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Practical approaches to the ESI-MS analysis of catalytic reactions

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Electrospray ionization mass spectrometry (ESI-MS) is a soft ionization technique commonly coupled with liquid or gas chromatography for the identification of compounds in a one-time view of a mixture (for example, the resulting mixture generated by a synthesis). Over the past decade, Scott McIndoe and his research group at the University of Victoria have developed various methodologies to enhance the ability of ESI-MS to continuously monitor catalytic reactions as they proceed. The power, sensitivity and large dynamic range of ESI-MS have allowed for the refinement of several homogenous catalytic mechanisms and could potentially be applied to a wide range of reactions (catalytic or otherwise) for the determination of their mechanistic pathways. In this special feature article, some of the key challenges encountered and the adaptations employed to counter them are briefly reviewed. Copyright © 2014 John Wiley & Sons, Ltd.

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Electrospray ionization mass spectrometry (ESI-MS) is a technique that at first blush seems ideally suited to the examination of catalytic reactions. It is a fast technique which possesses great sensitivity,[1] it can cope with mixtures intractable to many other techniques[2] and it has a high dynamic range.[3] These properties are all useful for analysis of complex reaction mixtures. The sensitivity allows for detection of trace intermediates. Its speed – one spectrum takes a second or less to acquire – enables dense data to be collected on reactions that are over in mere minutes, but can easily be extended to reactions lasting hours.[4] Catalytic reactions are almost by necessity a soup of reactants, products, byproducts, intermediates, resting states and decomposed material; intrinsic to the property of ESI-MS is that it produces well-separated and diagnostic signals for individual components, making it capable of dissecting such mixtures. Finally, a dynamic range across several orders of magnitude enables accurate measurement of abundant and traces components alike.[5]

Accordingly, ESI-MS was ear-marked as a promising technique for the analysis of catalytic reactions almost as soon as the first commercial machines appeared. The ground-breaking paper was the 1994 report by Canary,[6] detailing studying the mechanism of the Suzuki cross-coupling reaction. This paper introduced the idea of using a substrate that was especially amenable to the ESI-MS process, in this case a brominated pyridine. The pyridine, carrying as it did a peripheral basic site that was uninvolved in the reactivity but was easily protonated to provide $[M+H]^+$ ions, showed how the use of appropriate substrates for reactions would light up not only that species, but whatever intermediates, resting states and decomposition products that substrate was bound to. Canary used this property to take snapshots of the speciation of the reaction as it proceeded and obtained interesting insights into the nature of the reaction. However, despite the promising start, it is fair to say that progress has stuttered in the two decades following, with the vast majority of mechanistic studies still being conducted with other methods. The question of why ESI-MS was not a standard method for catalytic analysis was one we asked ourselves nearly ten years ago, and we've spent the intervening period finding out why, and developing solutions to the problems we encountered. Fortunately, we had the benefit of years of pioneering work by others, and the community has continued to inspire and innovate. This short review will, however, restrict itself to the approaches *we* employ to solve the problems and conclude with a short section on the information that can be obtained on catalytic reactions using these techniques. Many of the suggestions are simple precautions, tips and protocols which will be helpful for those looking to make better use of a technique available in most large research facilities and chemistry departments. Collectively, they can be used to enable researchers to gain insights that are beyond the capabilities of competing methods.

Cross contamination

Most spectroscopic methods do not need to concern themselves with what the previous user was examining. Provided the experiment uses clean apparatus, the only analyte being detected will be the intended one. However, ESI-MS has the notable feature that all samples pass through the same infusion system, and the sensitivity of the technique and variation in ionization response for different molecules and ions means that it is entirely plausible that an intense signal observed in a spectrum in fact originated from the previous user's sample. Safeguarding against such cross-contamination requires certain precautions.

A. Minimize shared apparatus. It is always necessary to share the capillary from which the spray emerges (and depending on instrumental design, an internal capillary designed to

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enhance desolvation), but the plumbing leading up to that point (typically flexible PEEK or fused silica tubing and the various chromatography fittings and syringe) does not, and indeed should not, be shared between experimenters. To maximize control over cross-contamination, each research group (or better, each individual) using a shared ESI-MS should possess their own infusion system (a simple such example is shown in Fig. 1).

B. Clean the infusion system offline. Before and after analysis, rinse several syringes of various solvents through the infusion system to waste. This should ensure that any species remaining in the infusion system will be washed out so as to not contaminate the next experiment using that infusion system.

C. Run a background spectrum. Too often, the first spectrum analyzed is that of the sample, in which case it is impossible to distinguish between residual peaks and the real thing. Background analysis is a trivially easy and quick step that can be conducted concurrently with the cleaning procedure. Substantial residual signal should be eliminated prior to analysis by thorough cleaning of the source and infusion system.

