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Distinct Mechanisms for the Oxidative Addition of Chloro-, Bromo-, and Iodoarenes to a Bisphosphine Palladium(0) Complex with Hindered Ligands

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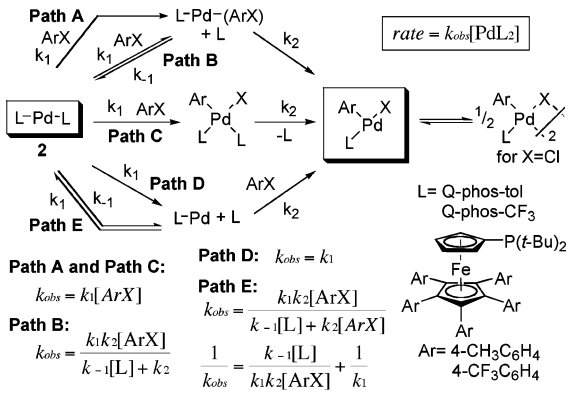
The oxidative addition of aryl halides is the first step in most palladium-catalyzed coupling reactions.[1] Previous mechanistic studies of this reaction have focused on additions of iodo- and bromoarenes.[2,3] Despite the identification of catalysts for mild couplings of chloroarenes,[4] few studies of the mechanism of the oxidative addition of these reagents have been conducted.[3,5] Studies on the oxidative addition of chloroarenes to Pd(0) complexes of hindered alkylmonophosphines, which generate highly active catalyst for coupling processes, have not been reported, and, most strikingly, no studies have been reported on the mechanism of the oxidative addition of chloro-, bromo-, and iodoarenes to the same Pd(0) complex. Without such studies, extrapolation of the data on the additions of iodo- and bromoarenes to the additions of chloroarenes is tenuous.

To compare the mechanisms of oxidative addition of chloro-, bromo-, and iodoarenes, we studied the addition of these reagents to [Pd(Q-phos-tol)$_2$] (Scheme 1). This complex adds all three types of haloarenes in high yields. Moreover, Q-phos[6,7] generates highly active catalysts for the arylation of amines and alkoxides,[7] malonates, cyanoesters, azlactones, and zinc enolates.[8] We report that the addition of iodo-, bromo-, and chloroarenes to the Pd(0) complexes of the sterically hindered Q-phos ligands occurs by three different mechanisms.

The oxidative addition of iodo- and bromoarenes to Pd(Q-phos)$_2$ (**1**) generates [Pd(Q-phos)(Ar)(X)].[9,10] Because the low solubility of complex **1** precluded mechanistic studies, analogous Pd(0) complexes, [Pd(Q-phos-tol)$_2$] (**2**) and [Pd(Q-phos-CF$_3$)$_2$] (**3**), containing *p*-CH$_3$ or *p*-CF$_3$ groups on the phenyl rings of the ligand were prepared. These substituted Q-phos complexes were sufficiently soluble in THF for kinetic studies.

The oxidative addition of PhI, PhBr, and PhCl to **2** at 30−65 °C in neat PhX produced [Pd(Q-phos-tol)(Ph)(X)] (X = I, **4**; X = Br, **5**; X = Cl, **6**) quantitatively, as determined by ^{31}P NMR spectroscopy (94, 53, and 82% isolated yield). Like the analogous Q-phos complexes, Q-phos-tol complexes **4** and **5** are monomeric. However, chloride complex **6** is dimeric in the solid state (X-ray diffraction) and in C_6H_6 solution (Signer method). The difference between the nuclearity of the aryl halide complexes does not affect our study because the dimerization occurs after the oxidative addition.

Scheme 1. Possible Mechanisms and Rate Expressions for the Oxidative Addition of ArX to **2**



PhI adds by path A, PhBr adds by path D and PhCl adds by path E

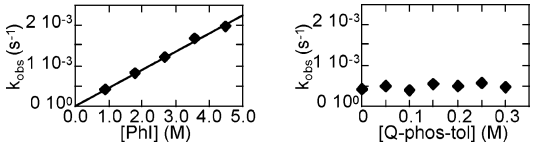


Figure 1. Plots of k_{obs} vs [PhI] and k_{obs} vs [Q-phos-tol] ([PhI] = 0.95 M) for the oxidative addition of PhI to **2** at 30 °C in THF.

