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Pressurized Sample Infusion for the Continuous Analysis of Air- And Moisture-Sensitive Reactions Using Electrospray Ionization Mass Spectrometry

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Summary: Air- and moisture-sensitive compounds pose handling difficulties for chemists requiring mass spectrometric analysis. A simple pressurized sample infusion (PSI) system for electrospray ionization mass spectrometry using a Schlenk flask is presented, which allows straightforward one-off analyses as well as continuous reaction monitoring at any temperature up to the boiling point of the solvent.

Mass spectrometry is a powerful analytical technique, but its application to organometallic and inorganic chemistry has been held back by the very real difficulties associated with keeping tiny quantities of highly reactive material away from air and moisture. A variety of methods to solve this problem have been introduced for different ionization techniques, ranging from an integrated glovebox for matrix-assisted laser desorption ionization (MALDI),[1] an adjacent glovebox for electrospray ionization (ESI),[2] glovebags for electron ionization (EI)[3] and fast atom bombardment (FAB),[4] and aspiration from a sealed vial or flask for liquid introduction field desorption ionization (LIFDI).[5]

ESI-MS has been increasingly applied to reactive organometallic compounds[6] and catalytic reactions, including olefin polymerization,[7] olefin metathesis,[8] hydroformylation,[9] palladium-catalyzed cross-coupling,[10] decarboxylation,[11] esterification,[12] and more.[13] It operates on dilute solutions of compounds that are inherently charged or easily oxidized or that readily associate with another charged species.[14] The simplest way to analyze reactive organometallic compounds anaerobically by ESI-MS is to fill a gastight syringe from a protected solution (e.g., from a Schlenk flask or in a glovebox) and infuse the contents into the spectrometer via syringe pump. The chromatography fittings required to do so need to be kept as rigorously free of oxygen and moisture as the flask and sample and so are best stored in a glovebox themselves and fitted to the syringe while inside. Having the glovebox adjacent to the mass spectrometer, thus avoiding exposure entirely, is ideal.[2] However, there is a need for a simpler system in which the overhead for anaerobic analysis is lower and samples can be submitted to a service and run at a convenient time. There is an equal need for a simple system to allow continuous monitoring of reactions under real conditions: i.e., in any solvent and at any temperature.

The pressurized sample infusion ("PSI") method we introduce herein requires apparatus common to all synthetic organometallic laboratories: a Schlenk flask, rubber septum, hose, and a supply of pressurized and regulated inert gas (the last of these is common to all ESI-MS laboratories). It also requires a short length of PEEK capillary tubing and a single PEEK chromatography fitting. The Schlenk flask is positioned as close as is practical to the ESI-MS source and connected to a source of pressurized inert gas via a short length of rubber tubing. One end of a piece of PEEK capillary tubing is then inserted through a punctured rubber septum into the Schlenk flask, while the other end is connected to the electrospray inlet (see Figure 1). A slight overpressure (1−5 psi) is applied to contents of the Schlenk flask to facilitate continuous introduction of the sample into the mass spectrometer. This method is essentially a cannula transfer using PEEK tubing. ***Caution!*** *Use an appropriate regulator capable of accurately delivering pressure in the recommended range. Overpressurization of the Schlenk flask is potentially dangerous.*

The sample must first be diluted to levels appropriate for ESI-MS. ESI-MS is an extremely sensitive technique, and concentrations typical of ^{1}H NMR—a few milligrams per

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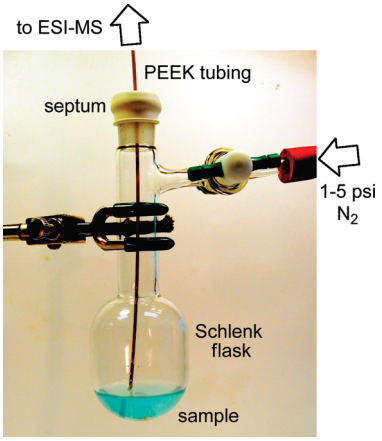

Figure 1. Setup for PSI direct from a Schlenk flask. The system is slightly pressurized (carefully regulated at 1−5 psi), forcing the reaction solution, cannula-style, through a 0.005 in. i.d. PEEK tubing into the mass spectrometer.

