Observation of Binuclear Palladium Clusters upon ESI-MS Monitoring of the Suzuki—Miyaura Cross-Coupling Catalyzed by a Dichloro-bis(aminophosphine) Complex of Palladium

Divya Agrawal,[†] Detlef Schröder,[*,†] and Christian M. Frech[‡]

[†]Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo náměstí 2, 16610 Prague 6, Czech Republic

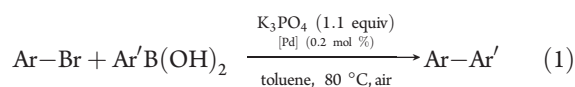[‡]Institute of Inorganic Chemistry, University of Zürich, Winterthurstrasse 190, 8057 Zürich, Switzerland

S *Supporting Information*

ABSTRACT: Electrospray ionization mass spectrometry (ESI-MS) is used for monitoring the progress of the Suzuki—Miyaura cross-coupling reaction between bromobenzene and arylboronic acids using a palladium dichloro-bis(aminophosphine) complex as a precatalyst. The ESI-MS studies demonstrate that initiation of the catalytic reaction requires the presence of a base and that the selectivity for cross-coupling is favorable at elevated temperatures. Interestingly, after completion of the coupling reaction, the palladium is present as a dinuclear Pd^0/Pd^{II} cluster, which still acts as an active catalyst when a new aliquot of reactants is added to the reaction mixture.
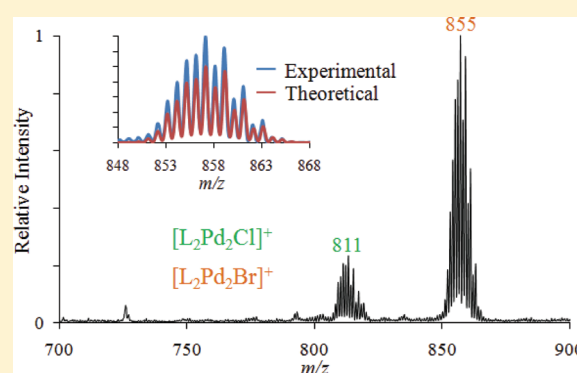
INTRODUCTION

Palladium-catalyzed cross-coupling reactions, such as the Suzuki—Miyaura reaction,[1] which is one of the most important methods for the formation of symmetric and nonsymmetric biaryls,[2] are nowadays an indispensable tool for C—C bond forming reactions in organic chemistry. Their outstanding importance has been demonstrated by the Nobel Prize in chemistry 2010, which was awarded to R. F. Heck, A. Suzuki, and E. Negishi, the pioneers of this area. However, despite the richness of preparative procedures, the mechanistic understanding is still limited in many reactions, and the proposals about the active forms of the catalysts range from mononuclear, molecular palladium species all the way to a crucial role of palladium nanoparticles.[3,4]

$$Ar-Br + Ar'B(OH)_2 \xrightarrow[\text{toluene, 80 °C, air}]{\substack{K_3PO_4 \ (1.1 \ equiv) \\ [Pd] \ (0.2 \ mol \ \%)}} Ar-Ar' \quad (1)$$

Recently, dichloro-bis(aminophosphine) complexes have proved to be excellent (pre)catalysts for the cross-coupling of arylboronic acids with aryl bromides, the Suzuki—Miyaura reaction (eq 1).[5,6] Here, we report on the stability and the catalytic activity of the palladium complex **1** in Suzuki—Miyaura reactions as probed by means of electrospray ionization mass spectrometry (ESI-MS), which is a useful complement to condensed-phase studies[7,8] and has been applied in a variety of mechanistic investigations of palladium-mediated reactions.[9] One of our intentions in this work was to follow the previously suggested[5] formation of oligomeric palladium species or even palladium nanoparticles using ESI-MS.[10]