D. Use a sequence of solvents to clean instrument. Rinsing with only the solvent to be used in analysis can be frustratingly slow to clear residual contaminants, particularly if their solubility in the solvent of choice is low. We have found a helpful sequence involves rinsing with a sequence of solvents starting with the most polar then covering the range to the most non-polar solvent regularly used in the instrument, then back to the solvent of interest. Such a protocol is effective at clearing the more polar contaminants as well as the greasiest ions in the system, but if it fails to clear the problematic signals, dismantling and cleaning the source thoroughly offline are probably required. Fortunately, an ESI-MS source is at atmospheric pressure, so even the extreme case of having to dismantle the source for cleaning can be done quickly and easily and does not require breaking the vacuum of the mass spectrometer proper.

E. Dilute sample appropriately. New users of the ESI-MS with a synthetic (rather than analytical) background are rarely prepared for the increase in sensitivity over other forms of analysis. A simple routine can ensure the instrument is not contaminated. Take ~1 mg of sample, and dissolve in a few drops of a suitable solvent (not necessarily the one to be used for analysis – THF for example is not an especially good ESI-MS solvent, but is an excellent solvent for a wide range of organometallic compounds). Make this solution up to 1 ml in the ESI-MS solvent (this is solution B in Fig. 2). Take a drop of this solution, and add it to 1 ml of the ESI-MS solvent (solution C). Repeat for solution D. These dilution steps take the concentration from approximately 1 mg/ml to a few ug/ml. Begin the analysis with solution D; often, this will be perfectly adequate for the acquisition of good data, but in cases where it is not (e.g. where the ESI-MS response of the analyte is low), solution C is still on hand. If solution B is required, chances are that ESI-MS is *not* the appropriate method for analysis and another analytical approach should be sought.

Avoiding aggregation

The sensitivity of ESI-MS often takes new users by surprise, especially when dealing with species that are inherently charged. As discussed above, a common error is to run spectra at concentrations typical of ^{1}H NMR, which will often result in contamination of the source and aggregation effects in the spectra, particularly in cases where ion pairing is strong. Series of peaks are observed of the form $[(\text{cation})_x(\text{anion})_{(x-1)}]^+$ ($x = 1, 2, 3\ldots$) in the positive ion mode and $[(\text{cation})_{(y-1)}(\text{anion})_y]^-$ ($y = 1, 2, 3\ldots$) in the negative ion mode. This is a sufficiently reliable phenomenon that sodium iodide solutions are frequently used to calibrate MS instruments, as aggregate peaks with spacing of 140 Da (NaI) extend beyond $m/z > 2000$. Running samples at lower concentrations is a rapid way of establishing whether an observed ion is an aggregate ion or not (Fig. 3). MS/MS studies can also often reveal the same information, as aggregates fragment cleanly through loss of (overall) neutral ion pairs.

Protection from oxygen and moisture

The injection system shown in Fig. 1 can be easily loaded inside a glovebox. Any decomposition will be limited by the length of the tubing and its small inner diameter (typically in the order of 100 microns). For longer analyses, another solution will be detailed later. More conveniently for extremely air-sensitive work, the glovebox can be located adjacent to the mass spectrometer, and a syringe pump located inside. The only modification necessary is placing a feedthrough in a location that will minimize the length of tubing required between pump and source (Fig. 4).[8]

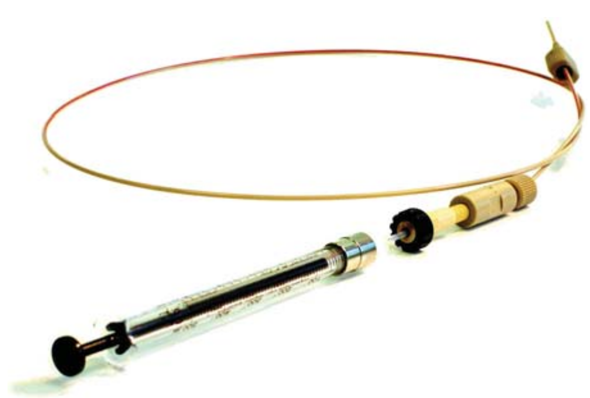

Figure 1. An air-tight syringe, PEEK tubing (or fused silica) and fittings are recommended for each research group (or individual) using an ESI-MS.

Figure 2. A milligram of sample (A), dissolved in 1 ml of solvent (B), diluted by a factor of 20 (C) and further diluted by a factor of 20 (D).

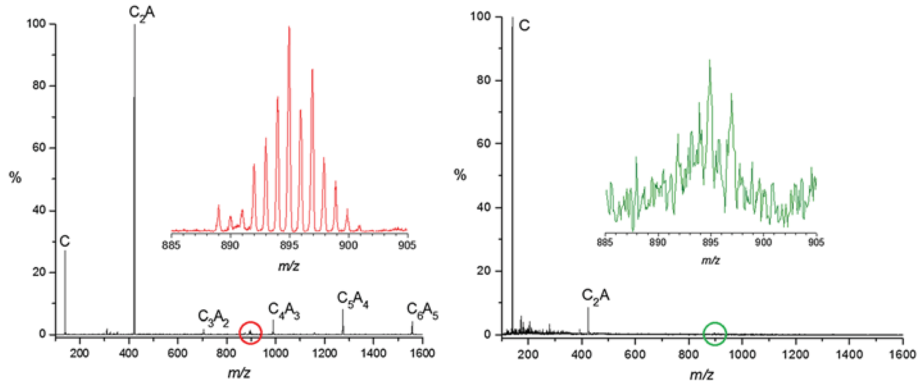

Figure 3. The ionic liquid [C4mim][PF$_6$] (=[C][A]), containing the catalyst [Ru(η^6-*p*-cymene)(κ^2-triphos)Cl]$^+$ diluted in methanol to concentrations of 10 (left) and 0.001 mmol l^{-1} (right). Note the disappearance of aggregates at low concentration (also note the metal complex is more difficult to detect).[7]

