

# Handling considerations for the mass spectrometry of reactive organometallic compounds

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## Funding information

NSERC

## Abstract

Mass spectrometry is a powerful tool in disparate areas of chemistry, but its characteristic strength of sensitivity can be an Achilles heel when studying highly reactive organometallic compounds. A quantity of material suitable for mass spectrometric analysis often represents a tiny grain or a very dilute solution, and both are highly susceptible to decomposition due to ambient oxygen or moisture. This complexity can be frustrating to chemists and analysts alike: the former being unable to get spectra free of decomposition products and the latter often being poorly equipped to handle reactive samples. Fortunately, many creative solutions to such problems have been developed. This review summarizes some key methods for handling reactive samples in conjunction with the various ionization methods most frequently employed for their analysis.

## 1 | INTRODUCTION

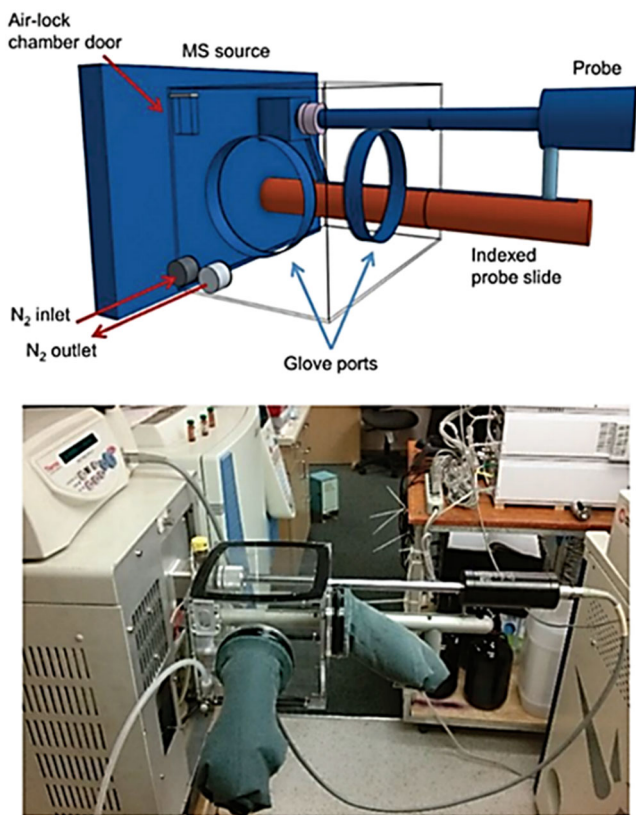
For the purposes of this review, a “reactive compound” is one that reacts in a deleterious way during routine mass spectrometric analysis. Mass spectrometry (MS) deals with very small amounts of material, so a compound that can survive brief exposure to the air as a bulk solid or as a concentrated solution may still appreciably decompose when exposed to oxygen and/or moisture as a few grains of material or a dilute solution. It is not always the case that the decomposition is obvious, either an oxidized ligand may decoordinate, a hydrolyzed product may oligomerize, or any number of other pathways may be unlocked. What these processes have in common is that they cause headaches for the analyst and the sample submitter alike. The procedures for handling these compounds all involve shielding the sample from exposure to air for even very brief periods and generally draw on standard laboratory procedures for handling reactive compounds. Gloveboxes (sometimes improvised) and adapted Schlenk techniques are commonly adopted solutions. We hope that this review provides people interested in employing MS to characterize reactive compounds with some sound ideas as to how to proceed with informative analyses.

## 2 | ELECTRON IONIZATION

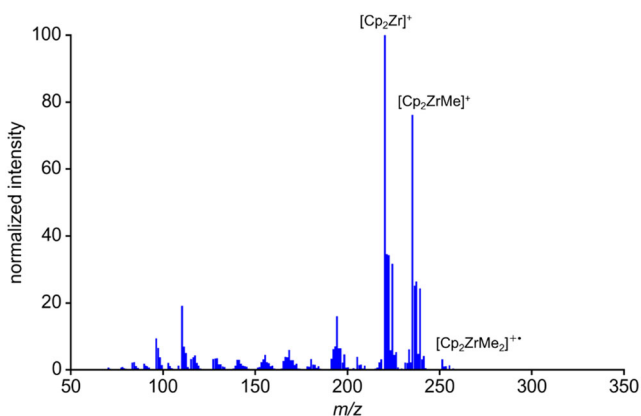
Electron ionization (EI) generates radical cations by using high energy electrons that interact with gas-phase molecules. Removing an electron imparts considerable internal energy to the ion and results in unimolecular decomposition of the ion.<sup>1,2</sup> EI has been used to study a range of robust organometallic compounds provided their masses are less than about 1000 Da.<sup>3,4</sup> In particular, metal carbonyls and metallocenes are commonly characterized by EI due to their high volatility and thermostability (e.g., ferrocene, which forms a highly abundant molecular ion).<sup>5,6</sup>

Sample introduction in EI can be directly into the source or as effluent from a gas chromatography (GC) column.<sup>7</sup> The sample introduction step in EI for air-sensitive compounds is problematic because the sample is exposed to air for a short time. There are a variety of different strategies for the analysis of such sensitive compounds.<sup>8,9</sup> These include injection of an analyte via a gas-tight syringe, working under a stream of inert gas, using a glovebag, or doing the sample introduction quickly to limit exposure to air.<sup>10–12</sup> Other modifications, such as a small purgeable glove chamber affixed to the front end of the mass spectrometer, can also be used in the analysis of reactive

organometallic species by direct probe methods.<sup>13</sup> This modification is more robust than a glovebag and does not require a full glovebox dedicated to analysis (Figure 1). Excellent EI spectra of air- and moisture-sensitive compounds such as  $\text{ZrCp}_2\text{Cl}_2$ ,  $\text{ZrCp}_2\text{Me}_2$ ,  $\text{TiCp}_2\text{Cl}_2$ , and  $\text{TiCp}_2\text{Cl}$  were recorded using the glove chamber (Figure 2).



**FIGURE 1** Top: Schematic of the glove chamber. Bottom: Glove chamber in place on direct probe electron ionization mass spectrum (EI-MS). Adapted with permission from Penafiel et al<sup>13</sup> Copyright (2016) Royal Society of Chemistry



**FIGURE 2** Electron ionization mass spectrum (EI-MS) of  $\text{ZrCp}_2\text{Me}_2$  ( $m/z$  250) obtained using the glove chamber. Adapted with permission from Penafiel et al<sup>13</sup> Copyright (2016) Royal Society of Chemistry

Volatile samples can also be analyzed by headspace analysis, where heating of the sample causes the analyte to vaporize into the headspace of the vial.<sup>14,15</sup> The sample can then be injected into a GC column without exposure to air using an autosampler. In EI, the sample is heated in an evacuated chamber, and the resulting gaseous analyte is subject to an ionizing beam of electrons. However, many air-sensitive compounds are not volatile and can decompose at the elevated temperatures required to generate an appreciable vapor pressure, limiting the use of EI to volatile and/or thermally stable compounds.

