Palladium Catalysis

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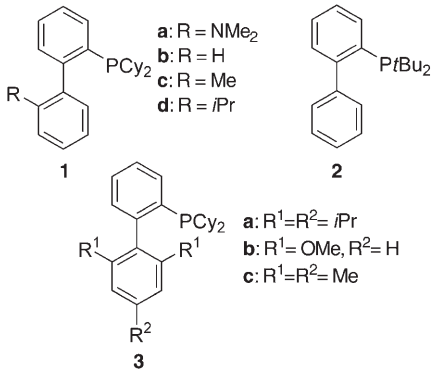
Evidence for the Formation and Structure of Palladacycles during Pd-Catalyzed C–N Bond Formation with Catalysts Derived from Bulky Monophosphinobiaryl Ligands**

*Eric R. Strieter and Stephen L. Buchwald**

One of the most general catalyst systems, in terms of their efficacy in C–C, C–N, and C–O bond-forming reactions, are those based on the bulky, electron-rich monophosphinobiaryl ligands (Scheme 1).[1] First introduced in 1998, the Pd^0 catalyst



Scheme 1. Bulky, electron-rich monophosphinobiaryl ligands used in Pd-catalyzed C–C, C–N, and C–O bond-forming reactions. Cy = cyclohexyl.

based on **1a** demonstrated exceptionally high activity, thereby allowing room-temperature Suzuki–Miyaura couplings of aryl bromides and chlorides as well as room-temperature aminations of aryl bromides, including the first room-temperature amination of an aryl chloride.[2] While searching for catalysts that display higher turnover numbers (TONs) than those observed with **1a**, ligand **2** was discovered, thus further expanding the scope of these cross-coupling reactions.[3] More recently, with the introduction of **3a** and **3b** into this class of ligands, the most general and active catalyst systems to date for Suzuki–Miyaura couplings, C–N bond-forming reactions, and Sonogashira reactions with aryl chlorides and tosylates have been revealed.[4]

[*] Dr. E. R. Strieter, Prof. Dr. S. L. Buchwald
Department of Chemistry
Room 18-490, Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
Fax: (+1) 617-253-3297
E-mail: sbuchwal@mit.edu

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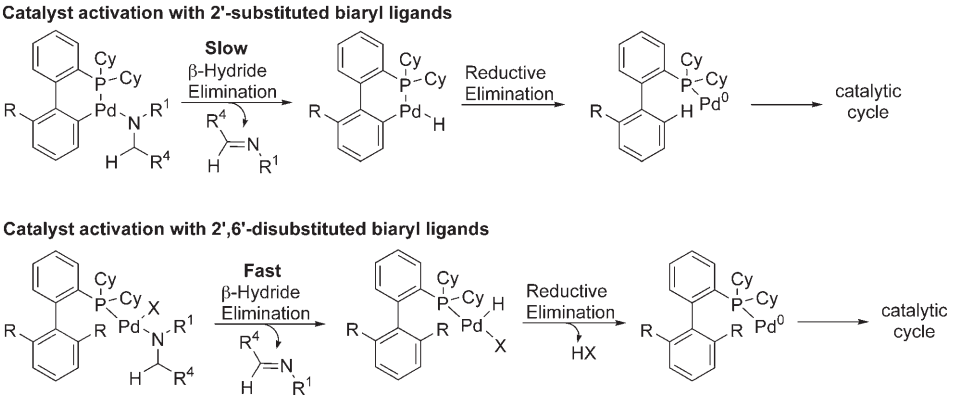
A recent mechanistic investigation of the Pd-catalyzed C–N bond formation has indicated that substituents at the *ortho* position of the bottom ring of the monophosphinobiaryl ligand play a critical role in the determination of both the activity and stability of the catalyst.[5] More specifically, the size of the substituent dictates catalyst activity, with larger substituents (namely, *i*Pr) leading to the most active catalysts.[6] Interestingly, catalysts derived from ligands with only one *ortho* substituent on the non-phosphorus-containing ring (that is, **1a–d**) exhibit remarkably different activities relative to those based on **3a**. Using the former catalyst systems, the reaction rate increases with TON, whereas in the latter case the reaction maintains a constant rate for each consecutive reaction. Although this difference in behavior was attributed to a slow activation process with catalysts based on **1a–d**, the structural origins of this discrepancy were not investigated. Our hypothesis is that Pd^{II} precatalysts have a tendency to form palladacycles when complexed with **1a–d**, which have previously been shown to result in a slow activation process (Figure 1).[7] In contrast, palladacycle formation would be prevented with ligands that lack *ortho* hydrogen atoms (2′,6′-disubstituted ligands) on the non-phosphorus-containing ring of the biaryl moiety (for example, **3a–c**), thus leading to the rapid formation of an active Pd^0 complex. The differences in the rate of activation may, in part, arise from the difference in the rate of β-hydride elimination (Scheme 2).[8] This process may be much faster in the case of catalysts derived from 2′,6′-disubstituted ligands than those based on 2′-substituted ligands, in which palladacycles may form. This reasoning is based on the observation that a small primary kinetic isotope effect is observed during the activation process with catalysts based on 2′-substituted ligands.[5]