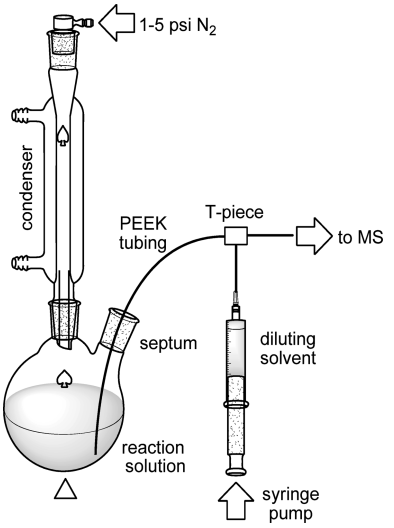

Figure 2. Setup for continuous monitoring of reactions by PSI at elevated temperature (at reduced temperature, the condenser is superfluous). Dilution (and quenching) is provided by an auxiliary supply of solvent introduced at a mixing T, which exits to the mass spectrometer.

milliliter—are generally much too high for mass spectrometric analysis. Performing serial dilutions is a simple solution, but the fact that even dry solvents contain a few parts per million of water can prove problematic. Add to this problem of trace amounts of water found on glassware, in tubing, and in the instrument itself and the fact that the desolvation gas is rarely perfectly dry, and the problems with sample decomposition become obvious—and often catastrophic. A partial solution to this problem can be achieved by running higher sample concentrations. The intensity of the resulting spectrum may be very high, especially if the species of interest is permanently charged, but contamination of the instrument can be mitigated by infusing the sample for only the few seconds it takes to get good data.

We use the setup described herein for the online monitoring of catalytic reactions. There are several further modifications that greatly expand the scope of PSI. One is to enable reaction monitoring at different temperatures and, in particular, to allow reactions to proceed under reflux conditions. Integrating a condenser into the Schlenk flask is a ready solution, though the same configuration using well-sealed ground glass joints is satisfactory, provided leakage is eliminated (Figure 2). Even under vigorous reflux, the infusion of the solution continues unimpeded. Lowering the sample concentration is not always practical in monitoring catalysis—the reaction still has to proceed at a reasonable rate—and so the requirement for dilution can be met by introducing a diluting solvent (from a syringe pump) at a T located immediately outside the flask. This modification can allow up to 100:1 dilution with careful adjustment of pressure and flow rates and has the further benefit of immediately quenching the reaction: the concentration of all species drops precipitously and the solution is cooled to room temperature, eliminating the complication of the reaction continuing in the PEEK tubing. The syringe and its contents should be as scrupulously dry as the rest of the inert system, and it provides a ready means of flushing the instrument before infusion of the sample solution.

We have implemented PSI on a variety of instruments from different manufacturers (Waters, Thermo Fisher, Bruker) and using different solvents (including water, acetonitrile, dichloromethane, methanol, dimethylformamide, and tetrahydrofuran). An example of the data provided by PSI is

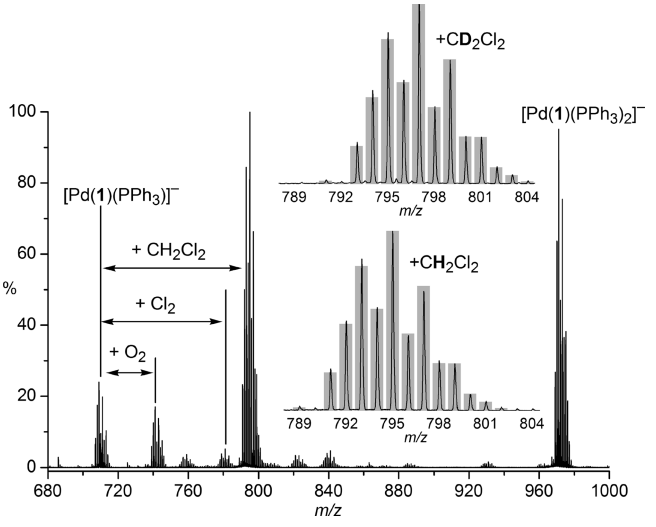

Figure 3. Negative-ion ESI-MS of $Pd(PPh_3)_4$ + [PPN][**1**] in an *aged* CH_2Cl_2 solution. Insets give isotope pattern matching for [Pd(**1**)(PPh_3) + CH_2Cl_2)]$^-$ and [Pd(**1**)(PPh_3) + CD_2Cl_2]$^-$ (the latter was collected in a different experiment, in which CD_2Cl_2 was used as the solvent).

shown in Figure 3. Solutions of $Pd(PPh_3)_4$ actually consist mostly of $Pd(PPh_3)_3$ and slowly decompose in dichloromethane, primarily through oxidative addition of the solvent to $Pd(PPh_3)_2$. Pd^0 species are very reactive (they readily add O_2, for example); therefore, this experiment also demonstrates the ability of the Schlenk flask approach to cope with highly air- and moisture-sensitive materials (see the Supporting Information for a spectrum of this solution collected at room temperature without precautions).