### 3 | DIRECT ANALYSIS IN REAL TIME

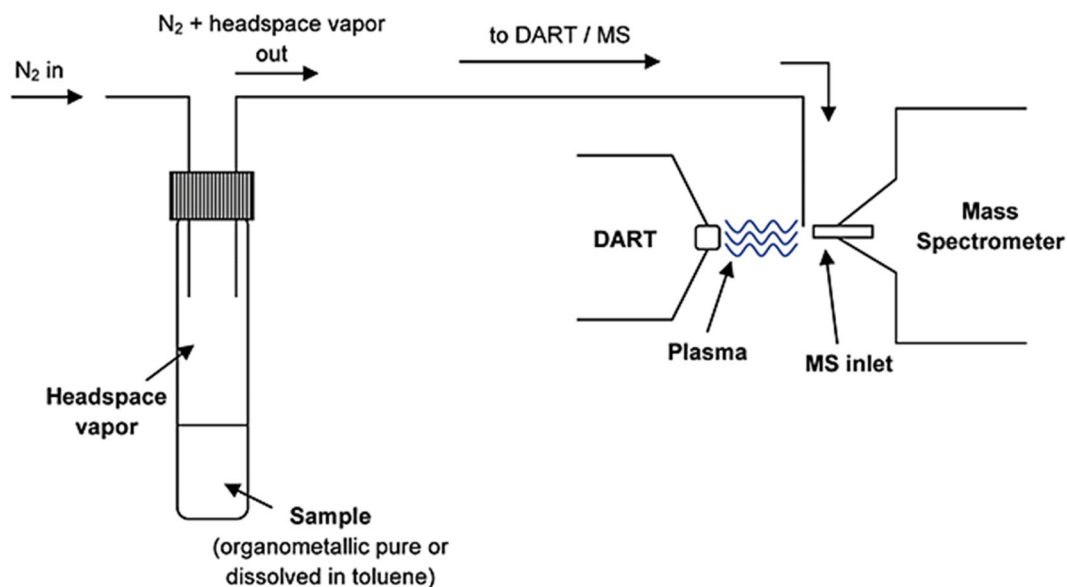
Direct analysis in real time (DART) is an ionization technique that uses high energy metastable atoms or molecules such as  $\text{He}^*$  or  $\text{N}_2^*$  to ionize molecules of interest.<sup>16</sup> Although samples are placed under vacuum in EI, DART analysis requires the sample to be brought to the source in air. This feature makes DART appealing for various applications but makes the analysis of air- and moisture-sensitive compounds very challenging.<sup>2,17</sup> However, DART requires minimum sample preparation as the analyte is simply held next to the source of excited atoms. Using this method allowed for analysis of organogallium and organoaluminium compounds.<sup>18</sup>

Borges et al conducted a systematic study of the use of DART in the detection of organometallic compounds.<sup>19</sup> The orifice of the DART ion source was positioned so that the stream of helium or nitrogen exiting the source was in line with the inlet orifice of the mass spectrometer (Figure 3). Samples were loaded as pure compounds or as solutions in toluene or methanol in glass vials sealed with a silicone septum.  $\text{N}_2$  was used as a purge gas, and the headspace vapors were directed to the inlet of the mass spectrometer. Several organometallic compounds of As, Fe, Hg, Pb, Se, and Sn were analyzed using this simple setup. Mazzotta et al also reported the analysis of fused ring heterocyclic organometallic compounds using DART.<sup>20</sup>

### 4 | FIELD IONIZATION

In field ionization (FI), the neutral sample is heated under vacuum and driven into the gas phase near a high surface area emitter. If the molecule gets sufficiently close, an electron tunnels to the anode, and the molecule is repelled and drawn into the mass spectrometer. It is called field desorption (FD) if the sample is adsorbed on the surface of the emitter.<sup>21</sup>

The main advantage of FD is the ability to form singly charged molecular ions for a variety of compounds, thus it has been widely used for the analysis of organometallic compounds.<sup>22–25</sup> Nonpolar compounds, which are generally difficult to study by ESI or MALDI due to poor ionization, can be analyzed by FD. The main drawback of FD is the sample preparation, as the sample must be introduced to the emitter under open air. The two methods used involve dipping the emitter quickly into the analyte or dropping a small amount of analyte



**FIGURE 3** Schematic representation of the setup for gas-phase sampling of organometallic compounds for detection by DART-MS. Adapted with permission from Borges et al<sup>19</sup> Copyright (2009) American Chemical Society. DART, direct analysis in real time; MS, mass spectrometry

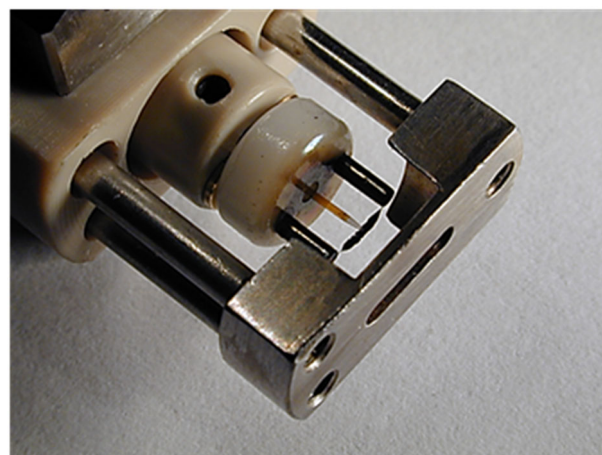
via microsyringe into the emitter.<sup>26</sup> These sample preparation methods make it very difficult to study air- and moisture-sensitive compounds by FD.

The development of liquid introduction field desorption ionization (LIFDI)<sup>27</sup> benefited the analysis of air-sensitive compounds by adding fused-silica tubing that connects the emitter to the external sample vial, as seen in Figure 4.<sup>28–33</sup>

This allows the capillary to be purged with inert gas from the headspace of the vial before being immersed in the sample solution. After sample injection, the capillary continues to draw inert gas from the headspace of the vial, ensuring an inert atmosphere throughout the analysis. This allows for easy analysis without breaking the vacuum and eliminates sample preparation under air. Figure 5 shows the LIFDI spectrum of some air-sensitive Ru complexes.

## 5 | PARTICLE BOMBARDMENT TECHNIQUES

Techniques such as fast atom bombardment (FAB) and liquid secondary ion mass spectrometry (LSIMS) have also been used to characterize organometallic compounds.<sup>34–37</sup> Both ionization techniques involve bombarding a sample dissolved in a liquid matrix with fast-moving particles, such as Xe atoms for FAB and Cs<sup>+</sup> ions for LSIMS.<sup>38,39</sup> Air-sensitive alkyl lithium compounds have been analyzed by FAB by making a solution in Nujol<sup>40</sup> or Schlenk techniques.<sup>41</sup> Using organic solvents as matrices, it is possible to analyze air-sensitive compounds by low-temperature secondary ion mass spectrometry (LT-SIMS). In this technique, the sample solution is frozen by applying it to the tip of the insertion probe maintained at  $-120^{\circ}\text{C}$  under a cold N<sub>2</sub> stream. (Me<sub>2</sub>AlNEt<sub>2</sub>)<sub>2</sub>, a highly air-sensitive compound, was analyzed using LT-SIMS.<sup>42</sup> The highest mass ion observed was

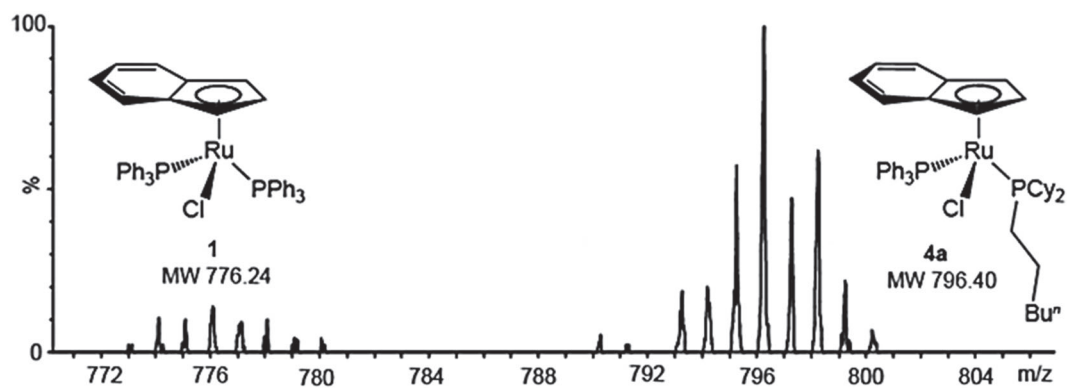


**FIGURE 4** Liquid introduction field desorption ionization (LIFDI) showing the capillary that carries the analyte and the emitter. Image provided courtesy of Prof H. Bernhard Linden

