryl tosylates[5a] and aryl halides[18] while $(t$-$Bu_3P)_2Pd$ is a popular third generation cross-coupling catalyst for several well-known coupling reactions involving challenging substrates such as aryl chlorides.[5c] In this study we also explored $[t$-$Bu_2(4\text{-}Me_2NC_6H_4)P]_2Pd$ catalyst for Cu-free Sonogashira reaction[19,20] of aryl bromides and found that it is the most active catalyst among the well-known preformed catalysts tested (Table 2). Using this information, we used $[t$-$Bu_2(4\text{-}Me_2NC_6H_4)P]_2Pd$ to couple aryl and heteroaryl chloride substrates with alkynes successfully using only 0.5 mol % catalyst loading, although higher temperature was required (Table 3). Noticeably, 0.5% catalyst loading is half of what

Table 2. Catalysts Screened for the Cu-Free Sonogashira Coupling of 4-Bromoanisole with Phenylacetylene for Comparison[a]



entry	catalyst	yield (%)[b]
1	$(t$-$Bu_3P)_2Pd$	73
2	$[Pd(\mu\text{-}Br)(t\text{-}Bu_3P)]_2$	61
3	$(PPh_3)_4Pd$	15
4	$Pd(PCy_3)_2Cl_2$	<5
5	$[t$-$Bu_2(4\text{-}Me_2NC_6H_4)P]_2Pd$	97

[a] Reaction conditions: 4-bromoanisole (1.5 mmol, 187 μL), phenylacetylene (1.8 mmol, 198 μL), 0.5 mol % Pd catalyst (7.5 μmol), Cs_2CO_3 (3.0 mmol, 977.5 mg), CH_3CN (2 mL), 80 °C, 4 h. [b] Isolated yields.

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(12) Thermal ellipsoids are shown at 50% probability (hydrogen atoms were omitted for clarity). Selected bond distances (Å) and angles (deg): C1−C2, 1.373(9); C5−C6, 1.512(9); Pd−C6, 2.062(7); Pd−Br, 2.644(1); Br−Pd−Br, 88.55(2); C1−Pd−C6, 281.1(3).

(13) Thermal ellipsoids are shown at 50% probability (hydrogen atoms were omitted for clarity). Selected bond distances (Å) and angles (deg): Pd−Br, 2.532(1); Pd−P1, 2.308(1); P1−Pd−P2, 163.38(2); P1−Pd−Br, 98.43(5).

(14) Other (diene)PdX_2 precursors such as $(NBD)PdBr_2$ also work effectively.

(15) This method was also tested to make $Pd(PPh_3)_4$ successfully.

(16) (a) All complexes were isolated in excellent purity as determined by elemental analysis and NMR. (b) ^{31}P NMR of $(o$-$tol_3P)_2Pd$ showed phosphine dissociation in solution. The extent of phosphine dissociation was found to be dependent on the concentratration of the complex, temperature, and the presence of air in the deuterated solvent. This observation is similar to the case of $Pd(PPh_3)_4$. (c) $(Q\text{-}Phos)_2Pd$ is a very insoluble compound in most common organic solvents, hence its ^{1}H NMR spectrum does not reflect the purity of the compound.

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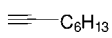
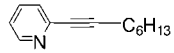
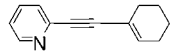
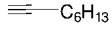
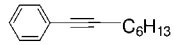
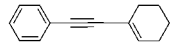
Table 3. Sonogashira Reactions of Aryl and Heteroaryl Chlorides with [*t*-Bu_2(4-$Me_2NC_6H_4$)P]$_2$Pd Catalyst

entry	substrate	alkyne	product	yield[a]
1				94
2				90
3				91
4				85

[a] Isolated yields. Reaction conditions: substrate (1.5 mmol), alkyne (1.8 mmol), 0.5 mol % of [*t*-Bu_2(4-$Me_2NC_6H_4$)P]$_2$Pd catalyst (7.5 μmol, 5.3 mg), Cs_2CO_3 (3.0 mmol, 977.5 mg), DMF (2 mL), 120 °C, 5 h.

is used in one of the most active in situ homogeneous catalyst systems reported so far,[20f] with no excess ligand being used.

In conclusion, we have demonstrated a highly efficient, general, and practical one-pot method for a family of (R_3P)$_2$Pd(0) complexes, using a stoichiometric amount of phosphine ligands and readily available air-stable Pd(II) precursors. The mechanistic stepwise pathway described in this study may throw more light upon the basic understanding of the reduction mechanism of L_nPd(II) to L_nPd(0) during catalysis as well as the intermediate formation in the catalytic cycle. The new L_2Pd(0) catalysts are being currently tested in various cross-coupling reactions. Preliminary results show that the [*t*-Bu_2(4-$Me_2NC_6H_4$)P]$_2$Pd has very good activity in a Cu-free Sonogashira reaction. Similarly ongoing work in our laboratory shows that (Cy_3P)$_2$Pd is a very selective catalyst for coupling of an aryl triflate in the presence of a chloride, while (*t*-Bu_3P)$_2$Pd exibits an opposite trend, as observed by Fu for the in situ systems.[21] More work is underway in this direction to expand the scope of the reactions.

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Supporting Information Available: Experimental procedures, characterization data, and X-ray crystallographic data of **2** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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