The necessity for scrupulously dry solvents and good atmosphere cannot be overstated – routine precautions used for synthesis are insufficient for ESI-MS analysis, because the technique is sensitive enough to detect species present at the part per million level. Unfortunately, most drying methods only get solvents dry to about 5–10 ppm (alkali metal stills, solvent purification systems), and to get solvents maximally free of water, dry solvent should be moved into the glovebox in a flask containing plenty of activated molecular sieve and left for a few days.[9] Evidence for the efficacy of this method can be gleaned from studies of very reactive compounds, for example the large aluminoxanate anions present in solutions of methylaluminoxane that stabilize the active component, [$AlMe_2$]$^+$.[10] These large anions contain considerable bound $AlMe_3$, which is readily hydrolyzed by water to form Al–OH groups in place of Al–Me. This transformation increases the mass of the anion by 2 Da for each such hydrolysis, resulting in additional peaks at higher *m/z*. Given that such anions can contain over 40 Al–Me bonds, all very susceptible to hydrolysis, the potential for trace water to wreak havoc with the analysis is high, not to mention causing issues with aggregation and ultimately blockage of the capillary used to spray the sample.

A further issue arises when the decomposition product has a higher ionization response than the original compound. A good example is in the analysis of phosphines, which are not especially basic and hence provide very weak [M + H]$^+$ ions. Phosphine oxides, on the other hand, provide very strong signals in association with alkali metals and with protons,[11] so even low levels of oxidation may lead to spectra dominated by [(R_3PO)$_n$ + M]$^+$ (M = H, Na, K; *n* = 1–4), even on samples which show very little or no oxide by ^{31}P NMR.

Figure 4. Glovebox adjacent to the ESI-MS. The syringe pump in use is located inside the glovebox.

Soft ionization conditions

'Standard operating conditions' for ESI-MS are typically targeted at complete desolvation of a large, multiply charged biomolecule in a fraction of a second. Such conditions are rarely optimal for ESI-MS analysis of transition metal complexes, and extensive fragmentation can occur under such circumstances (Fig. 5).

The degree to which the harshness of desolvation can be adjusted is quite remarkable, to the point that heavily solvated ions can be readily detected under certain source conditions. This is especially true in water, and protonated water clusters can be reliably used as a means of calibration. However, ions other than protons can be transported into the gas phase accompanied by dozens of water molecules, hence blurring the line considerably between what constitutes a gas phase ion and an ion contained in a very small solution. Under these conditions, lanthanide (Ln) ions may be observed as [Ln(H_2O)$_x$]$^{3+}$ ions, and if fragmented through collision-induced dissociation (CID), lose water and eventually undergo a charge-reduction process whereby an inner-sphere water ligand protonates an outer-sphere water molecule to form a hydroxy ligand and a solvated proton.[12] Both

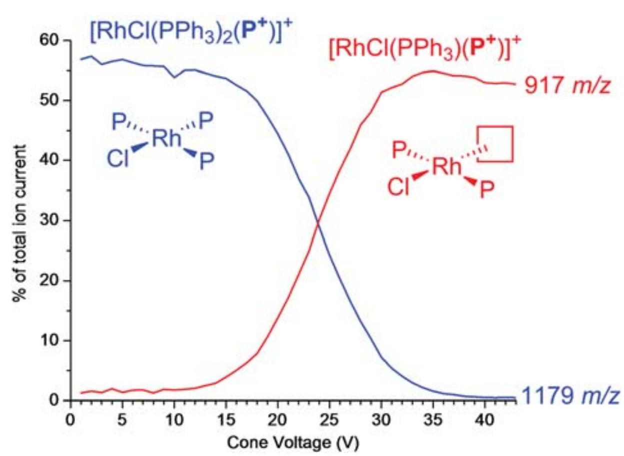

Figure 5. Sensitivity scales approximately linear with cone voltage, but at the cost of softness of ionization. Note the extent of fragmentation at high values. **P$^+$** is the charge-tagged phosphine ligand [$Ph_2P(CH_2)_6PPh_2CH_2Ph$]$^+$.

being positively charged, the ions separate into $[Ln(H_2O)_y(OH)]^{2+}$ and $[H(H_2O)_z]^+$, and the solvated proton evaporates from the larger droplet into the gas phase (Fig. 6 shows the mass spectrum for Ln = La).

Other ions can be similarly investigated; for example, differing levels of methylation of guanidinium ions produce quite different degrees of hydration.[13] There seems little reason why this approach could not be applied to a wide range of questions in chemistry that probe inner- and outer-sphere coordination and reactivity.