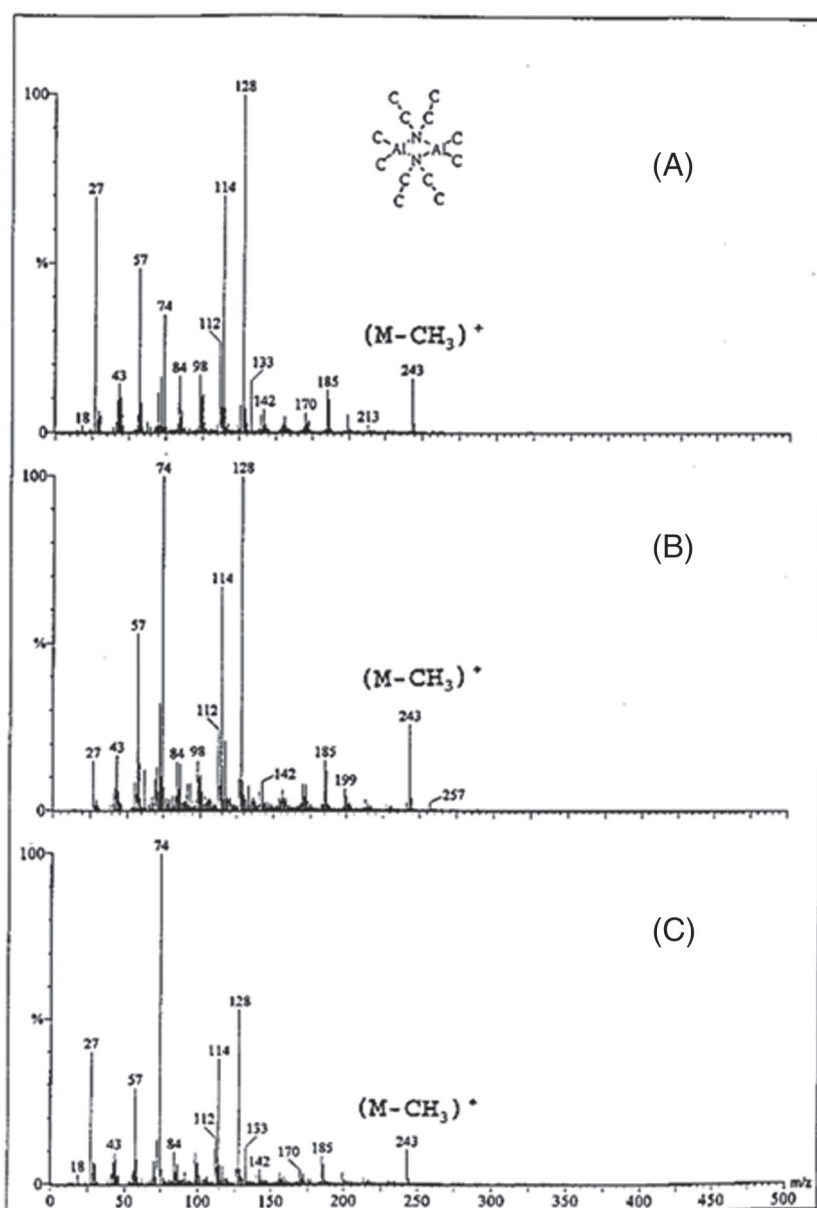
$[\text{M} - \text{Me}]^+$ , and the fragmentation pattern is similar in different solvents (Figure 6). The analyte's polarity was too low to allow dissolution in any viscous matrices used in LSIMS. Therefore, no signal could be obtained by using LSIMS to analyze this compound at room temperature.

## 6 | MATRIX-ASSISTED LASER DESORPTION IONIZATION

In matrix-assisted laser desorption ionization (MALDI), neutral samples are generally prepared by co-crystallizing the analytes with a matrix compound suitable for absorbing laser radiation.<sup>43,44</sup> The matrix



**FIGURE 5** Liquid introduction field desorption ionization (LIFDI) mass spectrometry (MS) data for a mixture of Ru complexes. Adapted with permission from Belli et al.<sup>28</sup> Copyright (2015) American Chemical Society

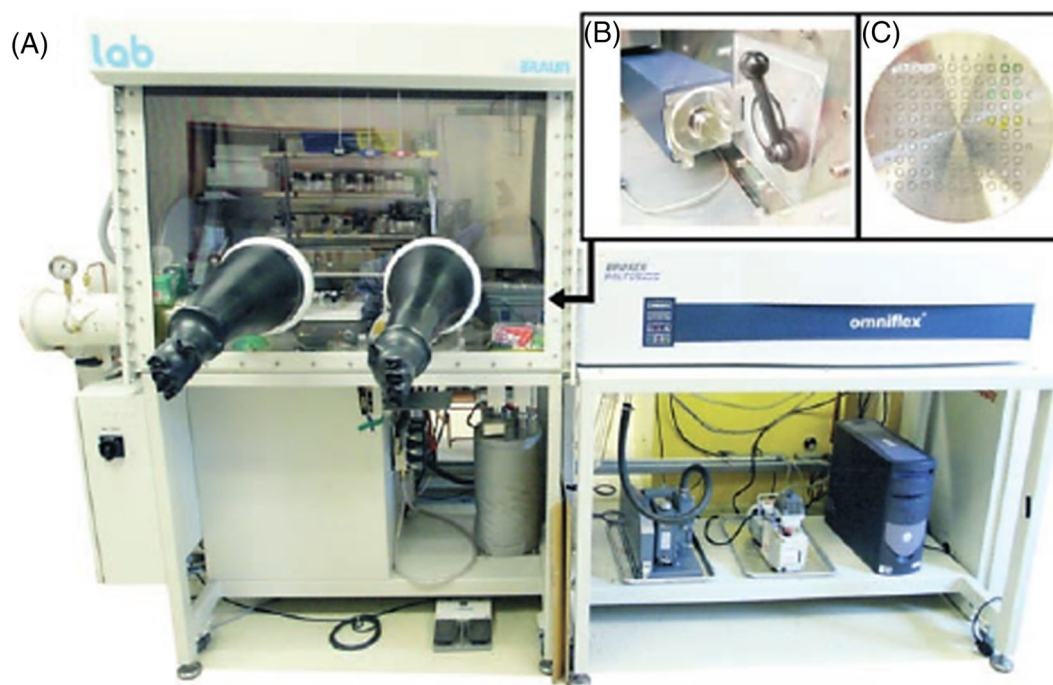


**FIGURE 6** Positive-ion low-temperature secondary ion mass spectrometry (LT-SIMS) of  $(\text{Me}_2\text{AlNEt}_2)_2$  (258 g/mol) dissolved in (A) benzene, (B) hexane, and (C) diethyl ether. Adapted with permission from Huang et al.<sup>42</sup> Copyright (1999) American Chemical Society

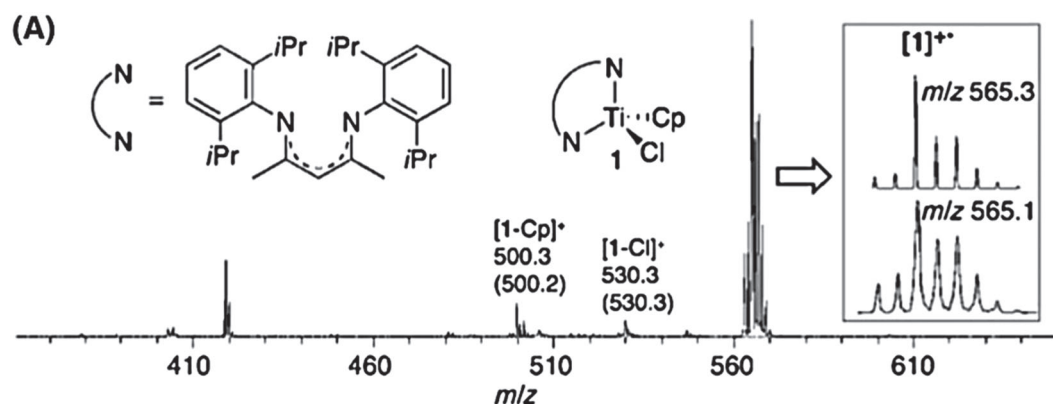
molecules absorb photons and are ablated into the gas phase, carrying the analyte molecules with them and ionizing them through protonation and/or oxidation.<sup>2</sup> Finding appropriate matrices for analysis of organometallic compounds is challenging, thus the use of MALDI in the characterization of organometallic compounds has been rare. However, Fogg and coworkers showed that unfunctionalized polyarenes such as anthracene and pyrene perform well as matrices for fragile metal complexes. They also interfaced an inert atmosphere glove box with a matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) to overcome problems regarding decomposition during sample transfer to the source, as seen in Figure 7.<sup>45,46</sup>

Using the above-mentioned MALDI setup, an oxygen-sensitive titanium (III) ethylene polymerization catalyst was analyzed, as seen in Figure 8. The MALDI sample was prepared by dissolving the analyte and pyrene in a volatile solvent ( $C_6H_6$  or  $CH_2Cl_2$ ) and spotting microliter aliquots of the solution on the MALDI target plate. After solvent evaporation, a thin film of the analyte and pyrene co-crystallized, with which MALDI-TOF was recorded.

