

Development of Solvent-Free Ambient Mass Spectrometry for Green Chemistry Applications

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Supporting Information

ABSTRACT: Green chemistry minimizes chemical process hazards in many ways, including eliminating traditional solvents or using alternative recyclable solvents such as ionic liquids. This concept is now adopted in this study for monitoring solvent-free reactions and analysis of ionic liquids, solids, and catalysts by mass spectrometry (MS), without using any solvent. In our approach, probe electrospray ionization (PESI), an ambient ionization method, was employed for this purpose. Neat viscous room-temperature ionic liquids (RTILs) in trace amounts (e.g., 25 nL) could be directly analyzed without sample carryover effect, thereby enabling high-throughput analysis. With the probe being heated, it can also ionize ionic solid compounds such as organometallic complexes as well as a variety of neat



neutral solid chemicals (e.g., amines). More importantly, moisture-sensitive samples (e.g., [bmim][AlCl₄]) can be successfully ionized. Furthermore, detection of organometallic catalysts (including air-sensitive [Rh-MeDuPHOS][OTf]) in ionic liquids, a traditionally challenging task due to strong ion suppression effect from ionic liquids, can be enabled using PESI. In addition, PESI can be an ideal approach for monitoring solvent-free reactions. Using PESI-MS, we successfully examined the alkylation of amines by alcohols, the conversion of pyrylium into pyridinium, and the condensation of aldehydes with indoles as well as airand moisture-sensitive reactions such as the oxidation of ferrocene and the condensation of pyrazoles with borohydride. Interestingly, besides the expected reaction products, the reaction intermediates such as the monopyrazolylborate ion were also observed, providing insightful information for reaction mechanisms. We believe that the presented solvent-free PESI-MS method would impact the green chemistry field.

reen chemistry is the design of chemical products and J processes that reduce or eliminate the use or generation of hazardous substances.¹ In order to minimize pollution before it is produced, green chemistry optimizes every element of chemical processing, including reagent, atom economy, molecular design, waste, etc.² Among these elements, solvent optimization is currently one of the most active research fields, which involves several hot topics: using water, alternative recyclable solvents (e.g., ionic liquids), and alternative nontoxic reaction media (e.g., supercritical fluids), or no solvent for chemical reactions.^{3,4} These nontraditional solvent systems have been applied to many organic and inorganic syntheses. Unfortunately, in the field of mass spectrometry (MS), the "solvent optimization revolution" has not gained popularity yet and is still in its infancy stage, although efforts were made toward developing "solvent-free" $MS.^{5-8}$ The reason for this might be due to the difficulty of eliminating the solvent use for analysis. Currently dominant ionization methods, such as electrospray ionization (ESI)⁹ and matrix-assisted laser desorption ionization (MALDI),¹⁰ typically need organic solvents like acetonitrile or methanol to dissolve/dilute samples or to prepare matrix solutions. The organic solvent also helps

droplet evaporation for ion generation during the ESI ionization process.

Solvent-free ionization MS analysis has been an attractive goal for chemical analysis. The reason is obvious. Solvent-free ionization not only results in easy sample handling but also leads to the analysis of a wide range of compounds, including moisture-sensitive samples and traditional MS solvent insoluble samples. More importantly, solvent-free analysis is environmentally friendly and in accordance with the concept of green chemistry. When being combined with green chemical synthesis, it makes the entire synthesis and subsequent analysis process "green". Furthermore, solvent-free ionization techniques also have unique applications for working in extreme environments, such as in volcanoes or in space, using miniaturized or unmanned mass spectrometers.¹¹ In literature, several atmospheric pressure solvent-free ionization methods were reported and demonstrated. Solvent-free MALDI^{5,12} is probably the most developed solvent-free ionization technique

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Figure 1. (a) PESI-MS apparatus using a stainless steel as the probe and (b) thermally assisted-PESI-MS apparatus using a soldering iron as the probe.