Data presentation

Inorganic and organometallic complexes tend to decompose in the gas phase in a predictable way, which allows a measure of structural elucidation in the form of MS/MS studies. ESI-MS is a soft ionization technique and so transfers ions into the gas phase essentially intact. There are, however, ways of depositing energy into the ions to cause them to fragment, and this end is usually achieved through CID. Essentially, it involves accelerating the ions in the presence of (effectively) stationary gaseous atoms or molecules (almost always argon or dinitrogen), and the resulting energetic collisions result in the ions heating up to the point that unimolecular decomposition occurs. For an organometallic complex containing L-type (neutral) and X-type (anionic) ligands, fragmentation usually involves loss of monodentate L-type ligands first, as neutral molecules. Metal carbonyl complexes will lose carbon monoxide; metal phosphines will lose neutral phosphine molecules, etc. In general, the first few losses are representative of what you might expect would happen in solution if you heated the complex.

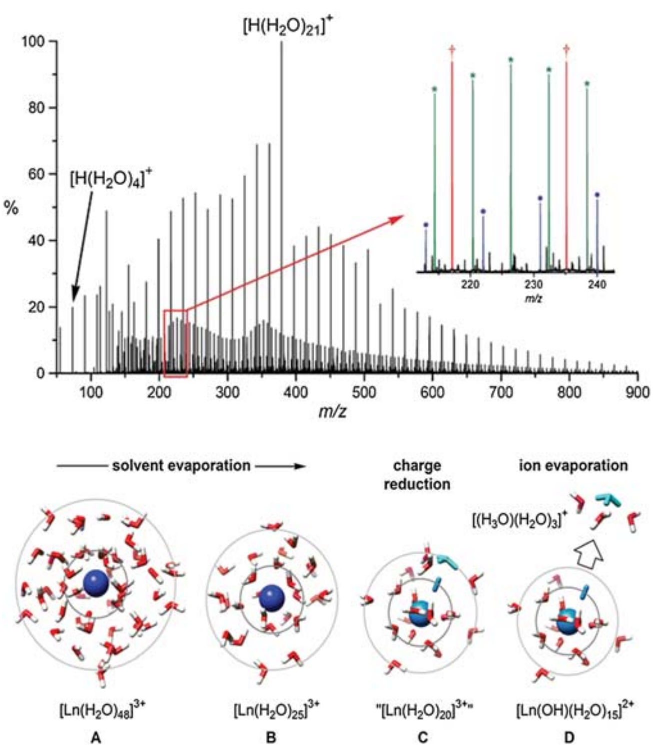

Figure 6. Positive-ion ESI mass spectrum of an aqueous solution of $LaCl_3$. The spectrum is dominated by water clusters (red †), in particular the 'magic' cluster $[H(H_2O)_{21}]^+$, but also present are $[La(H_2O)_n]^{3+}$ (green *) and $[La(OH)(H_2O)_n]^{2+}$ water clusters (blue •). The inset shows clearly the differences in spacing for the 1+, 2+ and 3+ clusters (18, 9 and 6 Da, respectively). Bottom: cartoon of the solvent/ion evaporation process.

Parsing all this CID data from product ion MS/MS spectra (the classic experiment for determining unknowns: select a particular ion in the first mass analyzer, fragment it in a collision cell and analyze the fragments in the second mass analyzer) is not trivial, not least because there is so much of it. Faced with the prospect of arbitrarily keeping some of the data and discarding the rest, we instead chose to keep all of it and display it in an alternative fashion: as a 3D surface, where *m/z* ratio and fragmentation energy (cone/collision voltage) are two of the axes, and ion intensity the third, an approach we call 'energy-dependent ESI-MS'.[14–17] An example is shown in Fig. 7, for the anionic metal carbonyl cluster $[H_3Ru_3(CO)_{12}]^-$.

No commercial implementation of this approach has appeared, but ramping the CID energy and observing the incremental changes are a helpful experiment even in the absence of a convenient means of depiction. In particular, it helps identify the unimolecular transformation most probable under heating. For example, CID of $(Ph_3P)(\mathbf{1})Pd(Ar)I$ (**1** = sulphonated PPh_3; Ar = aryl) results in phosphine dissociation, but CID of $(Ph_3P)(\mathbf{1})Pd(Ar)C_2Ph$ instead results in reductive elimination of ArC_2Ph, in keeping with the productive step of the Sonogashira cross-coupling protocol to form new C_{sp}–$C_{sp}2$ bonds (Fig. 8).[19]

Analysis in non-polar solvents

ESI-MS is notoriously limited to polar solvents, and though this problem is well-known it is generally described empirically in textbooks without a fundamental explanation. However, because at its heart, ESI is an electrochemical process[20,21] – in order to create an excess of positive ions, something needs to be oxidized, be it solvent, capillary or solute – we reasoned that perhaps the lack of conductivity was problematic. Accordingly, we tried using a supporting electrolyte in the form of an extremely lipophilic ionic liquid, $[P(C_6H_{13})_3(C_{14}H_{29})]^+[NTf_2]^-$. We found that at concentrations of approximately 10^{-5} M even alkanes behaved normally as ESI-MS solvents (Fig. 9).[22] Other non-polar solvents including toluene behaved themselves at even lower levels of adulteration, and solvents such as dichloromethane and fluorobenzene require no additional ions to provide satisfactory data.