Laser desorption MS uses a laser to ionize the analyte directly. The only difficulty is transferring samples to the mass spectrometer without any decomposition, which can be achieved by pressing samples between cellophane tape or into a KBr pellet. An inert gas purge



**FIGURE 7** (A) Inert-atmosphere matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometer; (B) open loading chamber projecting into the glovebox; (C) target plate. Adapted with permission from Eelman et al<sup>45</sup> Copyright (2008) Wiley-VCH



**FIGURE 8** Matrix-assisted laser desorption (MALDI) mass spectra of an oxophilic Ti (III) complex in a pyrene matrix. Adapted with permission from Eelman et al<sup>45</sup> Copyright (2008) Wiley-VCH

box for laser desorption/ionization MS of air-sensitive solids can be used if the user is worried about contamination from the matrix.<sup>47</sup> When a purge box is used, the air-sensitive sample is always under inert gas while transferring to the source. Using an inert gas purge box, laser desorption/ionization mass spectra of sensitive compounds  $\text{NbCl}_2(\text{C}_5\text{H}_5)_2$  and  $\text{Zr}(\text{CH}_3)_2(\text{C}_5\text{H}_5)_2$  have been reported.

## 7 | ELECTROSPRAY IONIZATION

Electrospray ionization (ESI) is a popular technique for characterizing and studying organometallic compounds.<sup>48-50</sup> In ESI, solution-phase ions are passed through a charged capillary, and the solution separates into tiny droplets from which the solvent is evaporated. The excess charges arrange themselves on the surface, and as charge density increases, ions are evaporated into the gas phase.<sup>51</sup>

Analysis of air-sensitive compounds can be achieved using a gas-tight syringe,<sup>52</sup> pressurized sample infusion (PSI),<sup>53</sup> or the more permanent solution of having a glovebox close to the mass spectrometer.<sup>54</sup> Capillary tubing (PEEK or PTFE) is passed through a small hole in the side of the glovebox directly into the mass spectrometer, and samples for analysis are then injected directly from inside the glovebox without exposure to air, as seen in Figure 9.

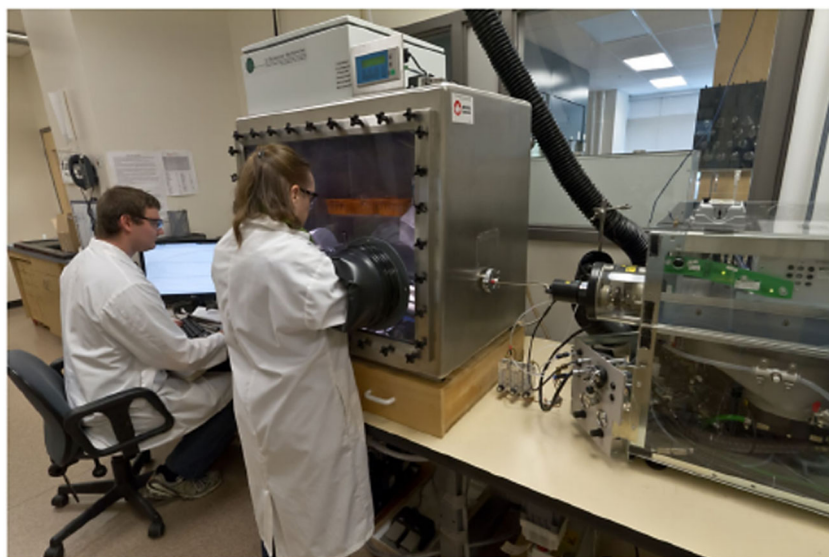
The electrospray ionization–mass spectrometry (ESI-MS) of a highly moisture-sensitive iron borylene complex  $[(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})_2\text{BNCy}_2][\text{BARf}_4]$  was reported with and without using the glovebox, as seen in Figure 10. When the iron complex was injected from outside the glovebox, decomposition of the iron complex by hydrolysis to  $[\text{NH}_2\text{Cy}_2]^+$  at  $m/z$  182 was reported. When the same sample was injected using a glovebox, the decomposition product was minimal in the same time frame, and an intense peak for the iron complex at  $m/z$  368 was observed. Another advantage of using a glovebox is that sealed samples can be brought into the glovebox and stored indefinitely. The samples can then be opened securely at leisure without fear of mishandling.

Reactions can be performed in syringes if stirring and temperature control are not critical.<sup>55</sup> The Koszinowski group has reported the use of a gas-tight syringe,  $\text{N}_2$  as a sheath gas, and a fused-silica tube (0.10 mm inner diameter) to analyze air-sensitive compounds.<sup>56-61</sup> The group recommended flushing the inlet system with dry solvent extensively before adding the organometallic sample.

Santos et al have reported the use of a microreactor that is coupled directly to the ESI source to study Ziegler–Natta polymerization, using a  $\text{Cp}_2\text{ZrCl}_2/\text{MAO}$  system.<sup>62</sup> Coupling the microreactor directly to the ESI source allows the detection of catalytically active species that are transiently present and the analysis of reaction times from 0.28 to 0.9 s.<sup>63</sup> Reaction mixtures can also be prepared inside a glovebox and taken out in a Teflon-sealed microsyringe for online monitoring.<sup>64</sup>

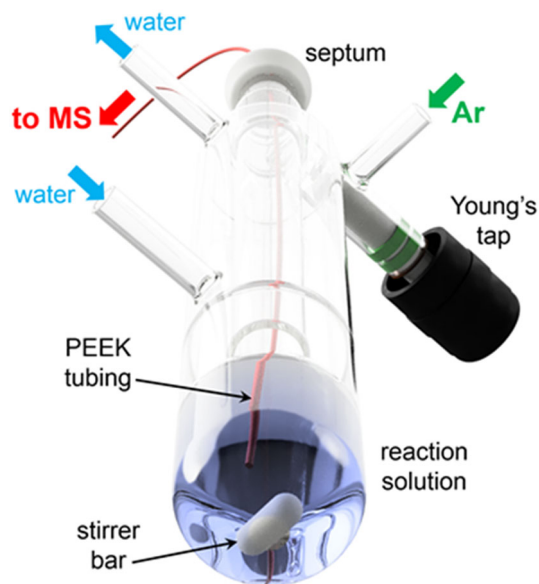
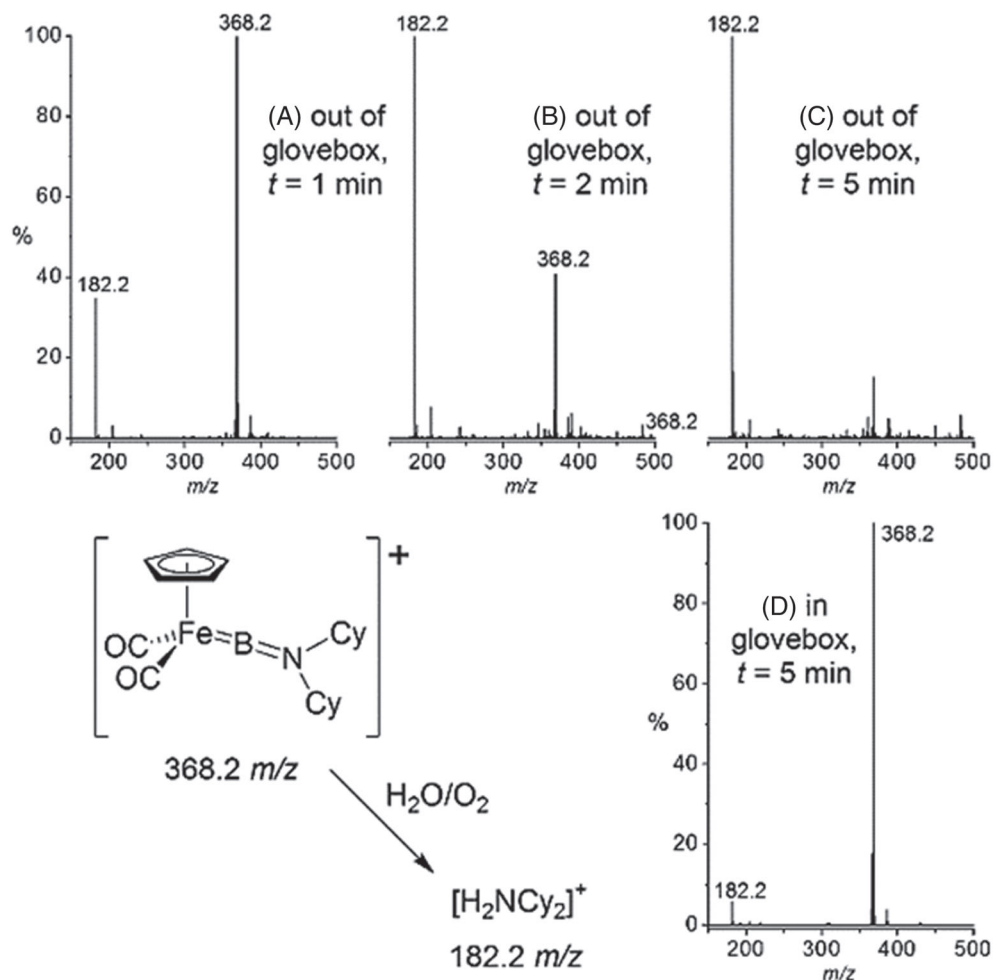
PSI can be used to analyze air-sensitive compounds undergoing reactions.<sup>53</sup> This technique can be thought of as a cannula transfer from a Schlenk flask directly to the mass spectrometer. The PSI flask is designed to have an inlet where inert gas (Ar or  $\text{N}_2$ ) is introduced, and this positive pressure allows the solution in the flask to be introduced to the mass spectrometer via PEEK/PTFE tubing.<sup>65</sup> Reactions can be conducted at temperatures up to the boiling point of the solvent, and the PSI flask is designed in a way that contamination from the rubber septum leaching from the solvent can be avoided entirely, as seen in Figure 11.<sup>66</sup> PSI is straightforward to implement in any laboratory and allows continuous reaction monitoring. PSI experiments can also be performed under the positive pressure of inert gas from a balloon.<sup>67</sup>