The specific catalyst **1** was chosen because it has a moderate catalytic activity,[5a] which is beneficial for the direct monitoring of reactions via ESI-MS.[7,9i] In the following, the 1,1′-(cyclohexyl-phosphanediyl)dipiperidine ligand is abbreviated as L; compound **1** can accordingly be written as $[L_2PdCl_2]$. In several cases, we observed also ions derived from the oxidized ligand, most likely the corresponding phosphine oxide $(C_5H_{10}N)_2$-$(C_6H_{11})P=O$, which in analogy is abbreviated as L_O.[11] In this context we note that the precatalyst **1** is deliberately employed with open access to air in order to reach full catalytic activity.[5a]

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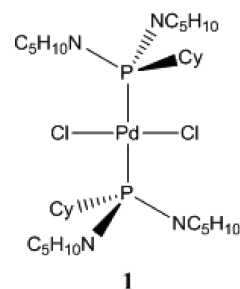
EXPERIMENTAL METHODS

Materials and Sample Preparation. The synthesis and characterization of the palladium complex **1** was described elsewhere.[5a] All
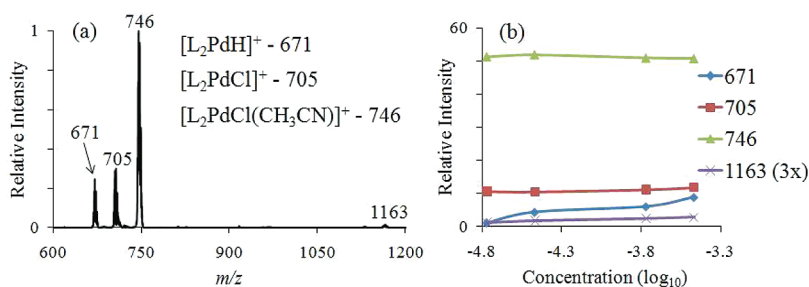
Figure 1. (a) ESI mass spectrum of catalyst **1** in acetonitrile under soft ionization conditions. (b) Effect of concentration in solution on the major signals in the ESI spectra of the catalyst solution.

other chemicals and HPLC-grade solvents were purchased from Sigma-Aldrich. Unless noted otherwise, the coupling reactions were performed by heating a solution of **1** and the desired aryl halide in toluene to 80 °C with or without addition of K_3PO_4 as a base.[12] Afterward, an arylboronic acid was added while stirring at 80 °C was continued. Deliberately, the reactions were performed with open access to air.[5a] In regular intervals, small samples were taken and either analyzed directly using GC-MS or diluted with acetonitrile in a 1:100 ratio and probed using ESI-MS.

Instrumentation. The sample solutions were studied with a Finnigan LCQ (ThermoFinnigan, San Jose, CA, USA) ion-trap mass spectrometer (IT-MS)[13] equipped with an ESI source.[14] Nitrogen was used as the nebulizer gas. Unless otherwise mentioned, the operating conditions were set as follows: spray voltage 5 kV, capillary voltage −132 V, heated capillary temperature 150 °C, tube lens offset −132 V, sheath gas flow rate 10 arbitrary units, auxiliary gas flow rate 10 arbitrary units. Under these conditions, the ionization in ESI is relatively soft, such that quasi-molecular ions as well as their aggregates with solvents can be observed (see below).[15,16] The samples were introduced into the ESI source via a silica capillary at a flow rate of 0.6 mL h^{-1}. Mass spectra were recorded from m/z 50 to 2000 in positive-ion mode. In order to support the assignments made, the masses of the most relevant cationic palladium complexes were further determined on a SYNAPT G2 mass spectrometer (Waters, Manchester, UK)[17] with a standard mass resolution of $m/\Delta m \approx 20\,000$ (see Supporting Information). Exploratory experiments on the IT-MS in negative-ion mode gave good ion abundances for various halide and boronic acid aggregates, but almost no organo-palladium species were found, and the anions were therefore not pursued any further.[18]

Dissociation of mass-selected parent ions was achieved through collisional activation of the mass-selected cluster ions using the helium buffer gas present in the ion trap as the collision partner. The collision energy was optimized for each experiment and is expressed in terms of the manufacturer's normalized collision energy (NCE, in %), where the range from 0 to 100% corresponds to a resonance excitation ac signal of 0−2.5 V (zero-to-peak) at the secular frequency of the ion of interest.[19] This energy depends on the m/z value of the parent ion and can be converted into an absolute scale by means of calibration.[20]

Parallel GC-MS analysis of selected reaction mixtures was performed with a DB-5 MS column (30 m × 0.25 mm × 0.25 μm) on an Agilent 6890N gas chromatograph coupled to an Agilent 5975B mass spectrometer using helium as a carrier gas.