so far, in which analyte and matrix are solvent-freely homogenized by grinding⁵ or sublimed vapor desorption.¹³ A major advantage of the method is its capability of ionizing insoluble/poorly soluble samples, such as polycyclic aromatic compounds,⁷ amyloid peptides,¹⁴ and fatty acids,¹⁵ et al.¹² Another solvent-free ionization technique is direct analysis in real time (DART),¹⁶ which desorbs and ionizes samples with electronic or vibronic excited neutral species. DART can solvent-freely analyze various samples including ionic liquids and polycyclic aromatics.^{8,17} In addition, the solvent-free analysis has also been achieved by DART-similar ionization methods, such as plasma-assisted desorption/ionization (PADI),¹⁸ flowing afterglow-atmospheric pressure glow discharge (FA-APGD),¹⁹ dielectric barrier discharge ionization (DBDI),²⁰ low-temperature plasma (LTP) probe ionization,² and beta electron-assisted direct chemical ionization (BADCI).²² However, current atmospheric pressure solventfree MS methods still require complex sample preparations or complicated instrumentation. In addition, the direct analysis of solvent-free reaction intermediates and products, present in sticky liquid or solid mixtures, is still missing in the literature. What could be a convenient solvent-free ambient ionization MS²³⁻²⁵ method for green chemistry applications? We found the answer to be probe electrospray ionization (PESI).

The term PESI was introduced by Hiraoka and co-workers.²⁶ In contrast with ESI of using a capillary for sample introduction, PESI employs a conductive solid probe on which a microliter droplet of analyte solution is deposited. When a high voltage is applied to the probe, the droplet deforms to a Taylor Cone at the tip of the probe to emit a spray.²⁷ Using PESI-MS, various chemical and biological assays were performed,²⁸ including imaging biological tissues,² monitoring chemical reactions in solution,³⁰ and analyzing living biological samples in real time.^{31,32} It was shown that PESI had high tolerance to salt³³ and detergent.³⁴ Some earlier work relevant to PESI was carried out by Shiea and co-workers,³⁵ in which copper wire,^{35,36} optical fiber,³⁷ or platinum rod³⁸ could be used as the probe. However, PESI was previously only used for ionizing samples in either aqueous or organic solvents. In our laboratory, we serendipitously found that highly viscous room temperature ionic liquids (RTILs) can be directly loaded on a needle probe and sprayed to generate gas-phase ions, without using solvent for sample dilution. This phenomenon is also applicable to ionic solid samples, in which the solvent-free PESI ionization can be achieved simply by heating the needle probe to convert the loaded solid sample into liquid followed by application of a high voltage to the probe for spray ionization. Such a solvent-free MS method provides opportunity to analyze moisture-/air-sensitive compounds. The surprising capability of PESI of directly spraying viscous liquid samples prompted us to use it for additional green chemistry-related applications such as monitoring solvent-free organic reactions as well as detecting organo-metallic catalysts in ionic liquids.

EXPERIMENTAL SECTION

Reagents. 1-Ethyl-3-methylimidazolium tetrafluoroborate ([emim][BF₄]), 1-butyl-3-methylpyridinium tetrafluoroborate ([bmpy][BF₄]), 1-ethyl-2,3-dimethylimidazolium bis-(trifluoromethanesulfonyl)imide ([edmim][NTf₂]), trihexyltetradecylphosphonium bis(2,4,4-trimethylpentyl)phosphinate ([P₆₆₆₁₄][TMPP]), 1-ethyl-3-methylimidazolium nitrate ([emim][NO₃]), 1-butyl-3-methylimidazolium tetrafluoroborate ($[bmim][BF_4]$), 1-butyl-2,3-dimethylimidazolium tetrafluoroborate ([bdmim][BF₄]), 2,4,6-triphenylpyrylium tetrafluoroborate ([TPP][BF₄]), perylene, 1-butyl-3-methylimidazolium tetrachloroaluminate ($[bmim][AlCl_4]$), cyclopentadienyl(p-cymene)ruthenium(II) hexafluorophosphate ([CpRu(p-cymene)][PF₆]), ferrocene, silver bis-(trifluoromethanesulfonyl)imide (AgNTf₂), pentamethylcyclopentadienyliridium(III) chloride dimer ([Cp*IrCl₂]₂), 1-naphthylamine, benzylamine, 1,5-pentanediol, phenylhydrazine, cyclohexanone, potassium borohydride (KBH₄), 3,5-dimethylpyrazole, 3-phenyl-5-methylpyrazole, indole, and benzaldehyde were all purchased from Sigma-Aldrich (St. Louis, MO). Bis(cyclopentadienyl)zirconium dichloride (Cp_2ZrCl_2) and 1.2-bis[(2S,5S)-2.5-dimethylphospholano]benzene(cyclooctadiene)rhodium(I) trifluoromethanesulfonate ([Rh-MeDuPHOS][OTf]) were purchased from Strem (Newburyport, MA). All the reagents were used without further purifications.