This decomposition reaction can be monitored by doping in a charged ligand,[15] in this case the anionic phosphine $[N(PPh_3)_2]^+[PPh_2(m\text{-}C_6H_4SO_3)]^-$ ([PPN][**1**]), which readily

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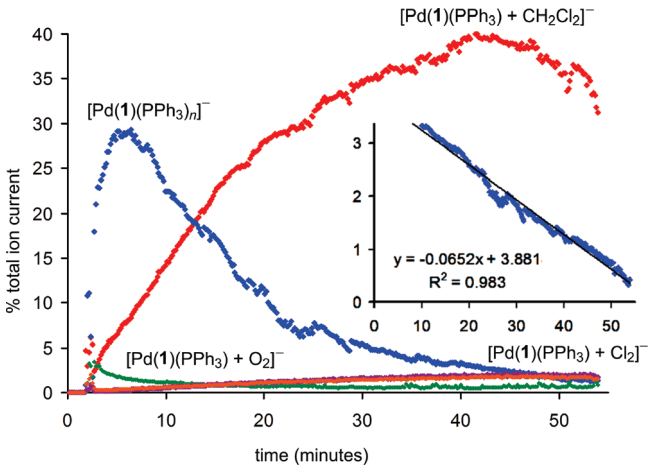

Figure 4. Intensities as a percentage of ion current (m/z 400−1500) for $[Pd^0(\mathbf{1})(PPh_3)_n]^-$ (n = 1, 2) (in blue) and $[Pd^{II}(\mathbf{1})(PPh_3) + CH_2Cl_2)]^-$ (in red). The Pd(0) species decays under first-order kinetics with $t_{1/2}$ = 10.7 (inset, plot of ln[X] vs t). Small amounts of $[Pd(PPh_3)(\mathbf{1}) + (CHCl)]^-$ (orange) and $[Pd^{II}(\mathbf{1})(PPh_3) + Cl_2]^-$ (violet) were also observed as minor byproducts, and the small amount of $[Pd^{II}(\mathbf{1})(PPh_3)(O)_2]^-$ (green) present at the start decayed away quickly.

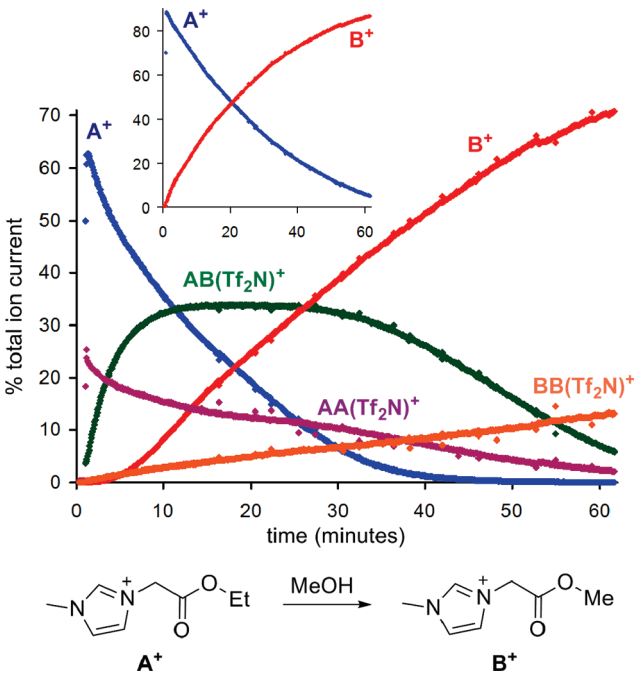

Figure 5. Intensities as a percentage of ion current for $[EtOOCCH_2mim]^+$ (in blue, $\mathbf{A}^+$, m/z 169) and $[MeOOCCH_2mim]^+$ (in red, $\mathbf{B}^+$, m/z 155) and aggregates of these ions with the bis-triflimide counterion: $[\mathbf{AA}(Tf_2N)]^+$ (violet, 618 m/z), $[\mathbf{AB}(Tf_2N)]^+$ (green, m/z 604), and $[\mathbf{BB}(Tf_2N)]^+$ (orange, m/z 590). The inset shows the result of summing the intensities contributing to the reactant and product. Twelve spectra were collected each minute.