PSI is ideal for the study of highly air-sensitive chemistry, exemplified by its use in the study of 1-hexene polymerization using a  $\text{Cp}_2\text{ZrCl}_2/\text{AlMe}_3$  system. Using this technique, new pathways for catalyst deactivation, including the formation of dimethylalane-stabilized complexes, were identified.<sup>68</sup> PSI helped demonstrate how these complexes were resistant to further addition of hexene. The technique was used to study alkyl exchange in methylalumoxane, a very dynamic, fast, and difficult system to

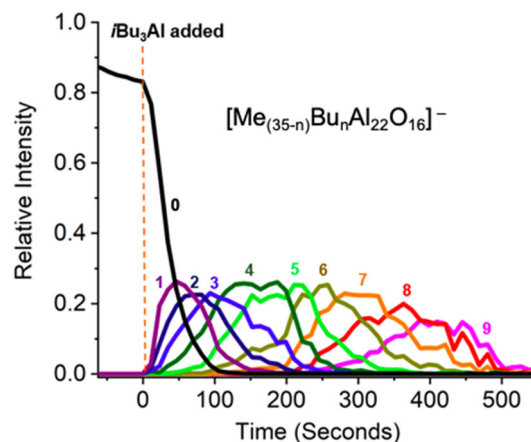


**FIGURE 9** Glovebox adjacent to the electrospray ionization–mass spectrometry (ESI-MS). The syringe pump in use is located inside the glovebox. Adapted with permission from Yunker et al<sup>12</sup> Copyright (2014) John Wiley & Sons, Ltd

**FIGURE 10** Handling the iron complex  $[(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})_2\text{BNCy}_2][\text{BArF}_4]$  (inset,  $m/z$  368.2) outside of the glovebox (A–C). Inside the glovebox very little decomposition is observed within the same time frame (D). Adapted with permission from Lubben et al.<sup>54</sup> Copyright (2008) American Chemical Society



**FIGURE 11** Pressurized sample infusion (PSI) flask. MS, mass spectrometry

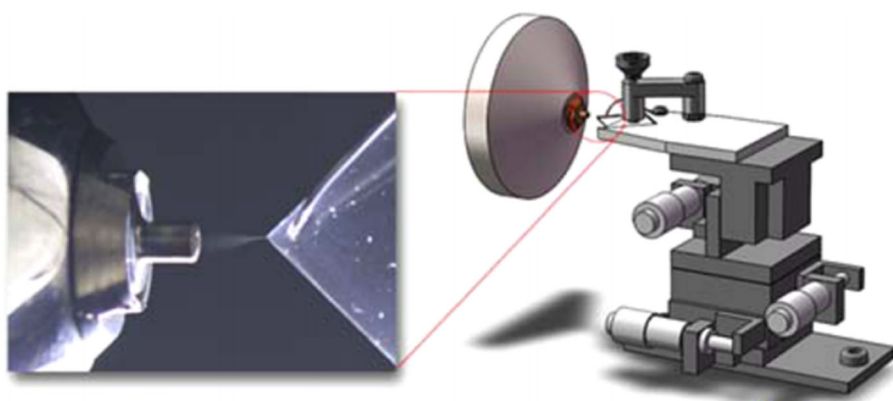


**FIGURE 12** Pressurized sample infusion (PSI) of 10 mol%  $i\text{Bu}_3\text{Al}$  modified MAO/OMTS with Al: OMTS 100: 1 in PhF. Adapted with permission from Zijlstra et al Copyright (2018) Royal Society of Chemistry

study.<sup>69</sup> A trace from one such PSI experiment is shown in Figure 12, where after the addition of  $i\text{Bu}_3\text{Al}$ , we could observe the kinetics of alkyl exchange in MAO.

Jiang et al have demonstrated the use of a glass slide for droplet spray ionization of a highly air- and moisture-sensitive sample, as seen in Figure 13.<sup>70</sup>

The experimental setup uses a glass slide that can hold sample volumes up to  $60\ \mu\text{l}$ . The corner of the glass slide is positioned so that the distance from the end of the tip to the MS inlet is 10 mm for



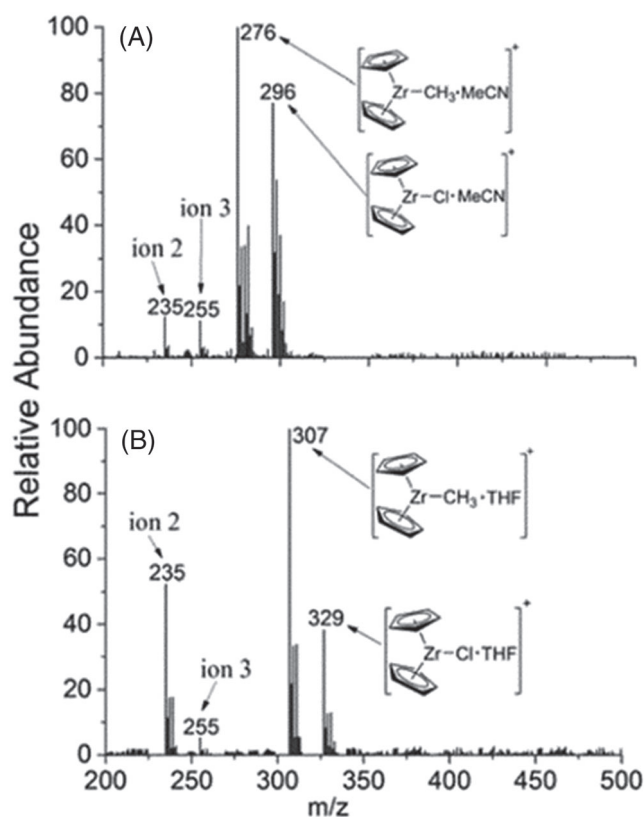
**FIGURE 13** Illustration of the droplet spray. The angle between the MS inlet and the tip-end is 10°. Adapted with permission from Jiang et al.<sup>70</sup> Copyright (2015) American Chemical Society

acetonitrile and 5 mm for THF and PhF. Using this simple setup, Jiang et al studied ethylene polymerization by a  $\text{Cp}_2\text{ZrCl}_2/\text{MAO}$  system and observed vital intermediates. Figure 14 shows the catalytically active species analyzed by droplet spray ionization. The Zr species, as well as methylalumoxane, are both sensitive to air and water and decompose very quickly.<sup>71–74</sup> The fact that the authors observe these sensitive cations by an open-air technique is remarkable. Possible reasons for this could be the proximity of the corner of the glass side to the MS inlet, the decomposition products being deposited on the glass slide and not making it to the MS, or most importantly, quenching by acetonitrile or THF making an adduct which is considerably less sensitive to air or moisture.