■ RESULTS AND DISCUSSION

The strategy of our investigation of the Suzuki−Miyaura coupling using compound **1** as a (pre)catalyst is based upon ESI monitoring of the progress of the reaction in subsequent steps. To this end, we begin with the characterization of the catalyst solution, then consider the changes upon addition of an aryl halide as well as potassium phosphate (acting as a base), and

then turn to the C−C coupling reactions in the presence of an arylboronic acid. In parallel, the progress of some of the reactions was followed by independent analysis via GC-MS.

We would like to stress at the very outset that the assignments of the various species mentioned further below are no more than plausible suggestions based upon the ion masses, the isotope patterns, the additional isotope labeling data, and the collision-induced dissociation experiments, none of which can replace a rigorous structural characterization via NMR spectroscopy or X-ray crystallography. A similar note of caution applies for the sampling of the species present in solution using ESI-MS, which is primarily sensitive to the ionic species present in solution or formed during the spray process. Nevertheless, the temporal variations of the ion abundance with the reaction time in the condensed phase as reported below demonstrate beyond any doubt that the ESI-MS data reflect changes due to chemical transformation occurring in the reacting solution.

In comparison to the preparative catalytic reaction, for the ESI-MS analysis the reagents were added to the catalyst stepwise with the gap of small intervals in the order depicted in the catalytic cycle of Suzuki−Miyaura cross-coupling reaction to allow the observation of all the important intermediates involved in the catalytic cycle. The amount of boronic acid used in the reaction was reduced to substoichiometric amounts relative to the aryl halide in order to avoid the predominance of the spectrum by borate clusters. As seen later in the article, this modification does not seem to hinder the study of the ions of interest, because similar ionic species appear in both cases. Last but not least, the reaction mixture was diluted 100 times with acetonitrile before subjecting to ESI-MS analysis, where CH_3CN serves as an assisting ligand.

Catalyst Solution. Under reasonably soft ionization conditions in the electrospray source,[15,16] the ESI mass spectrum of catalyst **1** dissolved in acetonitrile (ca. 10^{-4} M) shows the quasi-molecular ion $[L_2PdCl]^+$ along with the corresponding adduct ion solvated with acetonitrile ($\Delta m = +41$) at m/z 705 and 746, respectively (Figure 1a); note that all masses are given for the leading isotopes ^{106}Pd and ^{35}Cl, respectively. The reduced, coordinatively unsaturated 14e$^-$ Pd^0 complex of the type $[L_2Pd]$, which usually is assumed to be the catalytically active species, is observed in the protonated form at m/z 671 ($[L_2PdH]^+$). In addition, a small signal of the dinuclear cluster $[L_3Pd_2Cl_3]^+$ is detected at m/z 1163, which can be assigned to an aggregation of the palladium species in solution sampled by electrospray.[21,22] In order to probe the effect of the concentration in solution, ESI spectra were recorded for four different amounts of the catalyst dissolved in pure acetonitrile. Figure 1b shows gradually increasing relative abundances of $[L_2PdH]^+$ and
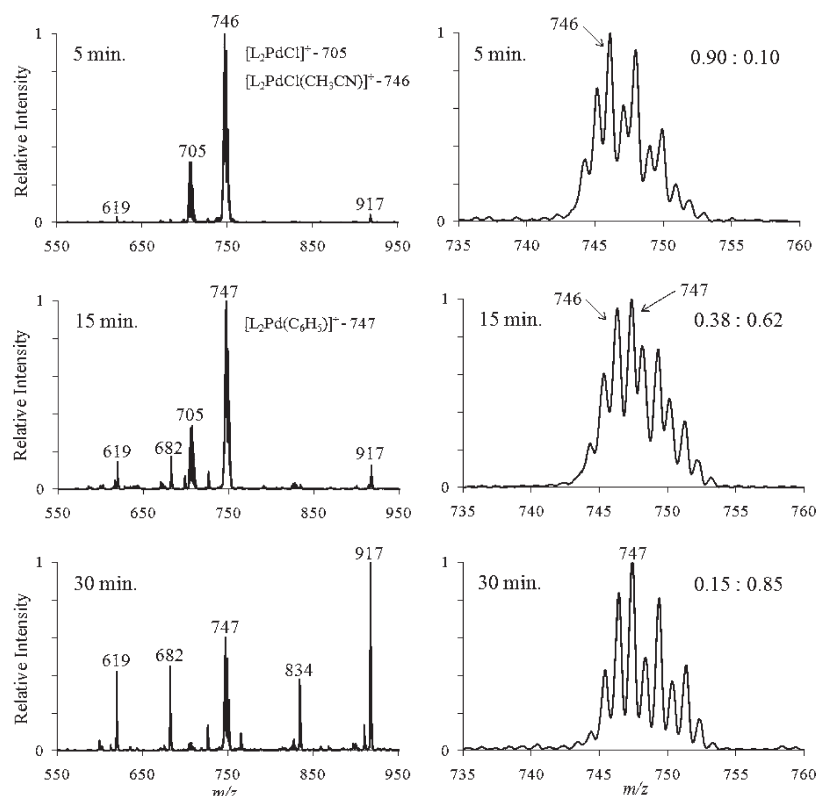
Figure 2. ESI mass spectra obtained after the addition of K_3PO_4 to the solution of the catalyst and bromobenzene in toluene at 80 °C. To the right of each spectrum is the corresponding expansion of the region from m/z 735 to 760, in which also the ratios of $[L_2PdCl(CH_3CN)]^+$ and $[L_2PdC_6H_5]^+$ are given. The somewhat different mass resolutions in the expanded spectra are due to slight overloading of the IT-MS with too many ions at short reaction times, which leads to Coulombic signal broadening.