Selection of suitable ions and counter-ions

To access the advantages of ESI-MS as a reaction-monitoring tool, the species of interest must be charged.[23,24] This can usually be facilitated by alkylation of a phosphine or an amine[25] on either an ancillary ligand,[26] or a reaction substrate.[27] The ideal tags provide similarly high responses in ESI mass spectra for all species containing the tag due to their high surface activity. Surface activity in the context of ESI is the propensity of an ion to find itself on the outside of an evaporating droplet rather than solvated and/or ion paired in the interior.[28] As the surface charge builds up as the solvent departs, the ions on the surface are those most likely to leave the droplet and hence consume the excess charge generated by the ESI process. Happily, charged tags bestow this property roughly equivalently to all species of similar *m/z*, so the total ion current (TIC) generally stays approximately constant over the course of the reaction. Large perturbations in the TIC indicate something problematic is going on (e.g. the formation of a zwitterion, generation of a multiply charged ion, precipitation/polymerization, etc).

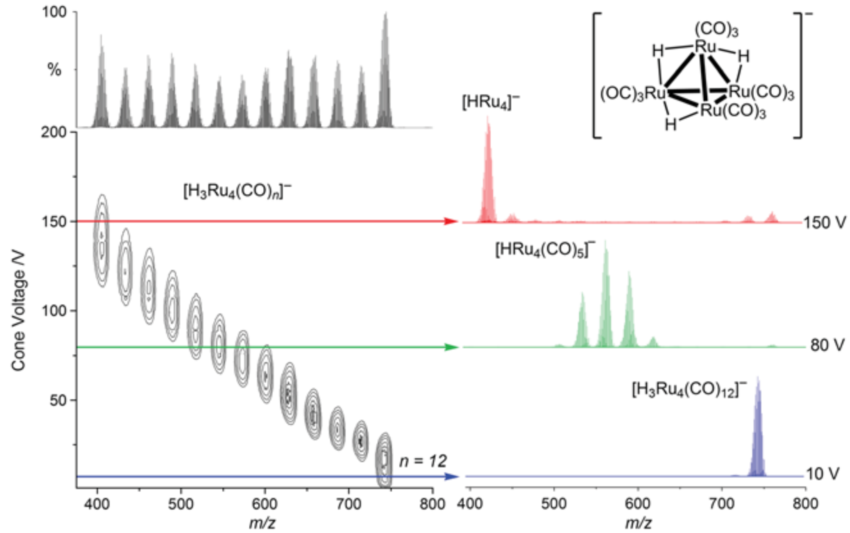

Figure 7. The left-hand contour plot of this EDESI-MS experiment on $[H_3Ru_4(CO)_{12}]^-$ clearly shows the loss of 12 CO ligands as the cone voltage is increased. The three conventional mass spectra at the right provide snapshots of the ligand stripping process, at 10, 80 and 150 V; note that only a fraction of the product ions appear in each spectrum. Figure adapted from reference.[18]

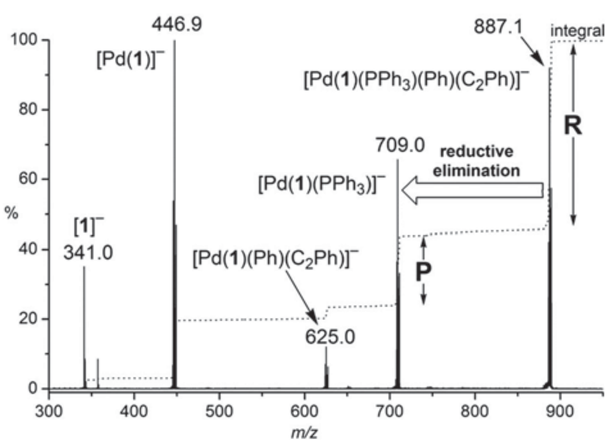

Figure 8. Negative-ion ESI-MS/MS of $[Pd(\mathbf{1})(PPh_3)(Ph)(C_2Ph)]^-$, showing the reductive elimination of PhC_2Ph as the principal fragmentation pathway. [19]

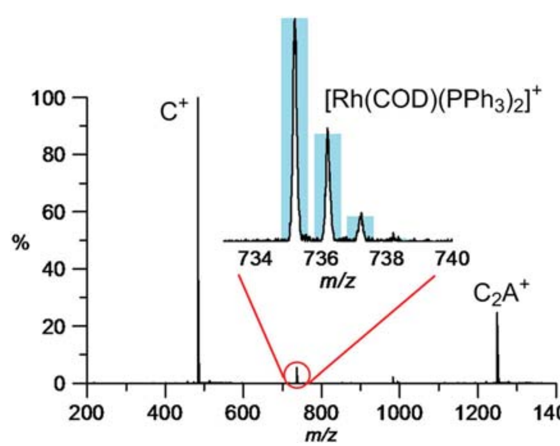

Figure 9. Positive-ion ESI-MS of $[Rh(cod)(PPh_3)_2]^+$ in cyclohexane and 10^{-5} mol l^{-1} $[P(C_6H_{13})_3(C_{14}H_{29})]^+[NTf_2]^-$. Inset: expansion of isotope pattern and match with calculated pattern (histogram).

