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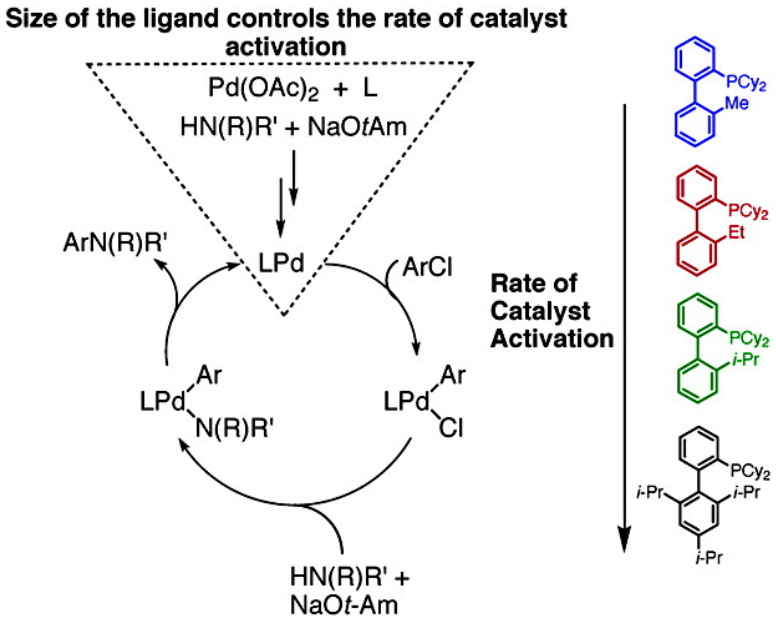

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Insights into the Origin of High Activity and Stability of Catalysts Derived from Bulky, Electron-Rich Monophosphinobiaryl Ligands in the Pd-Catalyzed C−N Bond Formation

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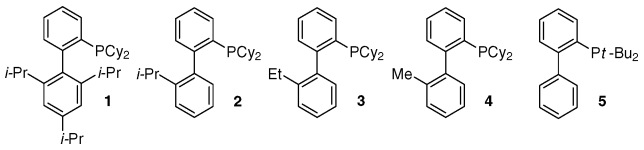
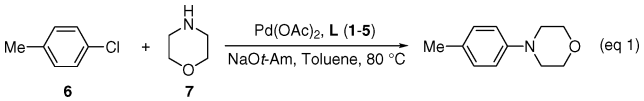
Recent improvements in Pd-catalyzed C−N bond-forming processes have been due primarily to the development of new ligands[1] such as bulky, electron-rich monophosphines. The employment of monophosphine ligands allows the use of less reactive substrates such as aryl chlorides and tosylates in cross-coupling reactions.[2] Despite these advances, specific classes of substrates have remained recalcitrant. Some of these limitations have recently been overcome by employing ligand **1**.[3] The catalyst system based on **1** exhibits both dramatically increased activity and stability relative to those based on simpler biaryl ligands (e.g., **2**−**5**). Despite this progress, little information is available as to the origin of the catalytic activity based on biaryl phosphine ligands. Recent studies suggest that the high activity of catalyst systems based on bulky phosphines may result from their ability to promote the formation of monophosphine complexes (L_1Pd^0).[4−6] We report herein a comparative kinetic examination between catalyst systems generated from ligands **1**−**5** for the coupling of amines and aryl chlorides. This study reveals that the bulk of the phosphine ligand not only controls the catalytic activity but also the rate of catalyst activation.



Differences in reaction rates for the catalytic systems generated from biaryl ligands **1**−**5**[7] were determined by monitoring the progress in sequential reactions using reaction calorimetry.[8] We have shown previously how such a protocol allows examination of features such as catalyst activation while also providing a complete kinetic profile for estimating reaction rate constants in a multistep mechanism.[9] This approach also helps to address the question of catalyst activation and stability by comparing initial rates for reactions commencing after the catalyst has already undergone numerous turnovers. In the case of a process in which catalyst activation is slow, the reaction rates for each subsequent reaction should increase, while catalyst deactivation or positive-order substrate dependencies will yield decreasing reaction rates as the turnover numbers increase.