the binuclear cluster $[L_3Pd_2Cl_3]^+$ at larger concentrations, but no major variations occur, such that the mechanistic studies should not be affected by the variation in catalyst concentration upon addition of reagents, etc. The catalyst solution is reasonably stable upon storage under air, but decomposes rapidly in the presence of water, which is associated with a significant decrease of the total ion abundance and the observation of several ions without Pd, such as $[(L_O)(C_5H_{12}N)]^+$, $[(L_O)_2]Na^+$, $[(L_O)_2-(C_5H_{12}N)]^+$, and $[(L_O)_3]Na^+$ at m/z 384, 619, 682, and 917, respectively, suggesting the precipitation of metallic palladium. These results and a number of additional control experiments are presented in the Supporting Information, to which further interested readers are referred to; in the text, we focus on the most significant findings concerning the various steps of the C−C coupling reaction.
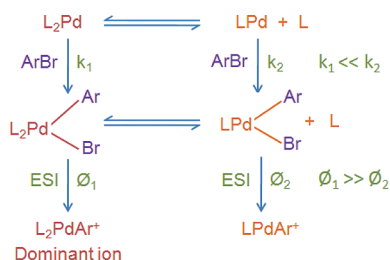
Addition of Aryl Halide and Base. In order to study the catalytic activity of **1** in the Suzuki−Miyaura cross-coupling, the progress of the reaction was monitored using ESI-MS. To this end, the catalyst (0.0013 mmol) was dissolved in toluene (1.7 mL) and stirred in an open flask at room temperature. After 15 min, 10 μL of this solution was dissolved in 1 mL of CH_3CN and subjected to ESI-MS analysis. The spectrum obtained was similar to the one shown in Figure 1a, except for lowering of the signals at m/z 671 and 1163 due to dilution. The solution was then treated with bromobenzene (0.63 mmol) and stirred further at 80 °C. Sampling this solution via ESI-MS after 5 and 60 min, respectively, does not reveal any significant differences from those obtained before (see the Supporting Information). Specifically, there was no indication for an oxidative addition taking

place, although the spectrum obtained after 1 h showed slow decomposition of the catalyst, as indicated by the appearance of the ion $[LH]^+$ at m/z 283 along with the sodiated species at m/z 619 and 917 that were already observed upon addition of water.