Potential mechanisms of oxidative addition of ArX to **2** and the corresponding rate expressions are shown in Scheme 1. Path A involves, under the conditions of oxidative addition, rate-limiting associative replacement of a phosphine ligand in **2** by PhX to generate a haloarene complex that is either bound η^1 through the halide[11] or η^2 through the arene.[12] This step is followed by carbon−halogen bond cleavage in the resulting monophosphine complex of the haloarene. The k_{obs} for this route depends on only [ArX]. Path B is similar to path A, but the replacement of ligand by ArX is reversible. The k_{obs} for this route depends on [ArX] and [L]. Path C involves irreversible oxidative addition of ArX directly to **2**, followed by ligand dissociation from the resulting four-coordinate arylpalladium halide intermediate. The rate expression for this route is identical to that for path A. Path D involves irreversible, rate-limiting dissociation of L from **2** followed by oxidative addition to the resulting monophosphine Pd(0) complex which might be stabilized by coordination of solvent. The k_{obs} for this route is independent of [ArX] and [L]. Path E is similar to path D, except that the dissociation of phosphine is reversible. The k_{obs} for this route depends on [ArX] and [L].

Studies of the oxidative addition of iodo-, bromo-, and chlorobenzene to palladium(0) complex **2** generate three distinct sets of rate data. The reaction of PhI was performed at 30 °C with [PhI] = 0.90−4.47 M and [L] = 0−0.30 M. As illustrated in Figure 1, the oxidative addition of PhI to **2** was first-order in [PhI] and independent of [L]. Reactions between 30 and 60 °C showed that $\Delta S^{\ddagger}$ was −19.8 ± 2.0 eu. These data are consistent with reaction of PhI with **2** by associative paths A or C.[13]

To differentiate between reaction of PhI by paths A and C, we studied the reductive elimination of iodoarene. If the reductive elimination of iodoarene from **4** or a closely related compound occurred by the reverse of path A, then the reaction would be independent of the concentration of added ligand; however, if the reductive elimination of iodoarene occurred by the reverse of path C, then the reaction would be first-order in added ligand.

Complex **4** did not undergo clean reductive elimination of PhI, even at 70 °C in the presence of 30 equiv of added Q-phos-tol, but the related complex [Pd(PBu$^t_3$)(*o*-tol)(I)] (**7**) undergoes reductive elimination of *o*-tolI upon addition of PBu$^t_3$ (Scheme 2).[14] The rate constants for this reductive elimination were measured by ^{31}P NMR

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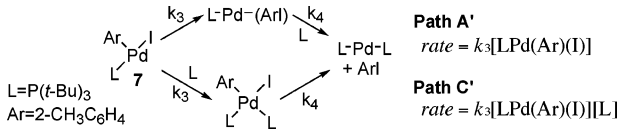
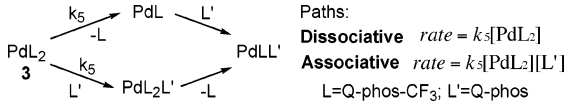
Scheme 2. Possible Mechanisms for the Reductive Elimination of ArI from **7**[a]



[a] Paths A′ and C′ are the reverse of paths A and C in Scheme 1.

Scheme 3. Potential Mechanisms of Ligand Exchange of **3**



spectroscopy with a 0.02 M concentration of the palladium complex and 0.2−0.4 M concentration of added PBu^t_3. Consistent with reaction by the reverse of path A but not by the reverse of path C, k_{obs} was independent of [PBu^t_3]. Assuming that the addition and elimination of haloarene to the palladium complexes ligated by PBu^t_3 and Q-phos-tol follow the same mechanism,[15] oxidative addition of PhI to **2** would follow path A. This finding is consistent with the low stability of four-coordinate arylpalladium halide complexes containing these sterically demanding ligands.[10]

The oxidative addition of PhBr followed a path that was different from that for oxidative addition of PhI. The rates of the oxidative addition of PhBr were measured at 50 °C with [PhBr] between 0.96 and 6.3 M and [L] between 0 and 0.45 M. The values of k_{obs} were independent of the concentration of PhBr and ligand; the value of k_{obs} from experiments with varied [Q-phos-tol] was $(6.2 \pm 0.8) \times 10^{-4}$ s^{-1}, and the value from experiments with varied [PhBr] was $(6.7 \pm 0.9) \times 10^{-4}$ s^{-1}. Further, the values of k_{obs} for reactions of RC_6H_4Br (R = 4-CF_3, 4-OMe, 2-CH_3) were indistinguishable from that for reaction of PhBr, and $\Delta S^{\ddagger}$ (−9.8 ± 3.8 eu) was small, albeit slightly negative.[16] Among the mechanisms in Scheme 1, these data are consistent with only path D, involving rate-limiting dissociation of L.

