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An Unexpected Pathway for Ligand Substitution in an Aryl Halide Complex of Palladium

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Dedicated to Professor Brian K. Nicholson on the occasion of his 65th birthday

Aryl halide complexes of palladium are interesting because of their intermediacy in many palladium-catalyzed cross-coupling reactions.[1] Their reactivity towards reagents such as alkyne derivatives, carbon monoxide, and isocyanide to give new organopalladium or organic compounds has been studied extensively.[2] Despite much effort having been expended on the synthesis and reactivity of these complexes,[3] less attention has been paid to the mechanism by which they are formed. For example, the preparation of $[Pd(PPh_3)_2(Ar)(I)]$ from [Pd(tmeda)(Ar)(I)] (Ar = aryl ligand, tmeda = tetramethylethylenediamine) has been described as proceeding "by replacement of the chelating N N ligand by PPh_3 and an isomerization process that is probably promoted by the great transphobia of the Ph_3P/Ar ligand pair".[4] The *trans* effect of a ligand is a measure of its ability to labilize the ligand coordinated on the opposite side of the metal complex to itself, and is most obvious in square planar complexes.[5] Ph^- is a strong *trans*-effect ligand, and amines exert a relatively weakly *trans* effect, so it is reasonable to expect that the tmeda (*trans* to the aryl group) is activated in preference to I^- (*trans* to a nitrogen donor of tmeda).

A high-yielding, convenient synthesis of $[Pd(PR_3)_2(Ar)(I)]$ complexes is the oxidative addition of an aryl iodide to $[Pd^0(dba)_2]$ in the presence of tmeda, and subsequent displacement of tmeda by two equivalents of phosphine (a reaction that works well for aryl iodides, but not for the other halides).[1] We wanted to use this reaction to make a charge-tagged version of $[Pd(PR_3)_2(Ar)(I)]$, where a positive charge was appended to the aryl group, because this species is an often-seen intermediate when following cross-coupling reactions using electrospray ionization mass spectrometry (ESI-MS).[6] ESI-MS is an increasingly popular method for studying organometallic and catalytic reactions,[7] and charge-tagging[8] enables this approach because ESI-MS detects only ions preformed in solution. Our recent introduction of pressurized sample infusion allows us to monitor reaction solutions in real time in a wide variety of solvents and at temperatures up to reflux, simultaneously generating dense data on the abundance of reactants, products, byproducts, and intermediates.[9]

The synthesis of the charge-tagged analogue itself presented an opportunity to study a ligand substitution reaction in detail, because both the precursor, $[Pd(tmeda)(Ar)(I)]^+$ (**1**, Ar = $C_6H_4CH_2PPh_3^+$ PF_6^-, see Figure 1 for structure) and product, $[Pd(PPh_3)_2(Ar)(I)]^+$ (**4**), are themselves charged. We expected a slow displacement of one of the tmeda donors by PPh_3, and subsequent rapid displacement of the other tmeda donor with a second molecule of PPh_3, with any isomerization that might occur which is invisible to our methods (as it does not involve a mass change). However, when we examined the reaction using PSI-ESI-MS in positive and negative ion modes, it was evident that the reaction proceeded quite differently; there was a very fast displacement of I^- by PPh_3 to form $[Pd(tmeda)(Ar)(PPh_3)]^{2+}$ (**2**), followed by a much slower displacement of tmeda and recoordination of I^- to form the product (**4**).

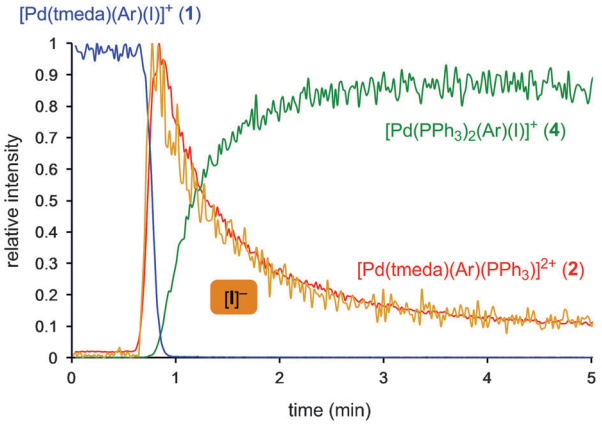

Figure 1. Reaction progress in methanol at 55 °C, as measured by positive-ion (traces for blue **1**, red **2**, and green **4**) and negative-ion mode (orange I^-, from a duplicate experiment) PSI-ESI-MS.