The analyte studied sometimes requires running at a higher concentration than is typical for MS ( $>10 \mu\text{M}$ ). This is often due to the high reactivity of the analyte with trace amounts of water and oxygen in the solvent, and therefore, analysis in dilute conditions increases the chance of sample decomposition. There is a range of strategies that can be employed to mitigate saturation effects in these experiments; this can often be achieved by simply detuning the instrument, which lowers the proportion of the sample entering the detector.<sup>75</sup> In the case of methylalumoxane and zirconium ions, the probe tip is kept adjusted close to the sample inlet of the mass spectrometer such that any reactions with air/moisture are minimized.

Analysis of highly reactive compounds also requires the use of exhaustively purified solvents. Solvents employed for ESI-MS of sensitive compounds are distilled and stored over activated molecular sieves for 3 days inside the glovebox before analysis.<sup>76</sup> Collecting spectra of extremely water-sensitive compounds can be negatively impacted by trace residual water from wet samples introduced to the instrument days, or even up to months beforehand. A good example is the  $[\text{Cp}_2\text{ZrMe}]^+$  cation, which readily reacts with any residual water giving  $\text{M} + 2$  species via  $[\text{M} + \text{H}_2\text{O} - \text{CH}_4]^+$  to produce  $[\text{Cp}_2\text{ZrOH}]^+$ . Trace amounts of water can complicate the analysis of methylalumoxane anions, as these anions can have dozens of Al-Me bonds, and multiple hydrolysis reactions could lead to very complicated spectra.

The collision gas also plays a significant role in getting reliable MS/MS spectrum.<sup>77</sup> When the system being studied is very sensitive to air and moisture, such as  $[\text{Cp}_2\text{Zr}(\mu\text{-Me})_2\text{AlMe}_2]^+ [\text{B}(\text{C}_6\text{F}_5)_4]^-$ , the



**FIGURE 14** Full-scan positive-mode droplet spray mass spectra of catalytically active species in different solvents: (A) acetonitrile/toluene and (B) THF. Ion 2 is  $[\text{Cp}_2\text{ZrMe}]^+$ , and ion 3 is  $[\text{Cp}_2\text{ZrCl}]^+$ . Adapted with permission from Jiang et al.<sup>70</sup> Copyright (2015) American Chemical Society

collision gas employed is often passed through a gas drying unit. However, moisture can also be in the collision chamber inside the mass spectrometer, which is very difficult to remove. Getting reliable MS/MS in such cases can be achieved by lowering the collision gas pressure.<sup>77</sup> Trace amounts of water in quadrupole ion traps (QIT) also complicate the analysis of moisture-sensitive compounds.<sup>78,79</sup>

The desolvation gas employed for ESI-MS experiments is usually of very high purity (e.g., 99.995%). The effects of switching the desolvation gas source from a liquid  $\text{N}_2$  dewar to an  $\text{N}_2$  generator are

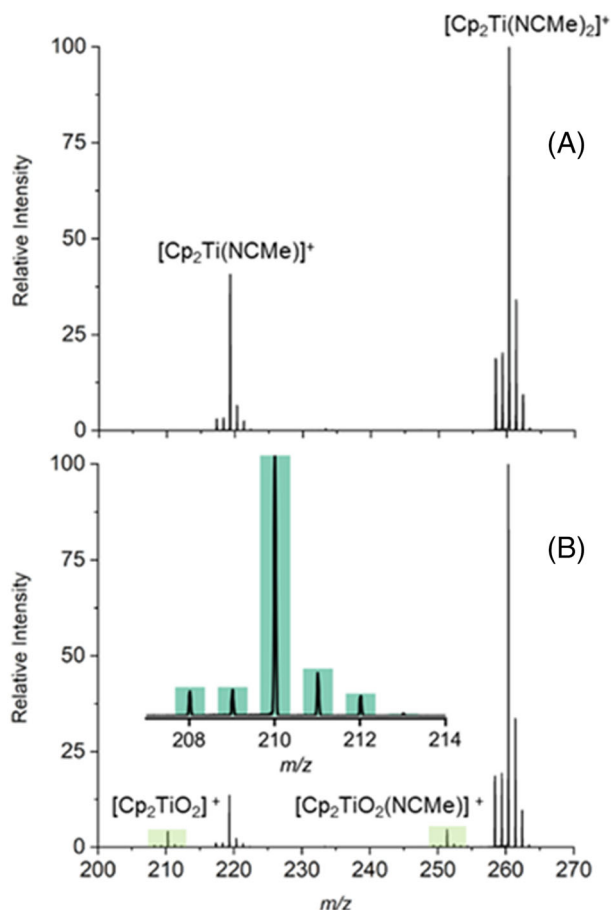


reported in the literature.<sup>77</sup> Even for very reactive compounds, such as the reduced titanium complex  $[\text{Cp}_2\text{Ti}(\text{NCMe})_2]^+[\text{ZnCl}_3]^-$  and the olefin polymerization precatalyst  $[\text{Cp}_2\text{Zr}(\mu\text{-Me})_2\text{AlMe}_2]^+[\text{B}(\text{C}_6\text{F}_5)_4]^-$ , very little oxidation was exhibited even when they were rendered coordinatively unsaturated through in-source fragmentation, as seen in Figure 15. Therefore,  $\text{N}_2$  generators could be employed for analysis of organometallic compounds without significant concern over oxidation of the sample (the extent of oxidation was <4% at the highest flow rate = lowest purity  $\text{N}_2$  examined).

Thoroughly rinsing the instrument before and after analysis is also necessary to avoid contamination from previous samples. While analyzing methylalumoxane, which is very sensitive to air and moisture, the source (i.e., sample cone and baffle) is rinsed periodically to prevent blockages, as seen in Figure 16.

## 8 | ATMOSPHERIC SOLIDS ANALYSIS PROBE

The atmospheric solids analysis probe (ASAP) was first reported in 2005 by McEwen et al.<sup>80</sup> By using this technique, mass spectra can be



**FIGURE 15** The  $[\text{Cp}_2\text{Ti}(\text{NCMe})_2]^+$  system with  $\text{N}_2$  supply from (A) 5.0 purity  $\text{N}_2$  cylinder and (B) generator. Inset in (B) shows the expected (highlighted) and experimental isotopic pattern of the oxidized  $[\text{Cp}_2\text{TiO}_2]^+$  species