Apparatus. A Thermal Finnigan LCQ DECA ion trap mass spectrometer (San Jose, CA) and an AB SCIEX Q-trap 2000 triple-quadrupole-linear ion trap mass spectrometer (Concord, Canada) were used for all experiments. The commercial ion source was removed for the accommodation of homemade PESI sources. Two different homemade PESI ionization probes, a regular PESI, and a thermally assisted-PESI were designed, which simply consisted of a stainless steel needle (Fisher Scientific, no. 70005-98033) and a soldering iron (Weller, WSB25HK), respectively, as the probe. The former probe (Figure 1a) was used for ionizing liquid samples only by applying a high voltage of 5 kV to the probe. The latter probe (Figure 1b) was used for the analysis of higher melting-point analytes like ionic solids, in which solid samples were loaded onto the probe and then heated to melting (30 $^{\circ}C \sim 300 {}^{\circ}C)$, by plugging the soldering iron in a power socket. The samples were ionized by PESI as soon as they were melted. The

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Figure 2. PESI-MS spectra of RTIL samples: (a) [emim][BF₄], (b) [bmpy][BF₄], (c) [edmim][NTf₂], and (d) [P₆₆₆₁₄][TMPP].



Figure 3. Thermally assisted-PESI-MS spectra of (a) [bdmim][BF₄] (mp 38–40 °C), (b) [TPP][BF₄] (mp 250–251 °C), (c) Cp₂ZrCl₂ (mp 242– 245 °C), and (d) pervlene (mp 276-279 °C). The red lines in the Figure 3c inset show the theoretically calculated isotopic peak distribution of Cp_2ZrCl^+ (*m*/*z* 255).

distance between the probe tips and MS inlet capillary varied from 0.5 to 5.0 cm.

RESULTS AND DISCUSSION

Direct Ionization of Ionic Liquids and Ionic Solids. RTILs are popular solvents used for organic reactions due to their recyclability.³⁹ The most common RTILs are imidazolium, pyridinium, pyrrolidinium, and phosphonium-based organic salts.⁴⁰ In previous ESI-MS studies, RTILs were used to increase the detection selectivity and sensitivity of analytes such as neutral polysaccharides or organometallic compounds because they could serve as good charge carriers.^{41,42} ESI-MS was also used to analyze ionic liquids;^{43,44} however, heated curtain/desolvation gas was required to reduce the sample viscosity,43 and the contamination to the mass spectrometer was often the major problem.⁴⁴ In our experiment, [emim]- $[BF_4]$, $[bmpy][BF_4]$, $[edmim][NTf_2]$, and $[P_{66614}][TMPP]$, were chosen as representative examples for PESI test, using the regular probe (Figure 1a). The results are shown in Figure 2. One microliter of each RTIL sample was loaded onto the needle tip and then ionized by applying a high voltage of 5 kV to the needle. In all cases, the continuous signal lasted for several minutes. As shown in the obtained positive ion spectra