Scheme 2. Catalyst activation with 2′-substituted and 2′,6′-disubstituted biaryl ligands.

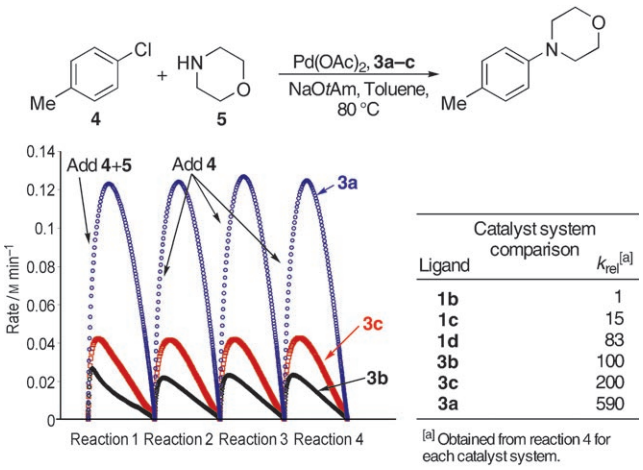
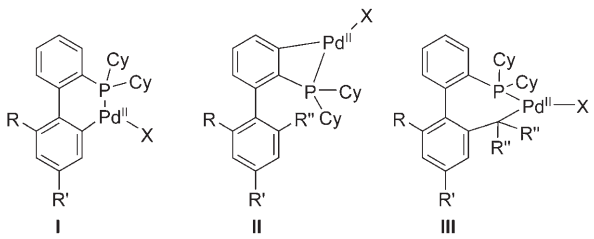


Figure 1. Sequential reaction experiment for the amination of *p*-chlorotoluene (**4**) ($4\times[\mathbf{4}]_o = 0.15$ M) with morpholine (**5**) ($[\mathbf{5}]_o = 0.74$–0.78 M). Conditions: $[NaOtAm]_o = 0.8$ M; blue data points: $[Pd(OAc)_2] = 4.2$ mM, $[\mathbf{3a}] = 12.7$ mM; red data points: $[Pd(OAc)_2] = 8.3$ mM, $[\mathbf{3c}] = 25$ mM; black data points: $[Pd(OAc)_2] = 8.3$ mM, $[\mathbf{3b}] = 25$ mM. Note: the L/Pd ratio is 3:1 for all of these reactions. *t*Am = *tert*-amyl.

The differences in reaction rates for catalytic systems generated from biaryl ligands **3a–c**, all of which are 2′,6′-disubstituted ligands, were determined by monitoring sequential reactions by reaction calorimetry to examine whether it is the size, substitution pattern, or both that controls the rate of catalyst activation. The coupling of *p*-chlorotoluene (**4**) with morpholine (**5**) in toluene at 80 °C was used as a model system.[5] The reactions were carried out with four consecutive injections of the reactants into a solution containing $Pd(OAc)_2$, biaryl ligand, and NaO*t*Am equilibrated at 80 °C for 1 h. The first injection contained a mixture of **5** (0.78 M) and **4** (0.15 M), whereas the subsequent injections contained an aliquot of **4** (0.15 M). The activity of catalysts based on **3a–c** is compared in Figure 1, in which the reaction rate is plotted as a function of reaction progress for a four-reaction sequence. The reaction rates follow a similar trend seen before, in which the larger the substituent on the bottom ring the more active the catalyst. Furthermore, each of these catalyst systems are more active than those based on **1a–d**, as evidenced by the k_{rel} values obtained for each catalyst system (also shown in Figure 1). Most importantly, however, the reaction maintains a constant rate for each consecutive reaction, consistent with a rapid catalyst-activation process. This behavior is in direct contrast to that observed for the catalysts derived from **1a–d**, in which the reaction rate increases with each consecutive reaction. Thus, not only does the size of the substituent on the bottom ring of the biaryl unit dictate the activity of the catalyst, but the substitution pattern also controls the rate at which the catalyst is activated.