In a separate, but similar experiment, the solution of the catalyst and bromobenzene was stirred at 80 °C for 5 min followed by the addition of K_3PO_4 (0.36 mmol). The resulting solution was subjected to ESI-MS after 5, 15, and 30 min (Figure 2). The spectra obtained show the gradual appearance of a new signal at m/z 747 after addition of the base, which is ascribed to the phenyl complex $[L_2PdC_6H_5]^+$ formed via oxidative addition. Due to overlapping isotope patterns of $[L_2PdCl(CH_3CN)]^+$ (m/z 746) and $[L_2PdC_6H_5]^+$ (m/z 747), the experimental data were deconvoluted by the simulated isotope pattern of the two species.[23] A reaction run in parallel under similar conditions and concentrations, but using deuterated bromobenzene shows a mass shift of the newly formed species to m/z 752, thus substantiating the conclusion that oxidative addition has taken place (see Supporting Information).

The results imply the occurrence of oxidative addition, which was suggested to occur in a dissociative manner for bulky phosphine ligands such as L (Scheme 1).[24,25] The dissociative mechanism involves the initial loss of L from PdL$_2$ to form a monophosphine Pd^0 complex, followed by oxidative addition of the aryl halide.[24,26] However, we cannot detect the accordingly expected species LPdAr$^+$ upon ESI-MS and instead observe L$_2$PdAr$^+$ (m/z 747) as the dominant ion in the spectrum. This finding implies either that k_1 can compete with k_2 in the oxidative

Scheme 1. Dissociative–Associative Mechanism for the Oxidative Addition of Pd^0 Species to an Aryl Bromide

Table 1. Observation of No (−), Significant (+), or Large (++) Amounts of the Insertion Species [ArPdL$_2$]$^+$ under Various Reaction Conditions

	ArBr (1.0 equiv)	K$_3$PO$_4$ (equiv)	time (min)	temp (°C)	[ArPdL$_2$]$^+$	degradation of **1**
1	C$_6$H$_5$Br		15	rt	−	
2	C$_6$H$_5$Br		5	80	−	
3	C$_6$H$_5$Br		60	80	−	slow
4	C$_6$H$_5$Br	0.5	5	80	+	
5	C$_6$H$_5$Br	0.5	30	80	++	slow
6	C$_6$D$_5$Br	0.5	30	80	++	slow
7	C$_6$D$_5$I		15	rt	−	rapid
8	C$_6$D$_5$I		15	80	−	rapid
9	C$_6$D$_5$I	0.5	15	80	+	rapid
10[a]	C$_6$D$_5$Br		60	80	−	

[a] In entry 10, an identical amount of bis(triphenylphosphine)palladium(II) dichloride rather than **1** is used as a palladium precursor.

addition or that heterolysis of the bisphosphine complex and its sampling via ESI-MS are much more favorable than for the monophoshine complex ($\phi_1 \gg \phi_2$).

Interestingly, the oxidative addition does not take place in the absence of a base. In order to probe if the base is required due to the low reactivity of bromobenzene in oxidative addition, deuterated iodobenzene was used instead under similar conditions. The resulting spectra obtained both at room temperature and at 80 °C show a signal at m/z 797 due to the replacement of the chloride ion in $[L_2PdCl(CH_3CN)]^+$ by iodide, but the aryl iodide causes rapid decomposition of the catalyst, and no occurrence of oxidative addition is evident (see the Supporting Information). At this point, base was added to the solution, and after 15 min at 80 °C the formation of the insertion product is observed, suggesting that the base can induce the reduction of Pd^{II} to Pd^0, i.e., preparing the metal catalyst for oxidative addition.[27] In order to study the influence of the aminophosphine ligands,[28] a reaction was performed under similar conditions, while using bis(triphenylphosphine)palladium(II) dichloride as the catalyst and deuterated bromobenzene as the halide counterpart, but no insertion is observed in the absence of a base (see Supporting Information). For a qualitative overview of this section, the results obtained under the various conditions are summarized in Table 1.