If the rate constant for the oxidative addition of PhBr corresponds to that for dissociation of ligand from [Pd(Q-phos-tol)$_2$], then an independent measurement of the rate constant for dissociation of ligand from [Pd(Q-phos-tol)$_2$] should give the same value. The rate constant for ligand dissociation from Q-phos-CF_3 complex **3** was determined by reaction of **3** with Q-phos.[17] The reaction was conducted with a large enough excess of Q-phos (10−50 equiv) that the equilibrium for ligand exchange lay far toward Q-phos complex **1** (Scheme 3). This ligand substitution was dissociative, as shown by the lack of dependence of k_{obs} on [Q-phos]. Most important for understanding the mechanism of oxidative addition, the value of k_{obs} for the exchange process in THF at 60 °C was $4.6 \pm 0.4 \times 10^{-4}$ s^{-1}, and the value of k_{obs} for the oxidative addition of bromobenzene to the same Q-phos-CF_3 complex **3** at 60 °C in THF solvent was $4.0 \pm 0.2 \times 10^{-4}$ s^{-1}. Likewise, the value of $\Delta S^{\ddagger}$ for the exchange process (−7.4 ± 3.6 eu) was indistinguishable from that for the oxidative addition to **2**.

The oxidative addition of PhCl to **2** occurred by a third mechanism. The oxidative addition of PhCl to **2** was measured at 60 °C with [PhCl] between 0.76 and 6.8 M and [L] between 0.050 and 0.33 M. As shown by the plots in Figure 2, the rate constant for addition of PhCl depended positively on [PhCl] and inversely on [L]. Of the mechanisms in Scheme 1, these data are consistent with only path E.

The inverse of the *y*-intercepts of both plots (2.0 ± 0.2 and $1.7 \pm 0.1 \times 10^{-3}$) corresponds to the rate constant for dissociation of Q-phos-tol from **2**. These values are nearly identical and match the rate constant for oxidative addition of PhBr to **2** at 60 °C ((1.9 ± 0.1) × 10^{-3} s^{-1}), which appears to occur by rate-limiting dissociation of ligand. The slope of the plot allows a calculation of the ratio of rate constants for oxidative addition of ArCl and reassociation of ligand to PdL (k_2/k_{-1}). Oxidative addition of PhCl to the [Pd(Q-phos-tol)] intermediate is only 30−50 times slower than simple coordination of Q-phos-tol to [Pd(Q-phos-tol)].

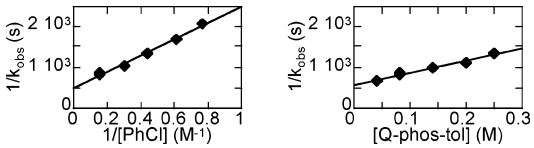


Figure 2. Plots of $1/k_{obs}$ vs 1/[PhCl] ([Q-phos−tol] = 0.08 M) and $1/k_{obs}$ vs [Q-phos−tol] ([PhCl] = 6.56 M) for the oxidative addition of PhCl to **2** at 60 °C in THF.

In conclusion, oxidative addition of chloro-, bromo-, and iodoarenes to sterically hindered **2** occurs through three different mechanisms. Addition of PhI occurs by associative displacement of a phosphine. Addition of PhBr occurs by rate-limiting dissociation of phosphine. Addition of PhCl occurs by reversible dissociation of phosphine, followed by rate-limiting oxidative addition. Future studies will explore the generality of these findings with palladium complexes of other hindered ligands.

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Supporting Information Available: Experimental procedures and additional kinetic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Unpublished studies that will be reported separately demonstrate that complexes of P(*t*-Bu)$_3$ and Q-phos react by analogous mechanisms when the system is free of acid.
(16) Mechanistic conclusions from $\Delta S^{\ddagger}$ values of ±10 eu should be interpreted cautiously: Atwood, J. D. In *Inorganic and Organic Reaction Mechanisms*; Brooks/Cole: Monterey, 1985; p 16.
(17) Ligand exchange was studied with Q-phos-CF_3 complex **6** because the ^{31}P NMR signals of Q-phos-tol complex **2** and the parent complex **1** could not be resolved, and ^{1}H NMR resonances of the methyl groups of free and coordinated Q-phos-tol could not be resolved.

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