We are particularly fond of alkyltriphenylphosphonium tags, because these tend to be straightforward to make, are not prone to ion-pairing effects, do not become involved with the reaction under study, and have high surface activity (i.e. high 'ESI-MS response'). We have published simple approaches to the preparation of these charged tags for phosphines,[29] aryl halides[30] and alkynes[31] using $[–CH_2PPh_3][PF_6]$ as the spectrometric handle, typically in two steps: treatment of triphenylphosphine with a functionalized alkyl halide followed by a salt metathesis to replace the halide counterion with a non-coordinating counterion. The more weakly coordinating the counterion, the better, in order to minimize ion pairing and enhance signal intensity. We typically use $[PF_6]^-$, as it rarely becomes involved with reactions, has good solubility characteristics in less polar solvents and also crystallizes well if structural confirmation is important.

Negatively charged tags can be important in cases where deleterious oxidation of the compounds of interest occurs in the positive ion mode. We noticed this in attempts to study Pd(0) species, which readily oxidize to cationic Pd(I) species when studied by ESI-MS in the positive ion mode. However, when we used a negatively charged sulfonated phosphine instead, the speciation showed no signs of electrochemical activity and quality spectra of the expected species were observed in the negative ion mode (Fig. 10).[19]

Ion suppression effects can be problematic in ESI-MS. This effect is similar to the matrix suppression effect seen in LC/ESI-MS, where the addition of one species alters the ionization efficiency of other species and will be over- or under-represented in the overall spectrum accordingly.[32] However, we have found it to be much less of a problem when all species are charged by virtue of a charged tag, because the tag confers high surface activity similarly well to all species to which it is attached.

Gas-phase reactions

Ion trap mass spectrometers will often have ions that appear due to reactions of the trapped ions with gas-phase molecules. Because ion traps operate at higher pressure than most other methods, residual solvent (especially water) molecules will react

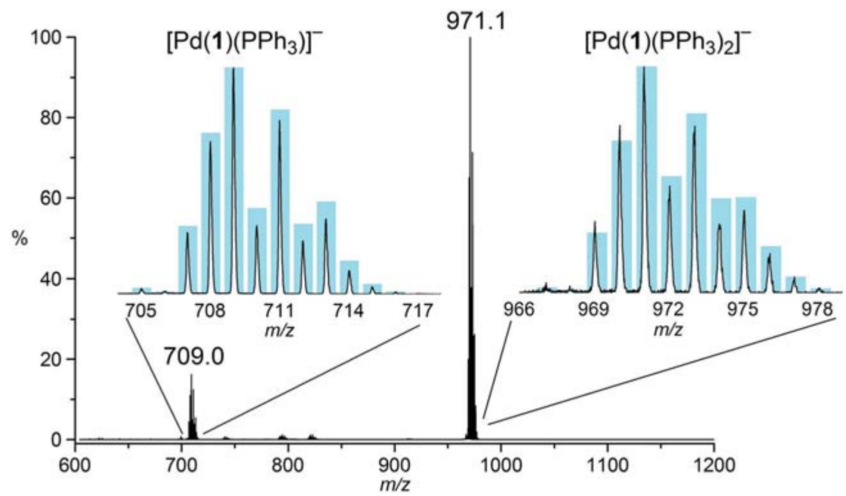

Figure 10. Negative-ion ESI-MS of $Pd(PPh_3)_4$ + [PPN][**1**] in CH_2Cl_2. Insets: isotope pattern matching for $[Pd(PPh_3)_n(\mathbf{1})]$ (n = 1 and 2). (**1** = $[PPh_2\{m\text{-}C_6H_4SO_3\}][(Ph_3P)_2N]$).

with ions that accept them. For reactive organometallics, this is especially probable since many metals are strongly oxophilic. Such reactions are usually not problematic, as understanding the source of such ions is typically sufficient for correct interpretation,[33] and the promiscuity of ions towards reaction offers an entirely new opportunity to push the instrument beyond a simple means of analysis, and instead using it as a reaction chamber. Details of such reactions are beyond the scope of this perspective (and have been well reviewed elsewhere),[26,34–39] but an example from our group is illustrative of the kind of experiment that can be conducted.