(Figure 2), cation peaks were clearly observed. For instance, in the case of [emim][BF₄] (Figure 2a), the intact cation (labeled as "C" and this denotation is applicable throughout the paper) was observed at m/z 111 along with the cluster ions C₂A, C₃A₂, and C_4A_3 (the denotation of "A" presents the corresponding anion, which is tetrafluoroborate in this case), appearing at m/z309, 507, and 705, respectively. The cluster ions provide information about the counteranions for the analytes. In addition, in the experiment, the ion signal immediately disappeared if the high voltage was turned off. By simply wiping the residue off from the probe, no leftover would be seen to influence subsequent runs, thus allowing highthroughput analysis. As a demonstration, three RTIL samples can be analyzed in less than 2.5 min (Figure 1S of the Supporting Information) without cross-talking and sample carryover effect. In contrast, if traditional ESI method was used for the analysis of the three samples, carryover issue occurred and both sample preparation and cleaning were timeconsuming (see Figure 2S and discussion of the Supporting Information). In addition to the advantage of being capable of high-throughput analysis, the PESI method is also highly sensitive. Good signal was obtained for RTILs as low as 25 nL (Figure 3S of the Supporting Information).



Figure 4. (a) PESI-MS and (b) ESI-MS spectra of $[\text{bmim}][\text{AlCl}_4]$ in the positive ion mode; (c) PESI-MS and (d) ESI-MS spectra of $[\text{bmim}][\text{AlCl}_4]$ in the negative ion mode. The red lines in the insets of (a and c) show theoretically calculated isotopic peak distributions of m/z 445 and 167, respectively.

In addition to liquid samples, solid samples can also be analyzed by PESI-MS with a new design of the ionization probe. In the new design (Figure 1b), the probe is replaced by a soldering iron on which solid samples could be thermally converted (heating the samples by soldering iron) to liquids for spray ionization. In this thermally assisted-PESI, the soldering iron tip was polished to a small triangle shape for promoting spray ionization because of the high electric field on the tip (analogous to paper tip used in the paper spray ionization method).^{45,46} Four different types of solid samples were chosen for demonstration, including ionic solids, organometallics, organic salts, and polycyclic aromatics. These compounds have melting points (MPs) varying from 38 to 279 °C. As soon as the sample started melting, the high voltage of 5 kV was applied to the probe to affect ionization. The collected spectra are shown in Figure 3, in which no fragmentation was observed. In contrast, directly ionizing the samples in solid state with PESI received no signal at all, proving that the heating for sample phase conversion was important to the ionization.

As depicted in Figure 3 (panels a and b), [bdmim][BF₄] and [TPP][BF₄] show intact cations as well as cluster ion peaks, similar to the liquid samples discussed above (Figure 2). This is reasonable as the solid samples are intrinsically organic salts but have MPs exceeding room temperature. Interestingly, solid organometallic compounds could also be ionized by thermallyassisted-PESI. For example, Cp_2ZrCl^+ was detected at m/z 255 (Figure 3c) for the organometallic complex Cp_2ZrCl_2 when the solid complex was melted around 240 °C on the probe and then sprayed with 5 kV applied to the probe. The observed isotopic peak distribution of m/z 255 agreed well with the theoretical simulation (Figure 3c, inset). In addition, its water adduct ion was observed at m/z 273. Equally interestingly, solid polycyclic aromatic compounds with high melting points such as perylene could also be ionized by thermally assisted-PESI-MS (Figure 3d). In the spectrum, the observed peak appears at m/z 252, which corresponds to the perylene radical cation and might result from ionization via corona discharge of the melted sample vapor. This result shows the strength of our PESI method because perylene, like other polycyclic aromatic compounds, is difficult to be ionized by ESI, as it is insoluble in traditional ESI solvents. For this reason, methods such as DART, solvent-free MALDI, and atmospheric pressure photo

ionization (APPI)^{47,48} were developed to ionize this type of nonpolar aromatic species. Herein, thermally assisted-PESI provides an alternative and simple solution.