The formation of **2** (and I^-) from **1** is fast under these conditions, and is complete in less time than it takes for the solution to move from reaction flask to mass spectrometer (≈10 sec). The reaction proceeds despite the fact that complex **1** is already cationic by virtue of the charged tag. Identical chemistry occurs for the neutral complex [Pd(tmeda)(Ph)(I)], though only intermediate $[Pd(tmeda)(Ph)(PPh_3)]^+$ is visible by ESI-MS (see the Supporting Information). Lowering the temperature and

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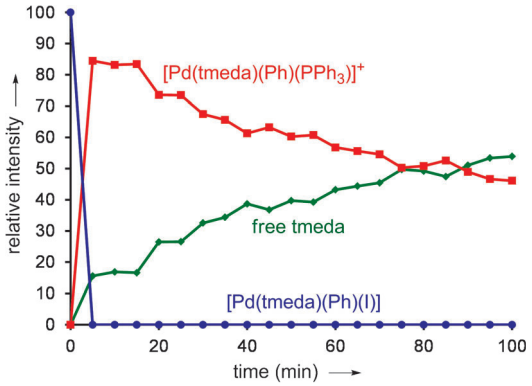


Figure 2. Reaction progress in CD_3OD at 22 °C, as measured by ^1H NMR using the methyl groups of the tmeda ligand.

having an understanding of the chemistry also allows the reaction to be tracked by ^1H NMR (Figure 2)

We decided to examine the structure of **1** (Figure 3) to see if it provided any insight as to why the iodide is displaced so readily. The strong *trans* influence of the aryl ligand is in evi-

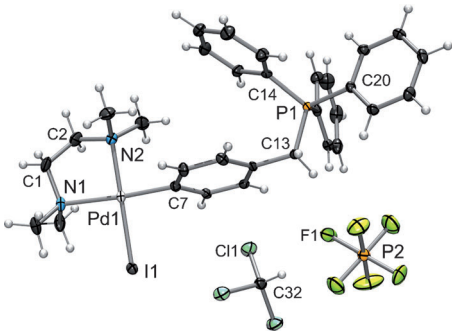


Figure 3. X-ray crystal structure of **1**, including the PF_6^- counterion and $CDCl_3$ of crystallization. Selected bond lengths (Å): Pd1–I1 2.5807(2); Pd1–N1 2.2009(15); Pd1–N2 2.1411(17); Pd1–C7 1.9842(17). Selected bond angles (°): C7-Pd1-N2 92.62(7); C7-Pd1-11 87.54(5); N2-Pd1-N1 83.72(6); N1-Pd1-I1 96.12(5). ORTEP plot drawn with ellipsoids at 30% probability.

dence, elongating the *trans* Pd–N bond to 2.20 Å compared with 2.14 Å for the Pd–N bond *trans* to the iodide ligand. However, the Pd–I bond length of 2.58 Å is unremarkable; Pd–I bond lengths in square planar complexes range from 2.41–3.14 Å, with an average of 2.64 Å and a standard deviation of 0.05 Å,[10] so if anything the Pd–I bond length in **1** is on the short side.

Without any strong structural insights, we proceeded to investigate the reaction mechanism in more detail. We could probe the fast initial step with more time resolution than in the initial experiment, because sensitivity is rarely a problem when studying charge-tagged compounds by ESI-MS. As such, bimolecular reactions can be slowed down by the simple expedient of dilution without fear of approaching the detection limit. The reaction was repeated at 10% of the prior concentration of **1**, and the amount of PPh_3 was decreased to one equivalent (down from ten equivalents). Accordingly, the fast initial