(eq 1)

A typical experiment for the coupling of *p*-chlorotoluene (**6**) with morpholine (**7**) in toluene at 80 °C (eq 1)[10] was carried out with four consecutive injections of the reactants to a solution containing the $Pd(OAc)_2$ precatalyst along with the ligand and NaO*t*-Am equilibrated at 80 °C for 1 h. The amine was either added with the catalyst prior to commencement of the first injection or added in the first injection with the aryl chloride. This reaction protocol allowed us to examine the influence of the presence of the amine on activation of the Pd(II) precatalyst.[11] Between 20 and 35 turnovers were accomplished in each reaction.

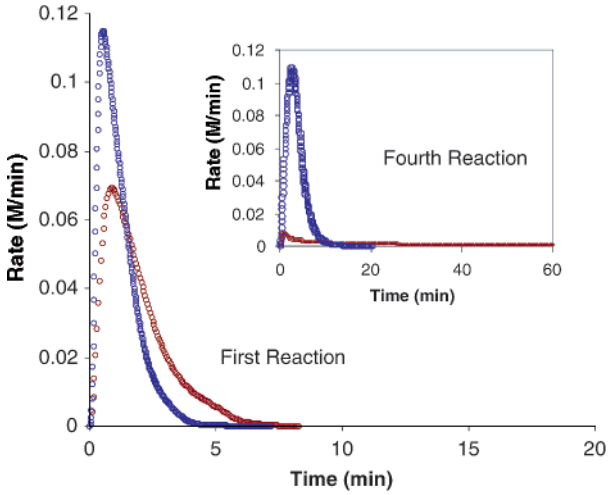


Figure 1. Reaction rate vs time for the coupling of morpholine ($[\mathbf{7}]_o$ = 0.74 M − 0.78 M) with *p*-chlorotoluene (4 × $[\mathbf{6}]_o$ = 0.15 M) using $[Pd(OAc)_2]$ = 4.2 mM and $[NaOt\text{-}Am]_o$ = 0.8 M: (blue ○) [**1**] = 16.5 mM, (red ○) [**5**] = 16.5 mM. (a) Reaction 1 is initiated by adding all of **7** and the first aliquot of **6**. The subsequent reactions are performed by adding additional aliquots of **6**. (b) Reaction 4 is taken after the reaction had undergone 110 turnovers (75 min into the reaction). Setting the time equal to 0 for reaction 4 is only for reference.

Figure 1 compares the initial activity as well as the long-term stability of catalysts derived from ligands **1** and **5**. Exceptional reactivity in Pd-catalyzed C−N bond-forming processes has been observed previously for catalyst systems based on these two ligands. Both catalyst systems are very active, with that derived from **5** giving an initial rate about 40% lower than that based on **1** (Figure 1a).[12] Their relative activity following three reactions (ca. 110 turnovers), however, is markedly different (Figure 1b). The catalyst with ligand **1** retains its original activity, while the reaction rate for catalyst/ligand **5** combination has decreased by more than an order of magnitude.

Figure 2 depicts activity and stability comparisons between catalysts based on ligands **2**−**4**, plotting the reaction rate as a function of reaction progress for a four-reaction sequence. The rates for all of these systems are significantly lower than that observed using ligand **1** (see Figure 1). It is important to note that the concentrations of $Pd(OAc)_2$ and **1** used in the sequential reaction experiment in Figure 1 are half of that used in the case of ligands **2**−**4**. The dramatic effect of the size of the substituent on the bottom

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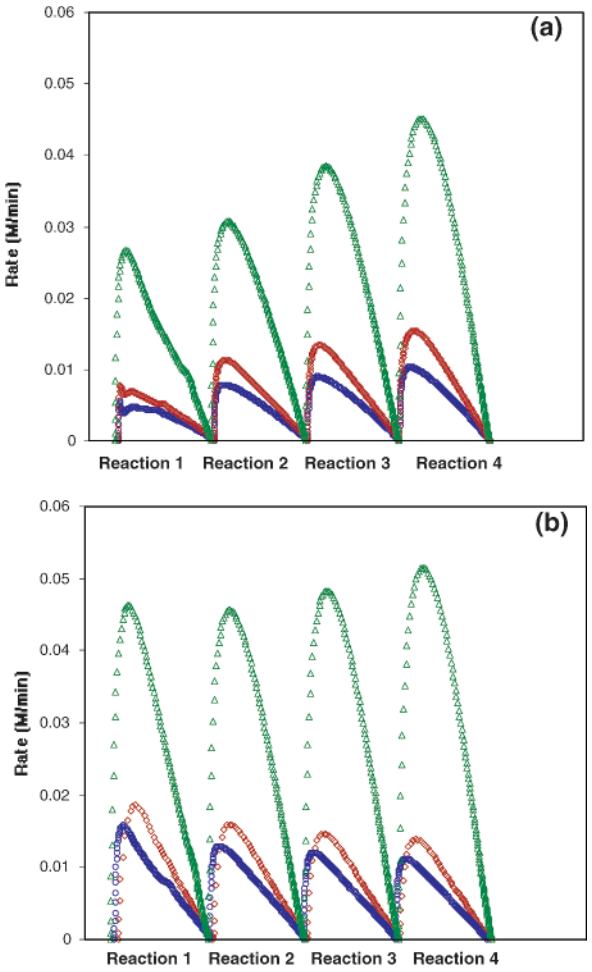