Noteworthy from a preparative point of view is that the spectrum obtained after 30 min (Figure 2) shows partial degradation of the catalyst. To ensure the stability of the catalyst in the presence of base, the former was treated with K$_3$PO$_4$ only, and the spectra were recorded both at room temperature and at 80 °C. The catalyst is not affected by the base at ambient temperature, but undergoes quick degradation upon heating (see the Supporting Information). This indicates that the solution obtained after adding base should immediately be treated with boronic acid in order to avoid the decomposition of the catalyst and allow cross-coupling to take place.

Addition of Arylboronic Acid. Next, 0.5 equivalent of phenylboronic acid relative to bromobenzene was added to a solution of bromobenzene and **1** in toluene after 5 min stirring at 80 °C in the presence of base. After 15 min and 2 h, respectively, aliquots of this solution were subjected to ESI-MS analysis. The two spectra obtained show the formation of a variety of borate clusters, whereas signals due to palladium-containing species are very low or absent. A GC-MS analysis of the 2 h aged aliquot shows the presence of 11% coupling product (biphenyl)[29] in the solution, thus demonstrating that the Suzuki–Miyaura cross-coupling is proceeding. An additional 2 h of stirring at 80 °C led to the disappearance of the borate clusters parallel with the gradual appearance of a binuclear palladium cluster at m/z 855, $[L_2Pd_2Br]^+$, which is most abundant at the end of the reaction

(see below). A parallel, independent GC-MS analysis of the 16 h aged aliquot shows the presence of 65% of the coupling product in the solution[29] and the complete disappearance of phenylboronic acid, thereby indicating the completion of the cross-coupling reaction. Further, an identical reaction employing deuterated bromobenzene also leads to the signal at m/z 855, indicating that the ion does not contain a phenyl group from the starting halide.

In order to avoid the predominance of borate clusters in the ESI spectra, an experiment was carried out where only 0.15 equivalent of phenylboronic acid relative to bromobenzene was added, and the reaction mixture was stirred at 80 °C and subjected to ESI-MS analysis in regular intervals. The spectrum obtained after 30 min shows a major signal at m/z 747, which is assigned to the phenyl complex $[L_2PdC_6H_5]^+$ (Figure 3a). A reaction run in parallel under similar conditions and concentrations but using p-tolylboronic acid shows the formation of an additional signal at m/z 761, in which the phenyl group of the oxidative addition product formally is replaced by a p-tolyl group, i.e., $[L_2Pd(p\text{-}CH_3C_6H_4)]^+$ (Figure 3b). This observed exchange of the aryl group bound to palladium by that of the boronic acid is suggested to occur via two different processes. Arylboronic acids act as strong Lewis acids at the boron atoms. During the first process, a fast acid–base reaction between coordinatively unsaturated 14-electron Pd^0 and the boronic acid looks obvious. This is followed by a migration of the aryl group to the electron-deficient positive palladium atom in the resulting intermediate. In the subsequent course of the reaction, this species would lead to an undesired self-coupling of the aryl groups of the boronic acid to afford Ar′–Ar′, rather than the desired cross-coupling product Ar–Ar′ according to reaction 1.[30] In a separate experiment, a solution of **1** and p-tolylboronic acid was treated with K$_3$PO$_4$ at room temperature and probed by ESI-MS after 10 min of stirring. A signal at m/z 761 observed in this experiment confirms that the corresponding species in Figure 3b is formed via transmetalation and not by aryl scrambling between the oxidative addition product of the aryl halide and the aryl boronic acid.