Strikingly, PESI can be used for direct analysis of moisturesensitive compounds as it does not need the use of a solvent. For demonstration, a moisture-sensitive ionic liquid, [bmim]-[AlCl₄], was analyzed. [Bmim][AlCl₄] is one of the earliest developed RTILs,⁴⁹ which is known to vigorously react with water (i.e., the hydrolysis of tetrachloroaluminate $AlCl_4^{-}$). The moisture sensitive property makes it difficult to be ionized using traditional ionization methods like ESI, which involve the use of solvent. Figure 4a shows the spectrum of [bmim][AlCl₄] analyzed by PESI-MS. In the spectrum, both the intact cation and the cation cluster ion C₂A appears at m/z 139 and 445, respectively. The observation of C₂A provides the information on the anionic component of the sample. The isotopic distribution of ion C_2A at m/z 445 matches well with the theoretical simulation (Figure 4a, inset), confirming the peak assignment. By contrast, the m/z 445 was completely missing, using ESI-MS analysis of the ionic liquid dissolved in MeOH/ H_2O with a dilution factor of $2/10^4$ (v/v) (Figure 4b), indicating depletion of anion AlCl₄⁻ in the solvent used for ESI. Typically, the cluster ions like C₂A would be detectable in ESI of moisture-stable ionic liquid samples (e.g., the example shown in Figure 2S of the Supporting Information). Indeed, when the negative ESI spectrum of [bmim][AlCl₄] was acquired, ions at m/z 131 and 149, resulting from AlCl₄⁻ hydrolysis, were noticed (Figure 4d). In contrast, the intact anion $AlCl_4^-$ was observed as the dominant peak at m/z 167 in the negative ion PESI-MS spectrum, with isotopic peak distribution fitting well with the theoretical simulation (Figure 4c, inset).

The results shown above demonstrate the strength of solvent-free PESI, as exemplified by its capability in ionizing ionic liquids, ionic solids, as well as moisture-sensitive species. These features of PESI prompted us to apply it to the analysis of solvent-free reactions and the detection of organometallic catalysts in RTILs, two applications with significance in green chemistry.

Direct Monitoring of Solvent-Free Reactions. With increased attention in the pursuit of green chemistry for reducing environmental pollution, people have begun utilizing solvent-free organic reactions for chemical synthesis. Other

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Figure 5. Thermally assisted-PESI-MS spectra of (a) the solid reaction product from the solvent-free reaction of 1 mmol ferrocene and 1 mmol AgNT f_{2j} (b) the solid reaction product from the solvent-free reaction of 1 mmol KBH₄ and 5 mmol 3,5-dimethylpyrazole; and (c) the solid reaction product from the solvent-free reaction of [TPP][BF₄] and 1-naphthylamine. Reaction equations are shown as figure insets.

driving forces for the development of dry media reactions in chemistry are economics (save money on solvents), ease of purification (no postsynthesis solvent removal), and high reaction rate (due to high concentration of reactants). However, solvents are usually still being used in traditional postsynthesis analysis. In our view, the monitoring/analysis of the solvent-free reactions without using any solvent would be ideal and in accordance with the green chemistry concept. It turns out that PESI is the method of choice for this purpose. Several solvent-free reactions were successfully monitored by PESI in this study.

The first example is the solvent-free synthesis of metalcontaining ionic liquids, in which ferrocene can be milled with silver salts to provide ferrocenium ionic liquids (see reaction eq 1 shown in Figure 5a).⁵⁰ The whole preparation was performed in a N₂ gas atmosphere glovebox as the product is air sensitive, following the reported procedure.⁵⁰ One mmol ferrocene and 1 mmol AgNTf₂ were mixed and grounded in a motor for 5 min. Dark color solid product was produced after grounding. The product was directly analyzed by thermally assisted-PESI-MS. In the collected spectrum (Figure 5a), the ferrocenium ion from the resulting product ferrocenium bis-(trifluoromethanesulfonyl)imide was observed at m/z 186 as the major peak.

