Direct observation of key intermediates by negative-ion electrospray ionisation mass spectrometry in palladium-catalysed cross-coupling†

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Negative-ion electrospray ionisation mass spectrometry with an anionic phosphine ligand enables detection of key intermediates in the Sonogashira reaction. MS/MS techniques are used to generate a Hammett plot for the key reductive elimination step.

Electrospray ionisation mass spectrometry (ESI-MS)[1] has great potential for exploring catalytic reactions, being fast, ultra-sensitive, and able to cope with complex mixtures.[2] Any ionic catalysts and their derivatives are abundant in the mass spectrum, while neutral reactants, solvents and products are absent. Palladium-catalysed cross-coupling reactions[3] have been analysed by ESI-MS since 1994,[4] and further reports have emerged regularly.[5] All have involved the positive-ion mode, and ionisation of the metal complexes of interest has proceeded through "sporting methods", for example loss of a halide ligand to produce $[M - X]^+$ ions, or oxidation to form $[M]^{\bullet +}$ radical cations. The latter is due to the fact that for every *excess* positive ion created in the ESI process, something must be oxidised at the charged capillary.[6] Often, this is oxidation of iron from the stainless steel capillary, but it can also be solvent or analyte; so Pd(0), being easily oxidised itself, loses an electron and forms the corresponding Pd(I) complex. And herein lies the difficulty with positive-ion ESI-MS analysis of low oxidation state electron rich metal complexes: whatever the reactivity of Pd(I) (little is known of this unusual oxidation state), it is unlikely to be the same as that of Pd(0). Similarly, $[M - X]^+$ ions are unlikely to react in the same fashion as the M precursor. Accordingly, we turned our attention to the negative ion mode. Pd(0) is easy to oxidise but hard to reduce, so a negative charge was attached to the metal complex *via* a charged ligand,[7] a derivative of the water-soluble monosulfonated triphenylphosphine, $[Na][PPh_2(m\text{-}C_6H_4SO_3)]^-$ ([Na][**1**]). By replacing Na^+ with $[(Ph_3P)_2N]^+$ (PPN) through salt metathesis, [PPN][**1**] is soluble in organic solvents and suitable for ESI-MS.‡

A dichloromethane solution of equimolar amounts of $Pd(PPh_3)_4$ and [PPN][**1**] provides a negative-ion ESI mass spectrum consisting of just $[Pd(\mathbf{1})(PPh_3)_n]^-$ (n = 1, 2). Bis(phosphino)palladium compounds are thought to be the key intermediates in a huge range of cross-coupling reactions,[8] and Fig. 1 represents the first direct MS observation of such a species unaltered by oxidation or ligand dissociation. Reactivity with trace O_2 can be eliminated by performing all reaction handling in an adjacent glovebox.[9]

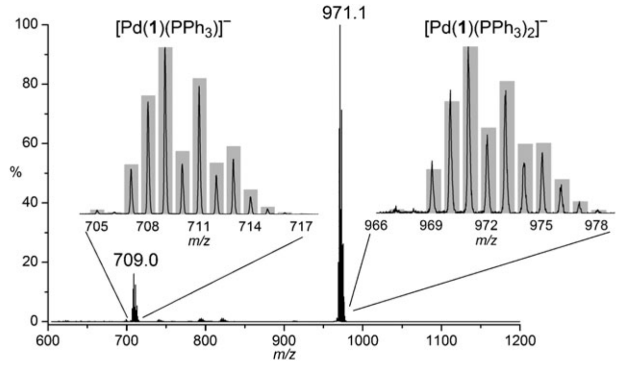

Fig. 1 Negative-ion ESI-MS of $Pd(PPh_3)_4$ + [PPN][**1**] in CH_2Cl_2. Insets: isotope pattern matching for $[Pd(PPh_3)_n(\mathbf{1})]^-$ (n = 1 and 2).