Figure 2. Sequential reaction experiment for the amination of *p*-chlorotoluene ($4 \times [\mathbf{6}]_o = 0.15$ M) with morpholine ($[\mathbf{7}]_o = 0.74$ M − 0.78 M) using $[Pd(OAc)_2] = 8.3$ mM and $[NaO\textit{t}\text{-Am}]_o = 0.8$ M: (green △) [**2**] = 16.5 mM, (red ◇) [**3**] = 16.5 mM, (blue ○) [**4**] = 16.5 mM, (a) without 1 h preincubation between the amine and catalyst and (b) with 1 h preincubation between the amine and catalyst.

ring of the monophosphinobiaryl ligand is emphasized by a 10-fold difference in reaction rate across the series **1**−**4**. Another intriguing feature of these reactions is the *increasing* reaction rates for each consecutive reaction using ligands **2**−**4** (Figure 2a).

In a separate set of experiments, where the amine is stirred with the catalyst/base mixture prior to the addition of the first aliquot of aryl chloride, the rate profiles are drastically different: the overall rate increases relative to that described in Figure 2a, yet the consecutive reactions display *decreasing* reaction rates using ligands **2**−**4** (Figure 2b). For comparison, the reaction rate of the *first* reaction in the sequence where preincubation was employed was higher than the *last* in the sequence with no amine preincubation (Figure 2a). In addition, the amine preincubation with the catalyst based on ligand **1** did not significantly influence the initial rates of consecutive reactions shown in Figure 1.

An increase in the initial rates of consecutive reactions implies that the concentration of active catalyst within the catalytic cycle is increasing over time, a process in which the amine is clearly implicated.[9] When consecutive initial reaction rates cease to show increases, or when they begin to decrease, it may be suggested that a steady-state concentration of active catalyst has ultimately been obtained. Under these conditions the intrinsic concentration dependences of the substrates may be observed.[13] Catalysts based on ligands **2**−**4**, i.e., those with less bulky substituents, appear to require longer exposure to the amine to become fully activated than do those based on the bulkier ligand **1**.

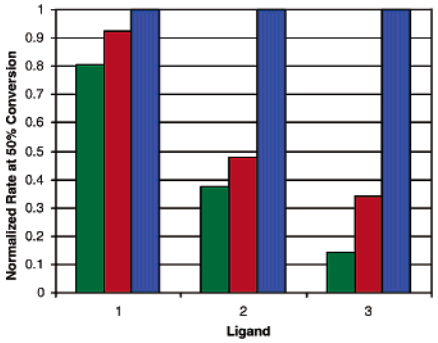
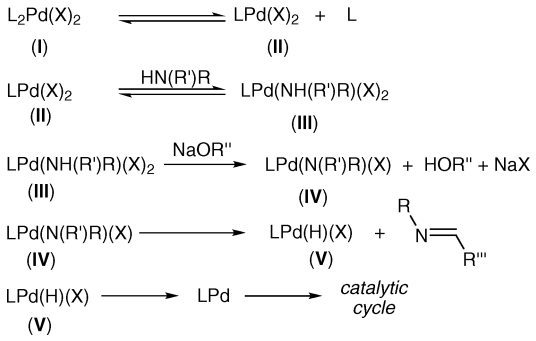


Figure 3. Normalized rate (rate at 50% conversion/ maximum rate) of ligands **1**−**3** with varying Pd:ligand ratios using the same conditions as in Figure 2. Ligand:Pd ratios: **4**:**1** (green), **3**:**1** (red), and **2**:**1** (blue).