Tris(pyrazolyl)borated metal salts are a class of intriguing catalysts because of their excellent thermal stabilities.⁵¹ As a synthesis precursor of catalysts, potassium tris(pyrazolyl)borate (KTp) can be prepared by reacting KBH₄ with pyrazoles. In our experiment, the solvent-free reaction was performed by mixing and grounding 1 mmol KBH₄ and 5 mmol 3,5dimethylpyrazole followed with heating to 220 °C for 4 h. After cooling, a white solid product was obtained. The product was directly analyzed by thermally assisted-PESI-MS. In the acquired spectrum (Figure 5b), tris(3,5-dimethylpyrazolyl)borate anion Tp^{Me2} (m/z 297; structure shown in Figure 5b) of the expected triply pyrazolylated product, potassium tris(3,5dimethylpyrazolyl)borate (KTp^{Me2}), was clearly observed. Upon collision-induced dissociation (CID), m/z 297 lost bis(3,5-dimethylpyrazolyl)borane to form the deprotonated pyrazole of m/z 95, consistent with its structure (Figure 4S-a of the Supporting Information). In Figure 5b, the deprotonated starting material pyrazole of m/z 95 was also seen. Interestingly,

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Figure 6. (a) PESI-MS spectrum of an oily reaction mixture from microwave-assisted alkylation reaction of benzylamine and 1,5-pentanediol catalyzed by $[Cp*IrCl_2]_2$. Thermally assisted-PESI-MS spectra of (b) the solid product from solvent-free reaction of phenylhydrazine and cyclohexanone, and (c) the gel product from solvent-free reaction of indole, benzaldehyde, and $[bmim][BF_4]$. Reaction equations are shown as figure insets.

the monopyrazolylborate intermediate ion was detected at m/z109. Upon CID, m/z 109 shows the losses of HN[•]-BH₂ and CH₃CH=CH[•], confirming the proposed structure (Figure 4Sb of the Supporting Information). The presence of the monopyrazolylborate intermediate in the reaction mixture is in agreement with the previously reported stepwise substitution mechanism.⁵² This monopyrazolylborate intermediate is moisture-sensitive. Indeed, in a comparison experiment, when the solid reaction product was dissolved in methanol and ionized by ESI-MS, m/z 109 was not observed (Figure 4S-c of the Supporting Information). In addition, the same phenomena were seen in the analysis of solvent-free reaction of KBH4 with another similar substrate, 3-phenyl-5-methyl pyrazole (Figure 5S of the Supporting Information). The capability of analyzing the moisture-sensitive species allows one to use PESI for detecting reaction intermediates, which provides valuable information for the reaction mechanism.

In another example of converting pyrylium to the pyridinium ion with primary amine, 53 1-naphthylamine (MP 47–50 °C)

was chosen as the nucleophile to attack pyrylium. The solventfree reaction was performed by mixing [TPP][BF₄] with 1naphthylamine (eq 3, Figure 5c), and then ionized by thermally assisted-PESI-MS. In the obtained spectrum (Figure 5c), both [TPP] cation (m/z 309) and the 1-naphthylamine radical cation from remaining starting materials (m/z 143, probably due to corona discharge involved in PESI) were observed. Meanwhile, the 1-(1-naphthyl)-2,4,6-triphenylpyridinium ion from the expected condensation reaction product was seen at m/z 434, which was produced during heating of the mixture on the PESI probe and instantaneously monitored by PESI-MS.

The solvent-free PESI analysis is also applicable to probe neutral reaction products generated in solvent-free organic reactions. The alkylation of amines is an important reaction in both pharmaceutical and chemical industries. Transition metals, such as iridium and ruthenium catalysts are known to promote alkylation using alcohols. For example, $[Cp*IrCl_2]_2$ can efficiently catalyze an atom-economical and solvent-free amine alkylation reaction using microwave irradiation (eq 4,



Figure 7. PESI-MS spectra of (a) 1 mM [CpRu(p-cymene)][PF₆] in [emim][BF₄] and (b) 1 mM [Rh-MeDuPHOS][OTf] in [bmim][PF₆]. The red lines in the insets show theoretically calculated isotopic peak distributions.