There has been much discussion as to whether mono- or bis-ligated palladium complexes are responsible for the oxidative addition of aryl halides, with a consensus coming down firmly in favor of the mono-ligated for bulky *N*-heterocyclic carbenes and phosphines, with the bis-ligated complex for less sterically demanding ligands and chelating ligands. The gas phase allows direct comparison between the reactivity of the direct species, since they can be selectively isolated and reacted without complications arising from decomposition, aggregation, solvent effects, etc. The gas phase also offers an ideal complement to computational approaches. We reacted each of the halobenzenes ArX (X = F, Cl, Br and I) with PdL and PdL_2 (Fig. 11; where L = PPh_3 or its monosulfonated equivalent). Only ArI reacted with PdL_2, but all of the halobenzenes reacted with PdL, with increasing reactivity for the heavier halogens and to a degree that was at least 3 orders of magnitude greater. However, computational results suggested that the observed reactivity was only as far as the adduct for X = F and Cl, and fortunately this hypothesis could be tested by employing an additional stage of MS/MS. CID experiments demonstrated that PdL(PhX) (X = F, Cl) decomposed by loss of P, but PdL(PhI) decomposed by loss of L. For PdL(PhBr), the two processes were competitive. The revised order of reactivity agreed closely with the theoretical predictions.[40]

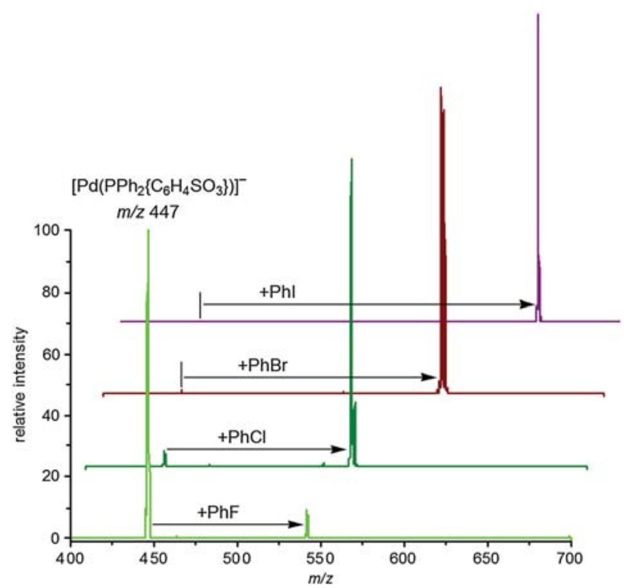

Figure 11. Reactivity of gas-phase monoligated anionic palladium phosphine complex $[Pd(PPh_2(C_6H_4SO_3)\}]^-$ with PhX (X = F, Cl, Br and I).

Continuous reaction monitoring

Probably, the most transformative change in the way we use MS came about from a simple development designed to transport reaction solutions directly into the mass spectrometer. We wanted to avoid use of any sort of pumping system, for two main reasons: the internal volume of even the smallest pumps is too high for this application, and pumps contain numerous different materials of varying resistance to the wide range of solvents, catalysts and substrates that would be passed through them. Accordingly, we turned to a time-honoured method in organometallic chemistry for transporting solutions from one place to another: the cannula transfer. In its usual incarnation, a double-ended stainless-steel needle is pushed through septa into two flasks. The flask with the solution is pressurized slightly, thus forcing the solution (through a filter, if necessary) through the needle and into the other flask. With the wide gauges used, the flow rates are quite high and the operation is quick and easy. However, with much narrower tubing, the flow rate drops dramatically, according to the Hagen–Poiseuille equation which can predict the flow rate for a particular change in pressure where the length and internal diameter of the tubing and the viscosity of the solvent are known. For most solvents and for overpressures of a few psi (safely handled in Schlenk-ware) in standard HPLC tubing, the predicted flowrates are around 10 microlitres a minute: disastrously low on a synthetic scale, but perfect for ESI-MS. The apparatus required is simple: a bottle of carefully regulated argon (or nitrogen, air, etc, depending on requirements),

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a Schlenk flask equipped with a septum and the minimum length of tubing required to reach from the reaction flask to the mass spectrometer (Fig. 12).[4,41]

The reaction ingredients are prepared off-line and the Schlenk flask degassed; the reaction is typically initiated by addition of the catalyst via air-tight syringe. The results we get from this simple setup demonstrate excellent point-to-point reproducibility, and fluctuations in intensity can be normalized against an internal standard or against the TIC. Below is a recent example: the disappearance of a charged alkyne during a catalyzed hydrogenation, to be replaced with the alkene and finally the alkane (Fig. 13).[31]

Charging the substrate allows continuous measurement of its abundance over time, but of course the charged tag will illuminate everything it is bound to, not just the substrate. So products, byproducts, intermediates, catalyst resting states, etc. can also be detected and measured, provided they include the charged tag. One such example was in the analysis of the palladium-catalyzed Sonogashira reaction, the combination of an aryl halide with a terminal alkyne to make a new C_{sp}–C_{sp2} bond. We could simultaneously detect the aryl iodide, the diaryl acetylene product, the aryl byproduct of dehalogenation and two palladium-containing intermediates, $L_2Pd(Ar)I$ and $L_2Pd(Ar)(C_2Ph)$ (Fig. 14).[30] The data on appearance of product was well-matched to data collected through other techniques (^{1}H NMR and UV/Vis analysis), and the data could be matched closely to a numerical model.

What's next?