Scheme 1. Proposed Mechanism for Catalyst Activation



The sensitivity of catalyst activation to the size of the substituent on the phosphine ligand suggests that dissociation of the phosphine from a bisphosphine Pd(II) complex is required for catalyst activation.[14] Slower catalyst activation may be the result of a slower rate of phosphine dissociation from bisphosphine complexes. This is supported by the observation that the rate displays a small dependence on the L:Pd ratio for the largest ligand **1**, while the rate dependence becomes more significant for the smaller ligands **2** and **3** (Figure 3).

The results from the amine incubation and the rate dependence on ligand concentration suggest that both the presence of the amine and the size of the ligand play a role in facilitating entry of active species into the catalytic cycle. A general mechanism as outlined in Scheme 1 is proposed to describe such an activation process.[15] Ligand dissociation from $L_2Pd(X)_2$ (**I**) generates the monophosphine complex **II**. This step should be sensitive to the size of the phosphine, with larger phosphines resulting in a more favorable equilibrium. Once the monophosphine complex (**II**) forms, amine association occurs which is followed by deprotonation resulting in the Pd(II)−amide (**IV**).[16] β-Hydride elmination then ensues to afford **V** which readily undergoes reductive elimination to generate the active Pd(0) species.[17,18]

The proposed role for the amine in activating the catalyst was investigated by studying the kinetic isotope effects (KIEs) using d_8-morpholine (d_8-**7**) as a substrate. For a catalyst system derived from ligand **4**, a primary KIE may be anticipated for the initial reactions when carried out *without* amine preincubation, because the overall reaction rate is influenced by the rate of catalyst activation (formation of **V** in the mechanism in Scheme 1). By contrast, no KIE would be expected using catalysts derived from ligand **4** in reactions carried out with amine preincubation, since catalyst activation is suggested to be complete prior to the beginning of the coupling reaction. Similarly, no KIE should be observed with

Table 1. Kinetic Isotope Effects

ligand	k_H/k_D 1st injection	k_H/k_D 2nd injection	k_H/k_D 3rd injection	k_H/k_D 4th injection
4	1.58 ± 0.01	1.53 ± 0.02	1.34 ± 0.03	1.17 ± 0.02
4 w/amine premixing	1.04 ± 0.02	1.03 ± 0.01	1.08 ± 0.04	1.08 ± 0.04
1	1.01 ± 0.07	0.90 ± 0.09	0.88 ± 0.08	0.96 ± 0.05

the bulkiest ligand **1**, since its consecutive initial rates were unaffected by the preincubation with amine. Results shown in Table 1 confirm these predictions, showing no KIE for catalysts based on ligand **1** and positive but steadily decreasing KIEs in reactions using ligand **4** under the same conditions as in Figure 2a, where catalyst activation is occurring concomitant with the catalytic reaction.

In summary, this study demonstrates a relationship between the steady-state concentration of active Pd and the ligand size of monophosphinobiaryl ligands used in the amination of aryl chlorides. These insights into the nature of catalyst activation help to highlight the importance of maintaining a stable catalyst concentration. The catalyst derived from the bulkiest ligand in the series, the tri-*i*-propyl ligand **1**, exhibits both accelerated rate and the increased stability required for practical application of this reaction.

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Supporting Information Available: General procedure for obtaining kinetic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Decreasing consecutive initial rates for reactions with successively lower initial [amine] suggests intrinsic positive order kinetics in [amine]; however, it could also be attributed to zero-order kinetics in [amine] and decreasing [catalyst] due to catalyst deactivation.

(14) An alternative explanation which is also consistent with the rate dependence on ligand concentration is the formation of $L_2Pd(0)$ rather than a $L_2Pd(II)$ complex as we propose here; see refs 4, 5, 6, and 9.

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(16) ^{31}P NMR spectroscopic studies involving mixtures of ligand **1** and $Pd(OAc)_2$ indicate the presence of a new complex at 41 ppm along with free ligand in a 5:1 ratio. Attempts to isolate this complex were unsuccessful. Moreover, both a mixture of **1**, $Pd(OAc)_2$, and NaO*t*-Am along with a mixture of **1**, $Pd(OAc)_2$, **7**, and NaO*t*-Am resulted in only free phosphine and a small residual peak that cannot be identified at 48 ppm: no phosphine oxide was present in either mixture. Thus, it is difficult to draw conclusions on the basis of these studies.

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