

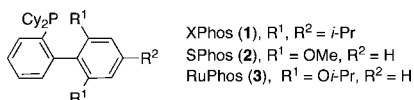
A New Class of Easily Activated Palladium Precatalysts for Facile C–N Cross-Coupling Reactions and the Low Temperature Oxidative Addition of Aryl Chlorides

Mark R. Biscoe, Brett P. Fors, and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received February 25, 2008; E-mail: sbuchwal@mit.edu

Although phosphine-ligated Pd(0) complexes constitute the active catalysts in many C–N bond-forming cross-coupling methodologies,^{1,2} such complexes are usually difficult to prepare and extremely air-sensitive. Pd₂(dba)₃, developed as a stable source of Pd(0), includes coordinating dba ligands that can significantly retard the formation of active catalyst and/or diminish its reactivity.³ The use of a Pd(II) salt such as Pd(OAc)₂, which circumvents problems of precatalyst instability, requires in situ reduction in order to generate the active Pd(0) complex. In light of the complications in forming phosphine-ligated Pd(0) complexes, we sought to develop a precatalyst scaffold constituting the source of Pd and phosphine ligand, which could form the active, monoligated Pd complex under mild conditions and without the need for exogenous additives.⁴ Herein, we report the development of a new class of air- and moisture-stable, one-component, Pd precatalysts that is activated under standard reaction conditions and ensures the formation of the active, L₁Pd(0) (L = biarylphosphine) complex. We also demonstrate these precatalysts to be convenient Pd sources for facile C–N bond-forming reactions. Finally, we show the efficient oxidative addition of PhCl to a LPd(0) complex at –40 °C.



Our group has recently reported the isolation of a phosphine-ligated Pd(II) complex bearing a free amine.⁵ Building on this result, we proposed that an intramolecularly coordinated amine complex would provide a stable, monoligated Pd precatalyst. Precatalysts bearing ligands **1**,^{6a} **2**,^{6b} and **3**,^{6c} (**4**, **5**, and **6**, respectively) were prepared in excellent yields via the route illustrated in Figure 1. Yields of >85% were obtained for each step of this sequence without the need for a glovebox and using only recrystallization for purification. The X-ray crystal structure of **5** is shown in Figure 2. Calorimetric analysis (Figure 2) shows that activation of **4–6** is complete after ca. 3 min when the complexes are treated with NaO-*t*-Am in dioxane at rt. In general, this activation process occurs readily with weak bases (e.g., K₂CO₃) at 80 °C, with alkoxide bases at room temperature, and with HMDS bases at –20 °C, as judged by ³¹P NMR.

Figure 3 shows the progress of cross-coupling reactions of 4-chloroanisole and aniline using 0.1% Pd at 80 °C employing ligand **1** with different Pd sources and different methods of activation. The use of Pd(OAc)₂/PhB(OH)₂,^{6a} [Pd(allyl)Cl]₂, and Pd₂dba₃ as the Pd source effects a maximum conversion of ca. 25% before loss of catalytic activity. However, the use of **4** allows complete conversion to be achieved in 35 min. These results demonstrate the limitations of Pd(II) activation methods and the deleterious nature of the dba ligand in cross-coupling reactions. Using precatalyst **4**, a highly active, L₁Pd(0) complex is readily accessed in the absence of potentially inhibitory complexing ligands and without the need for exogenous additives.

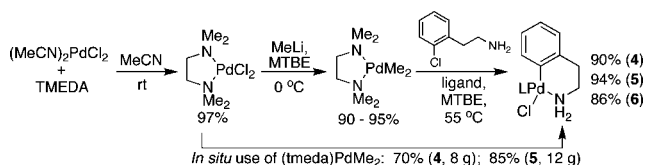


Figure 1. Synthesis of precatalysts **4–6**.