Formation of unsaturated $Pd(PR_3)_2$ followed by oxidative addition are widely considered to be the first steps in Pd-catalysed cross-coupling reactions involving aryl halides.[10] We chose to study the copper-free Sonogashira reaction, the coupling of an aryl halide (Ar–X) with a terminal alkyne (RC_2H).[11]

Addition of phenyl iodide to the solution resulted in immediate and complete consumption of all Pd(0) species and formation of the expected Pd(II) complex $[Pd(\mathbf{1})(PPh_3)(Ph)(I)]^-$, the first intermediate in the catalytic cycle. When subjected to MS/MS analysis, this ion decomposes exclusively by phosphine dissociation (of either **1** or PPh_3, see ESI†). Addition of phenylacetylene and NEt_3 to the mixture containing catalytic amounts of $[Pd(\mathbf{1})(PPh_3)(Ar)(I)]^-$ resulted in the formation of another intermediate, $[Pd(\mathbf{1})(PPh_3)(Ar)(C_2Ph)]^-$ (Fig. 2).

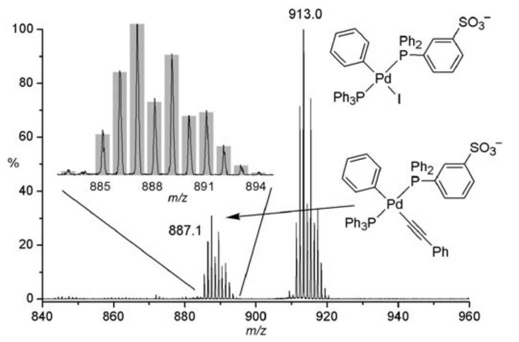

Fig. 2 Negative-ion ESI-MS of $Pd(PPh_3)_4$ + [PPN][**1**] + 100 × ($PhI + PhC_2H + NEt_3$) in CH_2Cl_2. Inset: isotope pattern match for $[Pd(\mathbf{1})(PPh_3)(Ph)(C_2Ph)]^-$.

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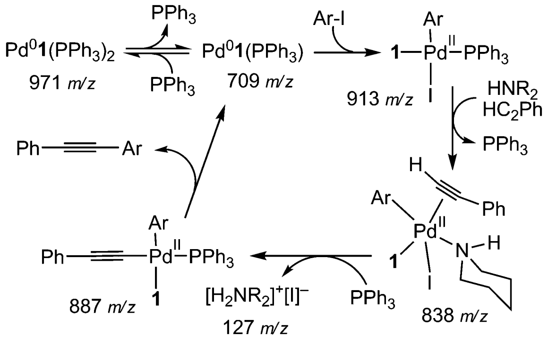
We see no sign of postulated anionic intermediates generated by halide addition, despite the iodide present.[12] Using morpholine or piperidine allowed observation of new amine-containing species including $[Pd(\mathbf{1})(HNR_2)(Ar)(I)(HC_2Ph)]^-$, in which both acetylene and amine are bound to the metal. This ion is related to the $Pd(L)_x(Ar)(X)(HC_2Ph)$ intermediate suggested elsewhere,[13] and is the first characterisation of such a species. Collision-induced dissociation (CID) of these complexes resulted in facile loss of HC_2Ph then the secondary amine (ESI†). No loss of benzene is observed, suggesting the alternative structure compatible with the composition of the 838 *m*/*z* ion, the six-coordinate Pd(IV) ion $[Pd(\mathbf{1})(HNR_2)(Ar)(I)(H)(C_2Ph)]^-$, is not present. Loss of the neutral ion pair $[H_2NR_2]^+[I]^-$ is also not observed (suggesting the ion is not a simple aggregate of two anions and a cation). The deprotonation step alone is disfavored in the gas phase as it would require the energetically prohibitive separation of $[H_2NR_2]^+$ from a dianion. Scheme 1 summarises the species observed.

The $[Pd(\mathbf{1})(PPh_3)(Ar)(C_2Ph)]^-$ ions are particularly interesting, because they undergo fragmentation pathways relevant to their chemistry, distinctly different to that of the aryl iodide complexes. As well as simple phosphine dissociation, a competing pathway is reductive elimination (RE) of the two carbon fragments to form the $[Pd(\mathbf{1})(PPh_3)]^-$ product ion (Fig. 3).