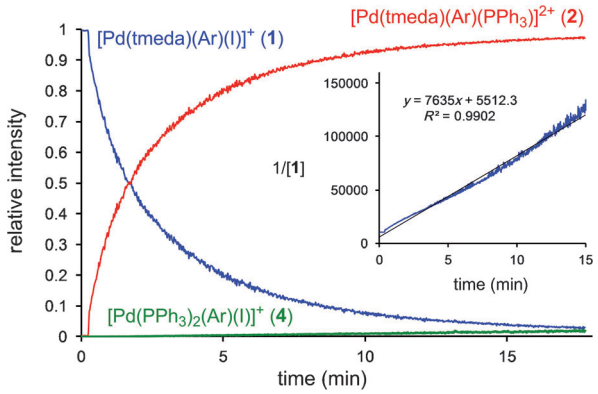
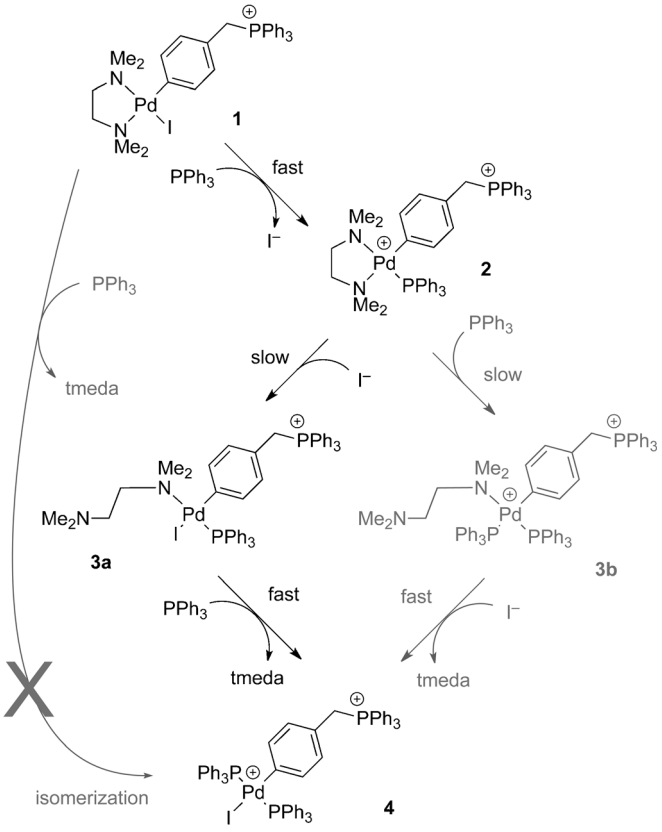


Figure 4. Reaction progress in methanol at 55 °C, as measured by positive-ion PSI-ESI-MS. The reaction has been lowered in rate by reducing the concentration of both reactants. Inset: fit of 1/[**1**] vs. time confirming a good match to second-order kinetics.

substitution was greatly slowed (by a factor of 1/1000th), and the kinetics were now demonstrably second order rather than pseudo-first order (Figure 4). The first few seconds of the reaction were still lost, but the reaction overall now took over 15 minutes to complete at 55 °C, so plenty of data were available to allow estimation of the second-order rate constant as $k_2 = 143 \pm 1\ L\,mol^{-1}\,s^{-1}$ (Figure 4, inset). The second-order kinet-



Scheme 1. Possible reaction pathways for the substitution of tmeda for 2×PPh_3. PSI-ESI-MS reveals the reaction to proceed via **1**→**2**→**3a**→**4**. Of these four complexes, only **3a** is not directly observed, but its involvement can be inferred by the effect of I^- vs. PPh_3 on the reaction **2**→**4**.

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ics suggest an associative mechanism, as is typical for square planar metal complexes.[11]

The slow step in the reaction is the formation of **4** from **2**, with $[Pd(\kappa^1\text{-tmeda})(PPh_3)(Ar)(I)]^+$ (**3a**) and/or $[Pd(\kappa^1\text{-tmeda})(PPh_3)_2(Ar)]^{2+}$ (**3b**) the presumptive intermediate(s) (Scheme 1). Neither **3a** nor **3b** could be observed during the reaction, suggesting that the rate of formation of **3a/b** from **2** is much slower than the consumption of **3a/b** to form **4**. The kinetics of the transformation of **2** into **4** are pseudo-first order, with $k_{obs} = 1.08\ s^{-1}$ at 55 °C with a fivefold excess of PPh_3. Distinguishing which of **3a** or **3b** is the most important intermediate is possible by examining the effect of iodide and PPh_3, respectively, on the second substitution reaction. Addition of ten extra equivalents of PPh_3 after formation of **2** had no effect on the rate of reaction (Figure 5). Conversely, addition of ten equivalents of I^- after the initial ligand substitution (**1** to **2**) greatly accelerates the reaction, suggesting that the route through **3a** is the important one (even though **3a** is not detected).