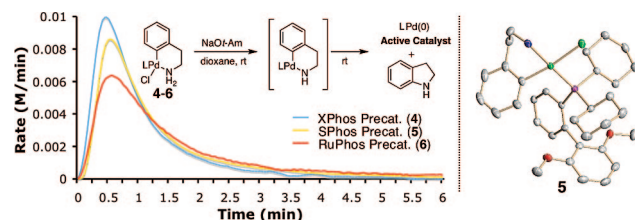


Figure 2. Calorimetric scans of the addition of precatalysts **4–6** to NaO-*t*-Am in dioxane at room temperature; X-ray crystal structure of **5**.

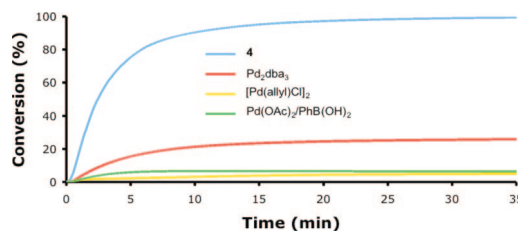
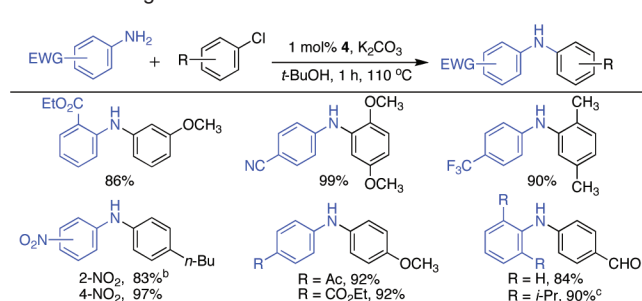


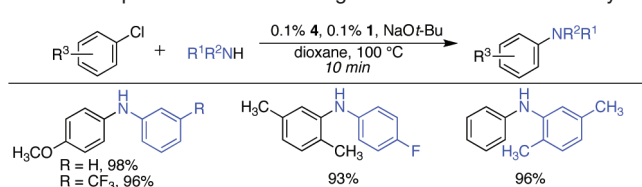
Figure 3. Effect of Pd source on the cross-coupling of aniline and 4-chloroanisole using 0.1% Pd and ligand **1** at 80 °C.

Because of their low nucleophilicity, electron-deficient anilines are typically difficult substrates to employ in C–N cross-coupling reactions. Using **4**, numerous highly electron-deficient anilines were successfully coupled with unactivated aryl chlorides in excellent yields (Table 1). 2-NO₂, 2-CO₂Et, 4-CF₃, and 4-CN anilines had not been previously employed in C–N cross-coupling reactions involving aryl chlorides. Further, we have achieved the first C–N cross-coupling reactions of anilines with aryl chlorides bearing unprotected aldehydes. The success of these reactions reveals the advantages of using a highly reactive Pd source in C–N cross-coupling reactions.

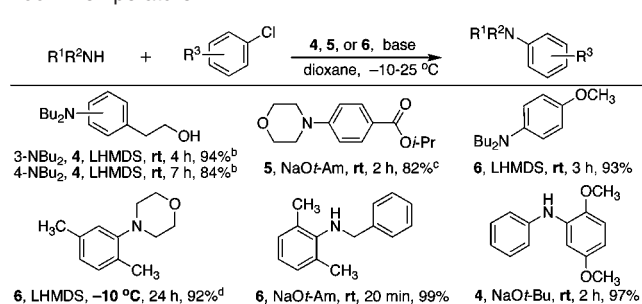
The ability to achieve high yields from cross-coupling reactions using low catalyst loadings with short reaction times is of great synthetic importance. Table 2 shows the use of **4** in several C–N cross-coupling reactions of unactivated aryl chlorides with anilines using 0.1 mol % of Pd. Few examples of C–N cross-coupling reactions using anilines have been previously demonstrated using catalyst loadings of less than 1 mol % of Pd. The products displayed in Table 3 are each obtained in excellent yield in fewer than 10 min despite the use of such low catalyst loadings.