The extent to which reductive elimination occurs is dependent on the nature of Ar (in contrast to the PPh_3 dissociation pathway, which proceeds to an approximately equal extent for all Ar, see ESI†). The *para*-substituted aryl iodides p-XC_6H_4I (X = NH_2, OMe, Me, H, F, COMe, CF_3, CN and NO_2) were subjected to collision-induced dissociation (CID) at identical energy, and the logarithm of the ratio of the product (P) ion $[Pd(PPh_3)(\mathbf{1})]^-$ to the reacting (R) ion $[Pd(\mathbf{1})(PPh_3)(Ar)(C_2Ph)]^-$ were plotted against the corresponding Hammett σ_p parameter for each substituent to generate a Hammett plot from CID MS/MS data (Fig. 4). Linear free-energy correlations are applicable to gas-phase ionic systems,[14] and O'Hair's ESI-MS/MS investigation of the deamination of protonated phenylalanine derivatives is conceptually the most similar to the data presented here.[15]



Scheme 1 Intermediates directly observed by negative-ion ESI-MS. Free iodide is also observed.

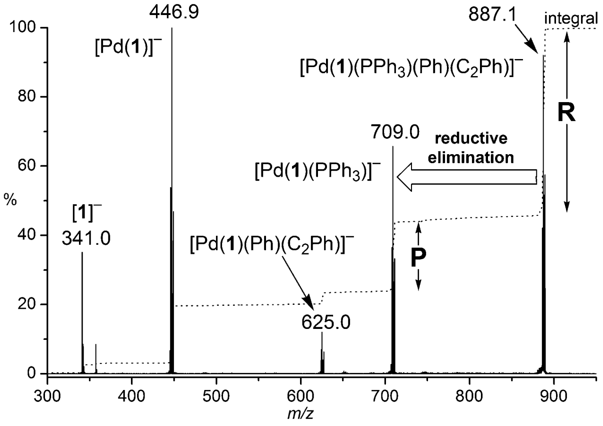


Fig. 3 Negative-ion ESI-MS/MS of $[Pd(\mathbf{1})(PPh_3)(Ph)(C_2Ph)]^-$, showing reductive elimination of PhC_2Ph, at a collision voltage of 15 V.

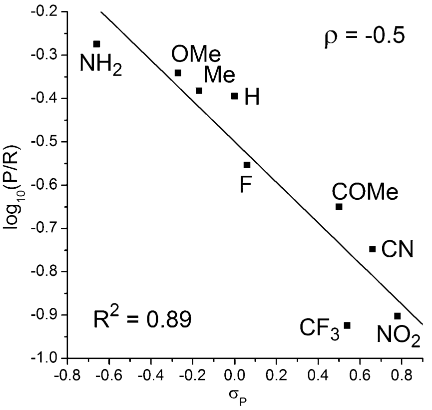


Fig. 4 Plot of $\log_{10}(P/R)$ *vs.* Hammett σ_P parameter.

The slope of the plot ($\rho = -0.5$) indicates that reductive elimination is most favorable for aryl groups with electron-donating substituents, consistent with results obtained for bis-aryl platinum complexes[16] and with theoretical methods.[17] What is remarkable about the experiment described here is that MS/MS allows an experiment to be conducted in the gas phase that is difficult (or even impossible) in solution due to the fact that $Pd(PR_3)_2(Ar)(C_2Ar')$ species have limited stability, decomposing through reductive elimination. As a result, conventional studies rely on conclusions drawn through model studies that examine related platinum complexes. However, doing experiments in the gas-phase is straightforward: no synthesis is required and all isolation and purification of the desired intermediate(s) is performed mass spectrometrically. This approach represents a remarkably fast way of gaining significant insight into fundamental steps in a catalytic cycle.