Figure 6a).⁵⁴ One millimole of benzylamine, 1 mmol of 1,5pentanediol, and 1% mmol [Cp*IrCl₂]₂ were added to a microwave vial. The vial was purged with N2 gas and then sealed for microwave irradiation. After 1 h, an oily reaction mixture was produced and directly analyzed by PESI-MS without heating. The protonated alkylation product 1benzylpiperidine was observed as the dominant peak (m/z)176, Figure 6a), which was confirmed by MS/MS spectrum, showing losses of piperidine and toluene (Figure 6S-a of the Supporting Information). In addition, the PESI-MS spectrum of the reaction mixture in absence of the iridium catalyst showed only the adduct ion of the protonated benzylamine and 1,5-pentanediol (m/z 212) without product ion (Figure 6S-b of the Supporting Information), indicating that the catalyst is essential for the occurrence of amine alkylation by alcohols. This example also demonstrates that PESI-MS is a good tool for reaction monitoring. In Figure 6a, another peak at m/z 192 was observed, probably corresponding to the protonated ion of the condensation product between benzylamine and 5hydroxypentanal, an impurity of 1,5-pentanediol.

Arylhydrazones are important precursors for synthesizing various nitrogen-containing compounds, such as nitriles, nitrones, pyrazoles, triazoles, and others. Phenylhydrazones can be easily prepared solvent-free by grounding aldehydes and ketones (eq 5, Figure 6b).⁵⁵ One millimoles of phenylhydrazine and 1 mmol cyclohexanone were mixed in a test tube. After stirring for 10 min, a yellow solid product was formed. The product was directly tested by thermally assisted-PESI-MS. A dominant peak was observed at m/z 189, which was confirmed as the protonated cyclohexanone phenylhydrazone, by observing the characteristic neutral loss of NH₃ via the Borsche–Drechsel cyclization pathway⁵⁶ upon CID (Figure 7S of the Supporting Information). Meanwhile, the dimer ion of the product cyclohexanone phenylhydrazone and the adduct

ion of the product and cyclohexanone appeared at m/z 377 and m/z 287, respectively.

The condensation reaction of aldehyde with indoles could be catalyzed by ionic liquid $[bmim][BF_4]$ at room temperature without using any additional organic solvent (eq 6, Figure 6c).⁵⁷ Five millimoles of indole, 2.5 mmol benzaldehyde, and $0.125 \text{ mmol } [BF_4]$ were mixed together for 2 h to yield a red gel product. The product was directly analyzed by thermally assisted-PESI-MS. In the obtained spectrum, the radical cation of the produced bis(indolyl)phenylmethane was observed at m/z 322 (presumably due to corona discharge ionization mechanism of PESI), as confirmed by its dissociation pattern showing losses of benzene and indole radicals upon CID (Figure 8S of the Supporting Information). In addition, the observed ion of m/z 206 might be a fragment ion m/z 322 by loss of an indole radical. These results are in line with the literature report using MALDI as the ionization method.⁵⁷ Compared to MALDI, our method is faster as no sample preparation is in need and more environmentally friendly because no organic solvent is used.

Detection of Organometallic Catalysts in lonic Liquids. Ionic liquids have become more and more popular reaction media for catalyst immobilization. However, the analysis of catalysts in ionic liquids remains problematic in part because in situ ¹H and ¹³C NMR analysis necessitates deuterated ionic liquids, which are extremely expensive. Furthermore, extraction of the catalyst after reaction is often not possible (at least for catalysts that do not easily leach), which prevents postreaction analysis. ESI was previously used for analysis of ionic catalysts in RTILs, in which the catalyst in ionic liquids was diluted with methanol by 10^3-10^6 fold to reduce the ion suppression effect of ionic liquids and catalysts of interest were detected with low signal intensity.⁵⁸ In this study, our results show that direct analysis of catalysts in RTILs

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by solvent-free PESI is possible, even without any dilution or using any solvent.