We continue to develop methodology for the real-time analysis of catalytic reactions, and ESI-MS will remain at the heart of our approach. However, it is rare that one technique can tell us everything we need to know, and in particular it would be useful to use other, complementary techniques in conjunction with ESI-MS to glean as much information as possible from the reaction in question. While the dynamic range of ESI-MS is sufficient to detect the more abundant intermediates at the same time as the substrate and product, to probe more deeply will require an exclusive focus on the metal-containing species with MS, while measuring the gross features of reaction progress using other spectroscopic methods. Particularly well-suited to this approach are compact spectroscopies easily coupled to flow methods, such as UV/Vis or FTIR, and we are currently implementing tandem apparatus of this sort in our laboratory.

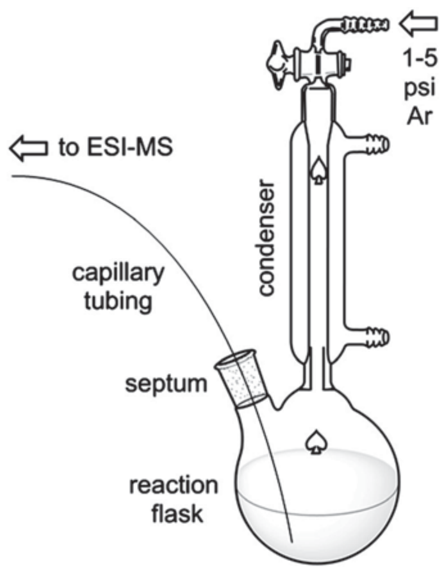

Figure 12. Schematic of a pressurized sample infusion ('PSI') experimental setup. The condenser can be omitted if reactions are carried out at temperatures below the boiling point, and the reaction carried out in an ordinary Schlenk flask.

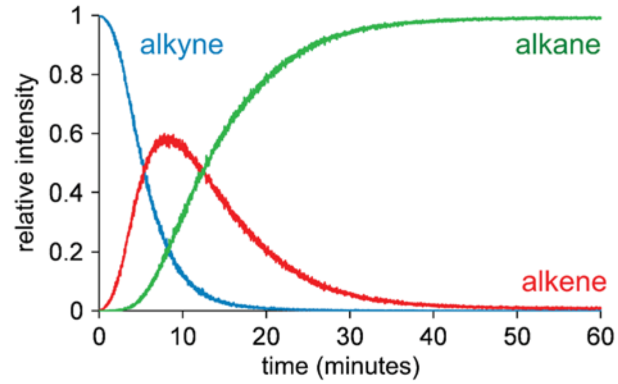

Figure 13. Relative intensity *versus* time traces for alkyne, alkene and alkane during hydrogenation mediated by Wilkinson's catalyst observed using a PSI apparatus connected to an ESI-MS. Data has been normalized to the total ion current of all charged tag-containing species.

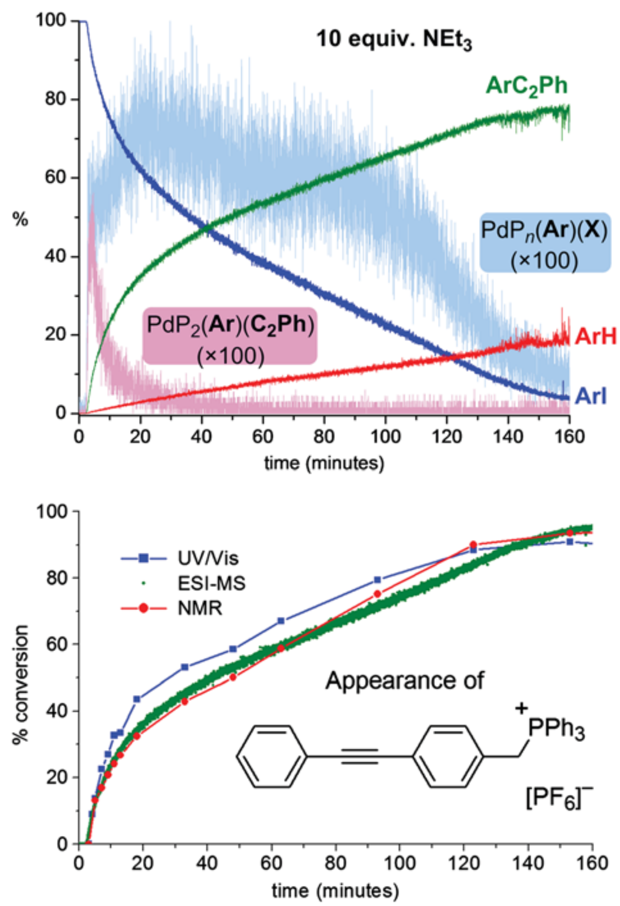

Figure 14. Top: normalized ESI-MS intensity data over time for all key species containing $Ar = [p\text{-}C_6H_4CH_2PPh_3]^+$ in a Sonogashira reaction. The intensity has been multiplied by 100 for the palladium-containing intermediates. Bottom: appearance of product, as tracked by UV/Vis spectroscopy, ^{1}H NMR and ESI-MS.

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