As the two classes of ligands afford two distinct patterns in their reaction-rate profiles, we sought to test whether the origin of this divergence arises from the formation of palladacycle intermediates.[7] The possible palladacycles that may form with these ligands are shown in Scheme 3. In the first case, a six-membered palladacycle **I** is formed through an attack on the coordinated Pd^{II} center by the bottom ring of the biaryl ligand. Significantly, a similar palladacycle has been successfully employed as a single-component catalyst for Pd-

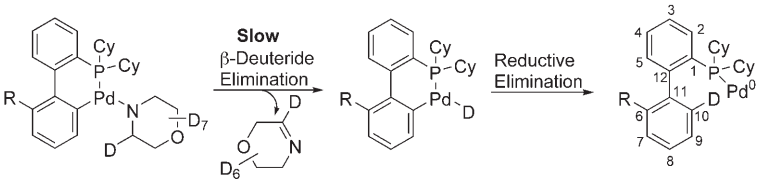


Scheme 3. Structures of potential palladacycles.

catalyzed amination processes.[9] In the second case, the top ring of the biaryl ligand attacks the Pd^{II} center in a similar fashion to that described for **I**, thus generating a four-membered ring palladacycle **II**.[10] Furthermore, on the basis of several studies that demonstrate the potential of Pd^{II}-mediated cleavage of sp^3 C–H bonds, **III** is also a potential intermediate.[11] Taking into consideration the substitution pattern of the two ligand classes, it would appear that the 2′,6′-disubstituted ligands are incapable of forming the first type of palladacycle, whereas all three types of complexes are possible with the 2′-substituted ligands.

To probe the existence and nature of the palladacycle intermediate, [D$_8$]morpholine ([D$_8$]**5**) was employed as the substrate and the extent of deuterium incorporation into the bottom ring of the monophosphinobiaryl was determined. If palladacycle formation occurs and the mechanism is consistent with an amine-induced pathway, then deuterium incorporation into the ligand should be observed with the 2′-substituted ligands (Scheme 4; a similar mechanism can be proposed for the four-membered ring palladacycles). With the use of 2′,6′-disubstituted ligands, however, deuterium incorporation should not occur as palladacycles are absent in this case. Importantly, Louie and Hartwig postulated a similar mechanism for the formation of Pd^0 from palladacycles derived from P(*o*-tolyl)$_3$; however, the relevance of these palladacycles to the catalytic process was not established.[12] The N-arylation of [D$_8$]morpholine was performed under the standard conditions. However, 1,2-bis(diphenylphosphino)ethane (dppe) was added at the end of the reaction to sequester the Pd and facilitate the separation of the monophosphinobiaryl ligand to investigate the isotopic incorporation.

^{2}H NMR, ^{13}C NMR, and ^{1}H NMR spectroscopic analysis was used upon isolation to analyze the free ligand. As indicated by ^{2}H NMR spectroscopy, **3a–c**, all of which are 2′,6′-disubstituted ligands, did not contain deuterium.[13] This observation was subsequently validated by mass-spectrometric analysis. In contrast, the ^{2}H NMR spectroscopic and mass-spectrometric analysis for both **1c** (6% ^{2}H-labeled)[14] and **1d** (15% ^{2}H-labeled)[14] displayed the presence of deuterium, thus confirming our original hypothesis that palladacycles do form with these precatalysts. Furthermore, the presence of a single resonance in the ^{2}H NMR spectrum indicates that a single carbon atom had been isotopically labeled. The chemical shift of this atom ($\delta =$ 7.07 ppm) rules out the possible formation of palladacycle **III**.



Scheme 4. Mechanism for deuterium incorporation into the monophosphinobiaryl ligands.

