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 dehalogenation intermediates in many palladium-catalyzed cross-coupling reactions.[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(PPh3)2(Ar)(I)] from [Pd(tmeda)(Ar)(I)] (Ar = aryl ligand, tmeda = tetramethylethylenediamine) has been described as proceeding by replacement of the chelating NN ligand by PPh3, and an isomerization process that is probably promoted by the great transphobia of the Ph,P/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(PR3)2(Ar)(I)] complexes is the oxidative addition of an aryl iodide to [Pd(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(PR3)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, by-products, 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 = C6H5CH2PPh3) and PF6-, see Figure 1 for structure) and product, [Pd(PPh3)2(Ar)(I)]+ (4), are themselves charged. We expected a slow displacement of one of the tmeda donors by PPh3 and subsequent rapid displacement of the other tmeda donor with a second molecule of PPh3, 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 PPh3 to form [Pd(tmeda)(Ar)(PPh3)]2+ (2), followed by a much slower displacement of tmeda and recoordination of I- to form the product (4).

The formation of 2 and 1 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)(PPh3)]+ is visible by ESI-MS (see the Supporting Information). Lowering the temperature and

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.

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having an understanding of the chemistry also allows the reaction to be tracked by $^1$H 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 evidence, 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, 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 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-
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(k-2-tmeda)(PPh3)(ArCl)][I] (3a) and/or [Pd(k-2-tmeda)(PPh3)2(Ar)][I] (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 $k_{obs}=1.08 \text{s}^{-1}$ at 55°C with a fivefold excess of PPh3. Distinguishing which of 3a or 3b is the most important intermediate is possible by examining the effect of iodide and PPh3, respectively, on the second substitution reaction. Addition of ten extra equivalents of PPh3 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).

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 $[\text{Pd(PR}_3)_2(\text{Ar})(\text{X})]$ (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 AgNO3,[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 $[\text{Pd(PPh}_3)_2(\text{Ar})(\text{X})]$ (X = Br, Cl, F) have been previously synthesized. Oxidative addition of ArX (X = I, Br or Cl)[13] to $[\text{Pd(PPh}_3)_2]$ 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 $[\text{Pd(PPh}_3)_2(\text{Ar})(\text{X})]$ 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 $[\text{Pd(PPh}_3)_2(\text{Ar})(\text{X})]$ (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 N2 using standard glovebox or Schlenk procedures. The aryl iodide [4-ICI6H4CH2PPh3]PF6 was prepared by a known method, as was [Ph3PMe]PF6.[8] 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-ICI6H4CH2PPh3]PF6 (0.13 g, 0.2 mmol), tetrathymethyleneediamine (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 CDCl3, Mp 97°C. 1H NMR (300 MHz, CDCl3): δ = 2.27 (s, 6H, NCH3), 2.60 (s, 6H, NCH3), 2.65–2.73 (m, 2H, NCH3), 2.48–2.54 (m, 2H, NCH3), 4.32 (d, J = 14 Hz, 2H, PCH3), 6.28 (dd, JH = 8 Hz, JF = 2 Hz, 2H, C6H4), 6.99 (d, J = 8 Hz, 2H, C6H4), 7.3–7.8 ppm (m, C6H4, 15H); 31P NMR (300 MHz, CDCl3): δ = 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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[10] Data extracted from the Cambridge Crystallographic Database on 1289 square planar structures containing Pd–I and three other ligands of any type. The range is much smaller for the 57 square planar complexes with Pd–I, two nitrogen donors and one other ligand: 2.55 to 2.60 Å.


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