Ruthenium-based organometallic catalysts are commonly used in ionic liquid media for catalyzing many hydrogenation reactions.^{59,60} In our PESI-MS experiment, organometallic catalyst [CpRu(p-cymene)][PF₆] was chosen as a test sample, which was dissolved in ionic liquid [emim][BF₄], a commonly used reaction medium, to be 1 mM (a typical catalyst concentration in ionic liquids which is $10^{-3}-10^{-4}$ folds lower than the ionic liquid concentration). Then the solution was directly analyzed by PESI without any pretreatment. In the obtained spectrum (Figure 7a), the cation peak of [emim]-[BF₄] and the cation cluster C₂A peak appeared at *m/z* 111 and 309, respectively. Strikingly, [CpRu(p-cymene)] cation (*m/z* 301) was observed in the spectrum (Figure 7a), with its isotopic peak distribution matching the calculated peak distribution (Figure 7a, inset).

[Rh-MeDuPHOS][OTf] is another type of important catalyst for asymmetric hydrogenation.⁶¹ But this catalyst is air sensitive and it is difficult to be analyzed by traditional MS methods. However, it has been reported that ionic liquids could stabilize the catalyst by protecting it from the atmospheric oxygen attack in the ionic environment of ionic liquids, and the asymmetric hydrogenations of methyl α -acetamidoacrylate and methyl α -acetamidocinnamate were catalyzed by [Rh-MeDuPHOS][OTf] with employment of $[bmim][PF_6]$ as the reaction media.⁶² For these reasons, it would be necessary and highly valuable to directly analyze the catalyst in the presence of ionic liquids. Our PESI-MS would be the method of choice for this purpose. For demonstration, the catalyst was weighted in a glovebox, dissolved in [bmim][PF₆], and diluted to 1 mM. Then the solution was directly analyzed by PESI-MS. As shown in the acquired spectrum (Figure 7b), in addition to the ionic liquid cation and cation cluster ions $(m/z \ 139 \ and \ 423)$, the intact catalyst cation [Rh-MeDuPHOS]⁺ was observed at m/z517, with isotope peak distribution matching with the simulation. This result also confirms that the compound can be stable in ionic liquid and can be directly visualized by PESI-MS. It also reveals the strength and potential of PESI-MS in green chemistry (e.g., monitoring catalyst transformation in ionic liquids).

PESI Ionization Mechanisms. In general, based on our observation, both ESI-like spray ionization²⁷ and APCI-like corona discharge ionization are involved in the solvent-free PESI ionization process. By applying a high voltage, an electrospray cone could be formed from the liquid droplet on the probe tip. In the case of solid analytes, samples can be thermally converted into liquids followed with spray ionization. The unique feature of the PESI used in this study is that no solvent is used; therefore, desolvation should not be involved in the ionization. Since neat ionic liquids already carry charges, the protonation/deprotonation is not in need either. But the declustering of ion aggregates into free cation or anion is required for ion detection. In addition, neutral amine or aromatic hydrocarbon compounds can also be ionized into protonated species or radical cations, respectively, which could be accounted for by the corona discharge mechanism. Due to the high potential applied to the probe and no solvent is used, the corona discharge of air occurs to form reagent ions like hydronium ions H₃O⁺ and N₂ radicals, which are responsible for forming protonated ions or radical cations via proton transfer or charge transfer.

CONCLUSIONS

In conclusion, the solvent-free PESI-MS is fast, sensitive, and versatile, with several unique green chemistry applications as demonstrated in this paper. Using PESI to analyze both intact ionic liquids and ionic solid samples is straightforward; and high-throughput analysis is possible. More importantly, it can be used for monitoring solvent-free reactions and analyzing moisture-/air-sensitive reaction products and catalysts in RTILs. We believe the PESI-MS technique would have many interesting utilities in the green chemistry field.

ASSOCIATED CONTENT

S Supporting Information

The data of high-throughput analysis, trace amount of ionic liquid analysis, and additional solvent-free reactions are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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