Two additional pieces of information allowed us to deduce which carbon atom was isotopically labeled. The first was the observation that the doublet ($J_{C\text{-}P} = 6.3$ Hz) at $\delta = 144$ ppm and the singlet at $\delta = 125$ ppm in the ^{13}C{^{1}H} NMR spectrum of the labeled material split into two sets of new peaks approximately 0.1 ppm upfield from the unlabeled resonances (Figure 2, labeled C11 w/C10-H/D and C9 w/C10-H/D). The appearance of these peaks is common with ^{13}C NMR isotope effects for the carbon atom two bonds away from the deuterium label.[17] The second piece of evidence was

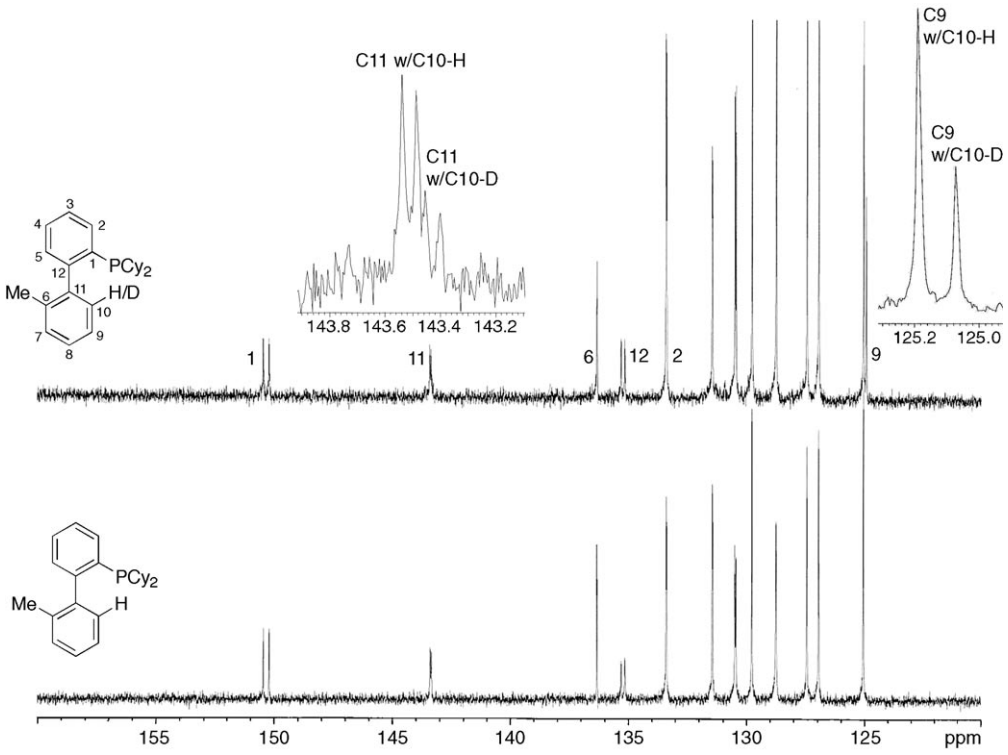


Figure 2. ^{13}C NMR spectroscopic data for ^{2}H-labeled **1c** (top) and unlabeled **1c** (bottom).

provided by 2D NMR experiments, in which the combination of HMQC and TOCSY experiments established that the carbon atoms experiencing an isotope effect reside on the same ring as the proton that decreases in intensity upon ^{2}H labeling ($\delta = 7.05$ ppm in the ^{1}H NMR spectrum). Similar results were obtained with **1d** (see the Supporting Information). Taken together, these data demonstrate that palladacycle formation occurs with the biaryl ligands containing *ortho* hydrogen atoms on the non-phosphorus-containing ring, whereas with the ligands lacking *ortho* hydrogen atoms it does not. Furthermore, the data support the formation of a palladacycle of type **I**.

In summary, we have provided evidence that palladacycles can form during the course of a Pd-catalyzed C–N bond-forming reaction through the use of isotope-labeling studies. This study provides insight into the structural origins of the differences in the catalytic activities observed between the catalysts containing 2′-substituted and 2′,6′-disubstituted biaryl ligands. Specifically, through the use of 2′,6′-disubstituted biaryl ligands palladacycle formation is avoided and optimal catalyst activity is achieved.

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[16] Although the resonance corresponding to C10 should also split into an observable 1:1:1 triplet, the intensity and $T1$ value may prevent its resolution.

[17] If C2 is ^{2}H labeled, which would result if palladacycle **II** formed, then the doublets at $\delta = 150.5$ (J(C-P) = 31.2 Hz) and 130.6 ppm (J(C-P) = 5.8 Hz) would also be split into two new sets of doublets approximately 0.1 ppm upfield from the unlabeled material; however, this splitting was not observed.