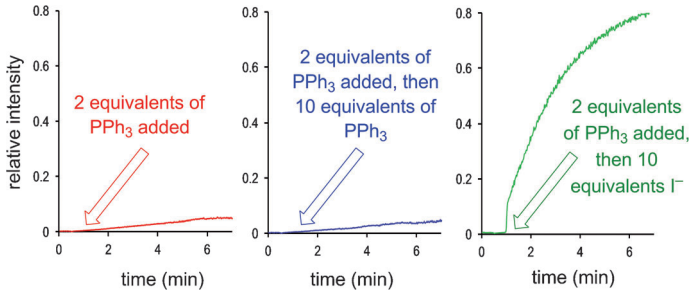

Figure 5. Rate of formation of **4** from **1** under different experimental conditions. Additional PPh_3 does not affect the rate, but additional I^- does.

The fact the substitution occurs via **3a** is interesting, because it suggests that addition of a different halide ion might offer a route to complexes of the form $[Pd(PR_3)(Ar)(X)]$ (X = Br, Cl, F, pseudohalide). Addition of an excess amount of NaBr or NaCl resulted in formation of the expected new halide complex, but the reaction competes with the remaining I^- and a mixture of products was formed (I^- is a better nucleophile than Br^-, which is better than Cl^-). A better approach is to add one equivalent of $AgNO_3$[12] to precipitate out AgI, and subsequent addition of the desired halide, and this reaction goes to completion very quickly in yields of >98% by ESI-MS (see the Supporting Information).

Complexes of the type $[Pd(PPh_3)_2(Ar)(X)]$ (X = Br, Cl, F) have been previously synthesized. Oxidative addition of ArX (X = I, Br or Cl)[1] to $[Pd(PPh_3)_4]$ requires high temperature, activated ArCl, and long reaction times,[13] and while improved methods have been introduced for specific halides,[14] a fast, high-yielding and general approach to this class of compounds has not been forthcoming. Details of the synthesis and characterization of $[Pd(PPh_3)_2(Ar)(X)[$ complexes through our new route will appear in later work.

Having an in-depth understanding of this ligand substitution mechanism allows modification of the reaction in a rational way. That the apparent substitution and isomerization that occurs in this reaction is, in fact, explicable by three ligand substitution steps is noteworthy and may well help account for similar phenomena in related systems. In particular, the involvement of iodide neatly accounts for the differential reactivity in substitution chemistry between complexes of the type $[Pd(PR_3)_2(Ar)(X)]$ (X = I, Br, Cl, F). The extent to which PSI-ESI-MS lays bare this mechanism is promising for future investigations of similar reactions.

Experimental Section

All syntheses and catalytic reactions were performed under an inert atmosphere of N_2 using standard glovebox or Schlenk procedures. The aryl iodide $[4\text{-}IC_6H_4CH_2PPh_3][PF_6]$ was prepared by a known method, as was $[Ph_3PMe][PF_6]$.[6] All chemicals were obtained from Aldrich and used without further purification. Solvents were HPLC grade and purified on an MBraun solvent purification system. Gases were obtained from Airgas (Calgary, Canada). All mass spectra were collected on a Micromass Q-ToF micro mass spectrometer in positive-ion and negative-ion mode using pneumatically assisted electrospray ionization. Further details are available in the Supporting Information.

Synthesis of 1: $[4\text{-}IC_6H_4CH_2PPh_3][PF_6]$ (0.13 g, 0.2 mmol), tetramethylethylenediamine (tmeda; 37 μL, 0.25 mmol) and $[Pd(dba)_2]$ (0.12 g, 0.1 mmol) were dissolved in acetone (8 mL) and stirred for 30 min at 30 °C until the solution changed color from red to yellow. The product was filtered and washed with cold diethyl ether and dried in vacuum overnight at 60 °C. Yield 72% (0.12 g, 0.14 mmol). Single crystals were grown from a solution of $CDCl_3$. M.p 97 °C. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.27$ (s, 6H, NCH_3), 2.60 (s, 6H, NCH_3), 2.65–2.73 (m, 2H, NCH_2), 2.48–2.54 (m, 2H, NCH_2), 4.32 (d, $J = 14$ Hz, 2H, PCH_2), 6.28 (dd, $^3J_{HH} = 8$ Hz, $^4J_{HP} = 2$ Hz, 2H, C_6H_4), 6.99 (d, $J = 8$ Hz, 2H, C_6H_4), 7.3–7.8 ppm (m, C_6H_5, 15H); ^{31}P NMR (300 MHz, $CDCl_3$): $\delta = 22.96$ ppm (s); ESI(+)-MS (solvent: MeOH): *m/z*: 701.1.

CCDC 942884 (**1**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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