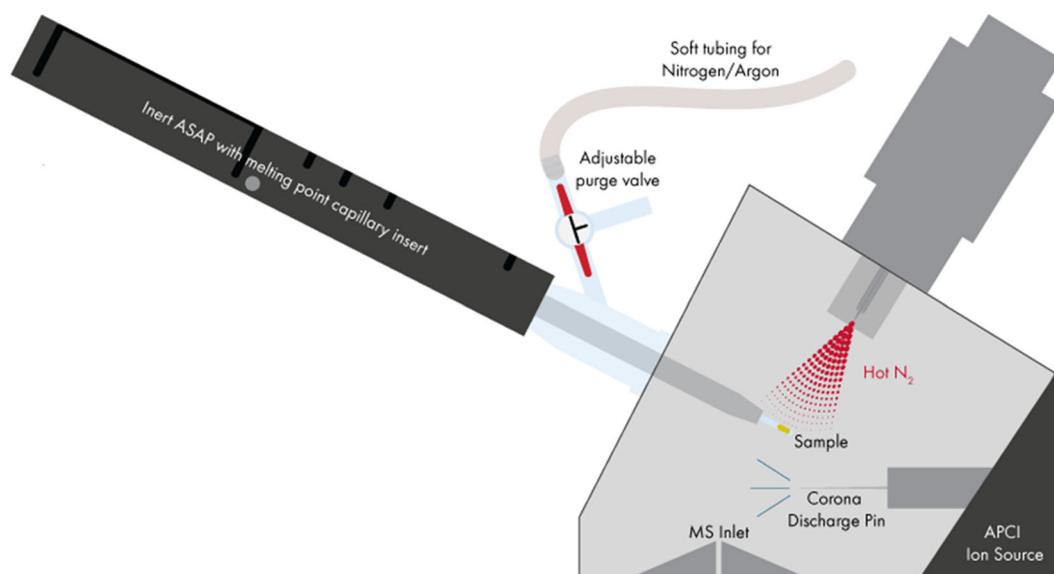


**FIGURE 16** Baffle cone (top) before and (bottom) after running methylalumoxane

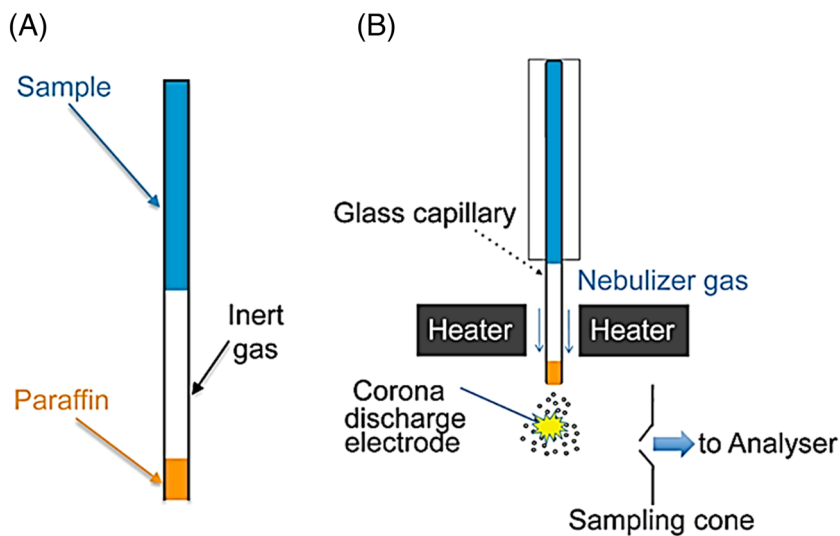
acquired very quickly because both vaporization and ionization occur at atmospheric pressure. A technique called inert atmospheric solids analysis probe (iASAP) uses the ASAP probe to analyze air-sensitive compounds. There have been two reports in the literature on iASAP by two different research groups. The first is a patent by Weis et al, and the analysis is done commercially by Advion using iASAP.<sup>81</sup> In this technique, a probe vessel is engaged with an ASAP. The probe vessel is configured so that the sample is introduced into an ionization system under inert gas. Figure 17 shows a probe assembly engaging with an ASAP probe and the capillary, which contains the sample. The whole assembly is then connected to an ionization system. The iASAP probe is designed to provide analysis in less than 30 s without sample decomposition.

Mosely et al reported using a melting point tube (MPT) in which they loaded the air-sensitive sample for analysis in a glovebox.<sup>82</sup> The MPT was enclosed in plasticine and then sealed with a flame after taking it out of the glovebox. The MPT is heated and stretched (2–3 cm away from the sample) and carefully broken to give a shorter length MPT. This is then inserted in an ASAP holder, which is modified slightly to incorporate shorter length MPT. The MPT is then broken inside the inert atmosphere API source housing with a baffle, and the sample is ionized by hot  $\text{N}_2$ . Using this technique, two highly air- and moisture-sensitive compounds were analyzed and compared with the standard ASAP procedure. A tungsten cluster was only observed by iASAP, and only decomposition products were observed with the ASAP technique.<sup>82</sup>

In 2020, Naim et al reported the analysis of air-sensitive solids and liquids by paraffin-inert atmospheric solids analysis probe



**FIGURE 17** The inert atmospheric solids analysis probe. Figure used with permission from Advion Inc. ASAP, atmospheric solids analysis probe; MS, mass spectrometry



**FIGURE 18** (A) Paraffin-inert atmospheric solids analysis probe (ASAP) glass capillary. (B) Paraffin-inert atmospheric solid analysis probe (piASAP) principle. Adapted with permission from Naim et al.<sup>83</sup> Copyright (2019) American Chemical Society

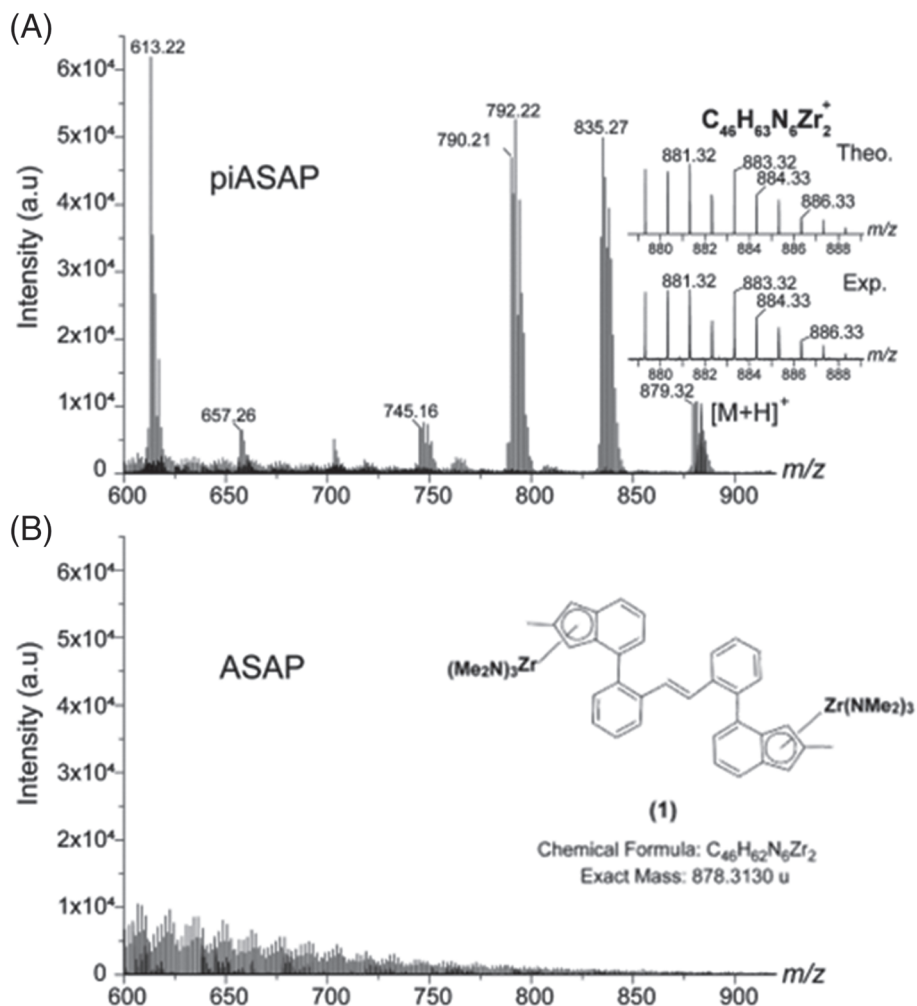
(piASAP).<sup>83</sup> This method allows the study of air-sensitive compounds using a glass capillary filled with a sample and then sealed by a paraffin plug to maintain the inert sample until the ionization process, as seen in Figure 18. The sample can then be taken out of the glovebox and inserted in the ASAP probe as long as the paraffin is intact. Because paraffin is a mixture of alkanes, it does not occlude the mass spectrum, as alkanes do not ionize readily compared with the analyte.

Using the piASAP technique, the air-sensitive dinuclear zirconium complex [BisInd] (Zr (NMe<sub>2</sub>)<sub>3</sub>)<sub>2</sub> [1] was characterized. As shown in Figure 19, when ASAP was done with the same compound in air, the spectrum showed a lack of [M + H]<sup>+</sup> or any related ions.