Table 1. Cross-Coupling Reactions of Electron-Deficient Anilines with ArCl Using a Weak Base^a

^a ArCl (1 mmol), amine (1.2 mmol), K₂CO₃ (1.4 mmol); average isolated yields of two runs. ^b Reaction time = 2 h. ^c Using precatalyst 6.

Table 2. Rapid C–N Bond-Forming Reactions with 0.1% Catalyst^a

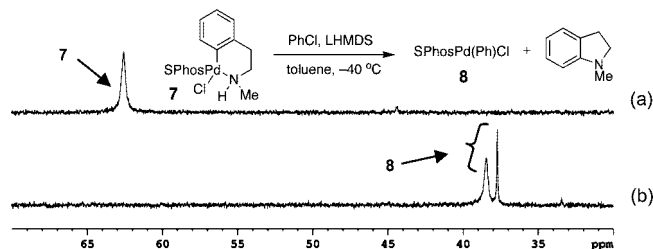
^a ArCl (1 mmol), amine (1.2 mmol), base (1.2 mmol); average isolated yields of two runs.

Table 3. C–N Bond-Forming Reactions Using ArCl at or below Room Temperature^a

^a ArCl (1 mmol), amine (1.2 mmol), base (1.2 mmol); average yield of two runs. ^b LHMDS (2.4 mmol). ^c NaOt-Am (1.02 mmol). ^d In DME.

To show the ease with which 4–6 can be activated, we performed numerous C–N cross-coupling reactions at or below room temperature (Table 3). These precatalysts are particularly useful for substrate combinations that are incompatible with elevated reaction temperatures. Previously, 4 days were required to achieve a 61% yield in the formation of the coupling product of dibutylamine and 3-chlorophenethyl alcohol.⁷ Using 4, we can now obtain an isolated yield of 94% in only 4 h. Similarly, the less reactive 4-chlorophenethyl alcohol can now be successfully employed as an analogous reaction. In addition, we have successfully demonstrated the compatibility of esters of secondary alcohols in room temperature cross-coupling reactions using an alkoxide base. Our ability to perform amination reactions of an aryl chloride at –10 °C further illustrates the ease with which these precatalysts undergo activation.

To demonstrate the reactivity of a L₁Pd(0) complex in the absence of competitive coordinating ligands, we prepared the *N*-Me derivatives of precatalysts 5 and 4 (7 and 9, respectively).⁸ As shown in Figure 4, chlorobenzene undergoes facile oxidative addition to SPhosPd(0) generated by deprotonation of 7 at –40 °C.⁹ This suggests that aryl chlorides should be usable in low-temperature C–C cross-coupling reactions using precatalysts 4–6. Previously, only aryl iodides have been employed in cross-coupling reactions conducted at such low temperatures.¹⁰

**Figure 4.** ³¹P{¹H} NMR spectra of (a) 7 in toluene/PhCl at –40 °C and (b) 7 in toluene/PhCl w/LHMDS (1 equiv) after 110 min at –40 °C.

The ability to generate L₁Pd(0) complexes in the absence of competing ligands is also very useful for mechanistic investigations. Precatalyst 9 was employed at room temperature to conduct a direct Hammett study of the oxidative addition of aryl chlorides to the XPhosPd(0) complex (see Supporting Information). The slope of $\rho = +2.3$ for Hammett's correlation is consistent with results previously obtained from (PPh₃)₂Pd(0) with aryl iodides, suggesting a concerted three-centered transition state for oxidative addition.¹¹ This is the first information of this type available for the reaction of aryl chlorides with monodentate ligands.¹²

In summary, we have developed a new class of Pd precatalysts bearing biarylphosphine ligands that are particularly useful in cases where a highly active Pd complex is required to promote a difficult cross-coupling reaction or where functional group instability requires the use of low temperatures. We have additionally demonstrated that an unactivated aryl chloride can undergo oxidative addition to SPhosPd(0) at temperatures as low as –40 °C. The use of these precatalysts should greatly expand the general scope of Pd-catalyzed cross-coupling reactions.

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Supporting Information Available: Procedural, spectral, and crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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