substitutes with labile PPh_3 and allows observation of the palladium-containing species.[16] The reaction was carried out at the boiling point of the solvent (40 °C). Disappearance of $[Pd^0(\mathbf{1})(PPh_3)_n]^-$ (n = 1, 2) occurred as a first-order process with $t_{1/2}$ = 10.7 min (Figure 4). The major product was $[Pd^{II}(\mathbf{1})(PPh_3)_n + CH_2Cl_2]^-$ (n = 0, 1), but $[Pd(PPh_3)(\mathbf{1}) + (CHCl)]^-$ and $[Pd^{II}(\mathbf{1})(PPh_3) + Cl_2]^-$ were also observed as byproducts. Their intensities change identically throughout, suggesting that their formation is related. The fact that $[Pd^{II}(\mathbf{1})(PPh_3) + CH_2Cl_2]^-$ fragmented in MS/MS studies by loss of phosphine rather than loss of CH_2Cl_2 tells us that the solvent is not weakly coordinated but instead has formed strong covalent bonds through oxidative addition, consistent with the known reactivity of $Pd(PCy_3)_2$ and $Pd(P^tBu_2H)_2$ with dichloromethane,[17] and so is best represented as $[Pd^{II}(\mathbf{1})(PPh_3)(CH_2Cl)(Cl)]^-$. That the Pd^0 disappears faster than the Pd^{II} appears indicates that perhaps the product is itself decomposing, and evidence for an additional process is seen at long reaction times (after ~40 min) when the various Pd^{II} species begin to drop in intensity. No new Pd-containing products are observed by ESI-MS, and therefore any further decomposition products are thought to be neutral.

The data are even better when applied to charged substrates rather than to metal complexes. The example shown in Figure 5 is for the transesterification of an ethyl ester[18] with methanol, a reaction that proceeds at room temperature without the addition of a catalyst. Five species are observed: the ethyl ester starting material, the methyl ester product, and aggregates of these with the bis-triflimide counterion, $[N(SO_2CF_3)_2]^-$.

No attempt has been made to extract kinetic information from this plot, as the relative response factors of the monomer and dimer are not known. The plot does, however, illustrate the excellent point-to-point reproducibility of the data.

Conclusions

PSI is an easily implemented and low-cost solution to two problems organometallic chemists face in applying ESI-MS to their chemistry: how to submit a sample for anaerobic analysis and how to continuously monitor reactions without the need for regular sampling, in any solvent and at any temperature. The ability of this particular experimental configuration not only to cope with low-abundance, fragile organometallic compounds but to also provide high-quality data on charged substrates is apparent at a glance, and the implications for the detailed kinetic analysis of catalytic reactions are obvious: simultaneous rapid measurement of reactants, products, and low-abundance intermediates across a wide range of concentrations, time scales, and temperatures.

Experimental Section

[PPN][**1**][16] and ethyl 1-methylimidazolium-3-acetate trifluoromethanesulfonimide, [**A**][Tf_2N],[17] were prepared by literature methods. Solvents were dried and purged using an MBraun solvent purification system. All other chemicals were obtained from Aldrich and used without further purification. Standard Schlenk and glovebox methods were used to prepare samples. Mass spectra were collected on a Micromass Q-ToF *micro* hybrid quadrupole/time-of-flight mass spectrometer in negative-ion mode using electrospray ionization.

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Pd(0) Decomposition. In a Schlenk flask under nitrogen that was fitted with a septum, palladium tetrakis(triphenylphosphine) (3 mg, 2.6 μmol) and [PPN][**1**] (1 mg, 1.1 μmol) were added. The flask was placed next to the ESI source and connected via a short length of PEEK tubing. The flask was pressurized to 1 psi, and data collection was initiated. Dichloromethane (10 mL) was injected through the septum and the reaction mixture stirred at 40 °C for 1 h. MS settings: capillary voltage, 2900 V; cone voltage, 10 V; extraction voltage, 0.5 V; source temperature, 40 °C; desolvation temperature, 80 °C; cone gas flow rate, 100 L/h; desolvation gas flow, 200 L/h; collision voltage, 2 V; MCP voltage, 2700 V.

Transesterification. In a Schlenk flask under nitrogen that was fitted with a septum, [$EtOOCCH_2$mim][Tf_2N] (1 mg, 2.2 μmol) was added. The flask was placed next to the ESI source and connected via a short length of PEEK tubing. The flask was pressurized to 1 psi, and data collection was initiated. Methanol (20 mL) was injected through the septum and the reaction mixture stirred at room temperature for 1 h. MS settings: capillary voltage, 2900 V; cone voltage, 15 V; extraction voltage, 0.5 V; source temperature, 80 °C; desolvation temperature, 100 °C; cone gas flow rate, 100 L/h; desolvation gas flow, 200 L/h; collision voltage, 2 V; MCP voltage, 2700 V.

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Supporting Information Available: A figure giving negative-ion ESI-MS of $Pd(PPh_3)_4$ + [PPN][**1**] in a CH_2Cl_2 solution in which no special precautions have been taken in the preparation of the sample. This material is available free of charge via the Internet at http://pubs.acs.org.