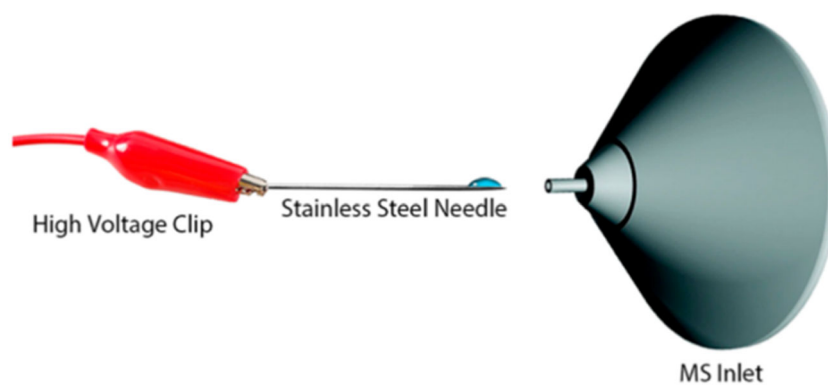
## 9 | PROBE ELECTROSPRAY IONIZATION

Efforts are being made to develop “solvent-free” MS techniques for green chemistry applications. This approach has advantages because solvent-free ionization enables easy handling of the sample, and a wide variety of compounds can be analyzed, including moisture-sensitive samples and samples which are not soluble in traditional MS solvents. Probe electrospray ionization (PESI) is an ionization technique that relies on “solvent-free” MS.<sup>84</sup> It employs a conductive solid probe on which a small amount of analyte can be deposited. The technique can be used to analyze moisture/air-sensitive compounds.<sup>85</sup> The technique involves heating the needle

**FIGURE 19** Analysis of E-Zr dimer (1) by piASAP and ASAP techniques. Panels (A) and (B) are mass spectra of piASAP and ASAP conducted under inert and aerobic conditions, respectively. The zoomed areas showcase the theoretical and experimental isotopic patterns of complex 1. Adapted with permission from Naim et al.<sup>83</sup> Copyright (2019) American Chemical Society



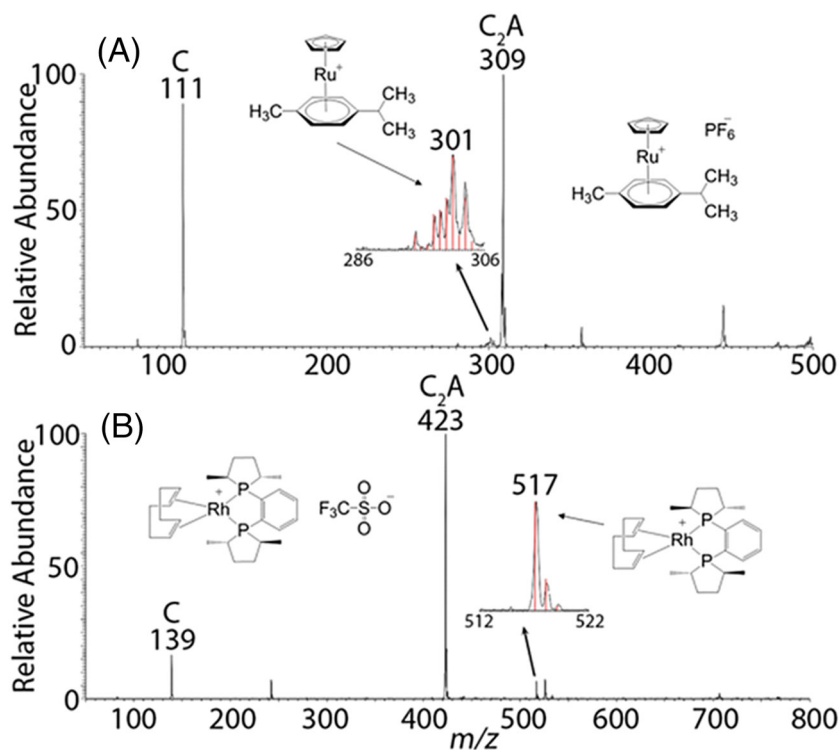
**FIGURE 20** Probe electrospray ionization-mass spectrometry (PESI-MS) apparatus using a stainless steel as the probe. Adapted with permission from Liu et al.<sup>85</sup> Copyright (2014) American Chemical Society



probe to convert the solid sample into a liquid, followed by applying a high voltage to the probe for spray ionization, as seen in Figure 20.

A highly moisture-sensitive sample 1-butyl-3-methylimidazolium (bmim)[AlCl<sub>4</sub>] was analyzed by this approach, and the results were compared against ESI. It was reported that the negative ion [AlCl<sub>4</sub>]<sup>-</sup> remains intact in PESI analysis and appears as a dominant peak, whereas in ESI measurements, the sample is hydrolyzed and ions

resulting from [AlCl<sub>4</sub>]<sup>-</sup> hydrolysis were seen. It should be noted that ESI measurements in this work are done in MeOH/H<sub>2</sub>O, so it is not at all surprising that the authors see a hydrolyzed spectrum. Analysis of the organometallic complex Cp<sub>2</sub>ZrCl<sub>2</sub> was also reported. In this case, a solid complex was melted around 240°C on the probe and then sprayed by applying 5 kV to the probe. The desired peak of the cation [Cp<sub>2</sub>ZrCl]<sup>+</sup> was observed, but a peak at +18 Da (water adduct) was also seen and reported.



**FIGURE 21** Probe electrospray ionization-mass spectrometry (PESI-MS) spectra of extremely air-sensitive Ru complexes. Adapted with permission from Liu et al.<sup>85</sup> Copyright (2014) American Chemical Society

The authors also reported the analysis of a ruthenium complex [Rh-MeDuPHOS][OTf], which is used as a catalyst for asymmetric hydrogenation. This catalyst is extremely air-sensitive and was analyzed in ionic liquids like [bmim][PF<sub>6</sub>]. The ionic liquid stabilized the catalyst by protecting it from oxygen, and PESI-MS was recorded after the catalyst was weighed in a glovebox, dissolved in [bmim][PF<sub>6</sub>], and diluted to 1 mM. Figure 21 shows the peak for the ionic liquid cation and cation cluster ions ( $m/z$  139 and 423) and a peak for intact catalyst cation [Rh-MeDuPHOS]<sup>+</sup>, observed at  $m/z$  517. Related successful analyses were previously performed for [Ru( $\eta^6$ -p-cymene)( $\eta^2$ -triphos)Cl][PF<sub>6</sub>] in [bmim][PF<sub>6</sub>] at nanomolar concentrations and below.<sup>86</sup>

A word of caution regarding PESI, however—in related experiments where an ionic liquid was analyzed directly from a wire attached to the charged capillary in an ESI-MS source, it was found that trace molecular solvent was largely responsible for facilitating analysis,<sup>87</sup> and this possibility has not been ruled out in the PESI reports published to date.

## 10 | CONCLUSION

Mass spectrometric analysis of air- and moisture-sensitive compounds can be extremely challenging, and this review covers a wide variety of problem-solving approaches taken by different research groups in this regard. The strategies employed depend on both the state of the sample of interest (gas, liquid, solid, and solution) and the ionization technique being employed (almost all of them, with creative modifications to suit the air and moisture sensitivity of the targets). The principal

difficulty stems from the mass spectrometric necessity for using very small quantities of material to avoid detector saturation, coupled with the reactivity of the material under study. Avoiding decomposition of the sample requires the application of methodologies adapted from synthetic organometallic chemistry to avoid the considerable frustration of a failed analysis.

## ACKNOWLEDGMENTS

JSM thanks the NSERC Discovery program for operational funding, and CFI, BCKDF and the University of Victoria for infrastructural support. Thanks also to previous workers in our team who developed various strategies for avoiding decomposition, especially Matthew Henderson, Krista Kobylanski, Zohrab Ahmadi, Jingwei Luo, and Johanne Penafiel.

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**How to cite this article:** Joshi A, Killeen C, Thiessen T, Zijlstra HS, McIndoe JS. Handling considerations for the mass spectrometry of reactive organometallic compounds. *J Mass Spectrom.* 2022;57(3):e4807. doi:10.1002/jms.4807