Negative-ion mode ESI-MS in conjunction with a negatively-charged ligand offers a fruitful approach to analysis of low oxidation state, electron-rich metal complexes in catalytic reactions. Characterisation of catalyst precursors and plausible intermediates during a reaction is straightforward. Simple CID experiments can be employed to rapidly generate a Hammett plot for the reductive elimination step, whose construction would be laborious or even impossible by conventional means.

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Notes and references

‡ Experimental details: all synthesis was performed under an inert atmosphere of N_2 using standard glovebox or Schlenk procedures. Solvents were HPLC grade and purified on an MBraun solvent purification system. All other chemicals were used as obtained (Aldrich, Oakville, Canada). Gases were obtained from Airgas (Calgary, Canada). NMR spectra were collected on either an AV-300 or AV-360 Bruker spectrometer. Internal references to $CHCl_3$ (1H δ = 7.26 ppm) and external reference to 85% aqueous H_3PO_4 (^{31}P) were used as appropriate. $[NH_4][\mathbf{1}]$[18] (11.38 g, 31 mmol) was dissolved in 100 mL warm deionised water, and bis(triphenylphosphine)iminium chloride (17.34 g, 31 mmol) was dissolved in 60 mL dichloromethane. The two solutions were mixed together, stirred vigorously for 5 min and transferred to a separating funnel. 30 mL of water containing ammonium chloride was added, the mixture was shaken and allowed to settle. The lower organic layer was collected, and the majority of the solvent was removed by rotary evaporation. The resulting material was left under vacuum overnight to obtain the product as a white solid (24.21 g, 89% yield). ^1H NMR (300 MHz, CD_2Cl_2) δ = 7.14–7.20 (m, 1 H), 7.22–7.32 (m, 10 H), 7.44–7.52 (m, 25 H), 7.62–7.68 (m, 6 H), 7.80–7.86 (m, 2 H). ^{31}P NMR (300 MHz, CD_2Cl_2) δ = −4.5 (s, $PPh_2C_6H_4SO_3^-$), 21.6 (s, $N(PPh_3)_2^+$). All the mass spectra and gas phase experiments were performed on a Micromass Q-ToF *micro* hybrid quadrupole/time-of-flight mass spectrometer in negative-ion mode using pneumatically-assisted electrospray ionisation. Capillary voltage: 2900 V. Cone voltage: 10 V. Extraction voltage: 0.5 V. Source temperature: 30 °C. Desolvation temperature: 60 °C. Cone gas flow: 100 L h^{-1}. Desolvation gas flow: 200 L h^{-1}. Collision voltage: 2 V (for MS experiments). Collision voltage: 15 V (for MS/MS experiments). Collision pressure: $2.05 \pm 0.05 \times 10^{-5}$ mbar. Low and high mass resolution: 10.0. MCP voltage: 2700 V. Solutions were run in dichloromethane and introduced to the mass spectrometer by a syringe pump at a rate of 20 μL min^{-1}. MS/MS experiments were conducted with argon in the collision cell. The appropriate peak was mass selected (usually with a broad enough window to accommodate the full isotope pattern, *i.e.* ~8 *m*/*z*) and the selected ion fragmented at the stated voltage(s) in the argon-filled collision cell. All mass spectra were collected for a sufficiently long period to obtain a signal-to-noise ratio of at least 20 : 1; this ranged from a few seconds for ordinary mass spectra to 10 minutes for some of the MS/MS experiments. For each experiment, palladium tetrakistriphenylphosphine (0.006 g, 5 μmol) and **1** (0.004 g, 5 μmol) were dissolved in 5 mL dichloromethane. For reductive elimination experiments, the catalyst solution was then mixed with the appropriate *para*-substituted aryl iodide (0.4 mmol), and phenylacetylene (0.044 mL, 0.4 mmol) and triethylamine (0.055 mL, 0.4 mmol) were added. The reaction mixture was allowed to stand for 10 min, and then injected into the MS at 20 μL min^{-1}. The amounts correspond to a 1.25% catalyst loading (and 1.25% loading of the charged ligand).

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