The region between m/z 820 and 830 in Figure 3a shows two overlapping signals with m/z 823 and 825 for ^{106}Pd, which correspond to so-far-unidentified palladium species. In a corresponding experiment using p-tolylboronic acid, the signal at
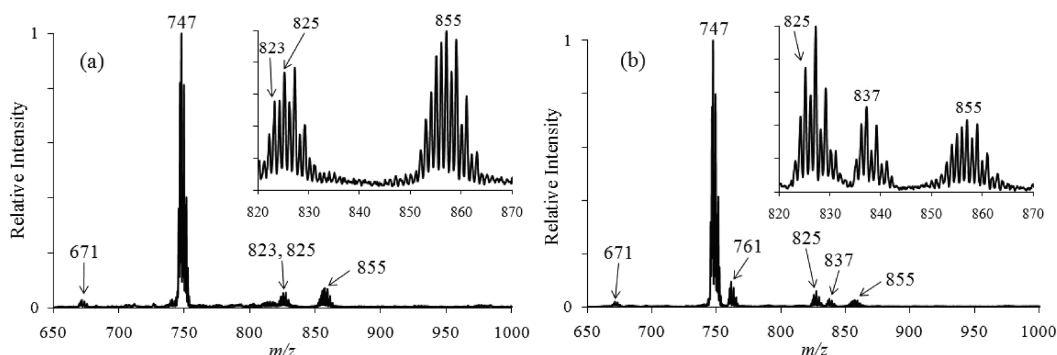
Figure 3. ESI mass spectra obtained at 80 °C in 30 min after the addition of (a) phenylboronic acid and (b) p-tolylboronic acid to a solution of $[L_2PdC_6H_5]^+$. The insets show the expanded mass regions from m/z 820 to 870.

m/z 825 remains unaffected, whereas that at m/z 823 shifts to m/z 837 (Figure 3b). The corresponding experiment using p-tolylboronic acid and the fragmentation patterns upon collisional activation as well as the isotope patterns (see the Supporting Information) indicate that the signal at m/z 823 formally corresponds to $[PdL_2(C_6H_4\text{-}C_6H_5)]^+$, but the actual ion structure is unknown. Similarly, the signal at m/z 825 is assigned to the diphosphine Pd^{II} complex $[L_2PdBr(C_6H_4)]^+$, but again with uncertain structure.[31] A simulated isotope pattern[23] of the two overlapping signals at m/z 823 and 825 in the ratio of 1:1.3 agrees well with the experimental isotopic pattern obtained. In addition, the dinuclear cluster $[L_2Pd_2Br]^+$ already mentioned above is observed at m/z 855.

A further 30 min of stirring of the solution from which the spectrum shown in Figure 3a was taken leads to the disappearance of the insertion product (m/z 747) as well as the signals at m/z 823 and 825, while $[L_2Pd_2Br]^+$ predominates the spectrum (Figure 4). The experimental isotope pattern of this ion corresponds very well with the simulated pattern (see inset in Figure 4). Concomitant with this signal, another dinuclear cluster appears, which is assigned to $[L_2Pd_2Cl]^+$ (m/z 811) with the expected isotope pattern (see the Supporting Information). Formally, the $[L_2Pd_2X]^+$ clusters (X = Cl, Br) can be viewed as adducts of the Pd^{II} species $LPdX^+$ with the Pd^0 compound LPd, where the latter is the active species suggested in the dissociative–associative mechanism (Scheme 1). Alternatively, $[L_2Pd_2X]^+$ can be regarded as a cluster of two Pd^I centers.[32,33] With $[ArPd_2(dba)_2]^+$ ions observed upon ESI measurements, Sabino et al. reported a precedence of such type of clusters when starting from dinuclear $Pd_2(dba)_3$ as a catalyst precursor (dba = dibenzylideneacetone).[9f,34−36]

The abundant signals due to $[L_2Pd_2Cl]^+$ and $[L_2Pd_2Br]^+$ in Figure 4 indicate that the catalyst may be present in the form of a dinuclear cluster attached to either chloride or bromide during the Suzuki−Miyaura cross-coupling reaction. These species may act as the catalyst's resting state, but even the catalytic activity of the binuclear cluster itself cannot be excluded.[37] To determine whether or not the dinuclear species is still able to catalyze the coupling reaction, a GC-MS monitoring of the reaction followed by addition of more reagents to the catalyst was performed. To this end, a reaction mixture of 0.2 mol % catalyst with equimolar amounts of C_6H_5Br, K_3PO_4, and phenylboronic acid was reacted to completion (as monitored by GC-MS), which led to the binuclear cluster at m/z 855 as the major signal upon ESI-MS analysis. Then, a new aliquot of reactants, i.e., equimolar amounts of C_6D_5Br, K_3PO_4, and phenylboronic acid, was added to the
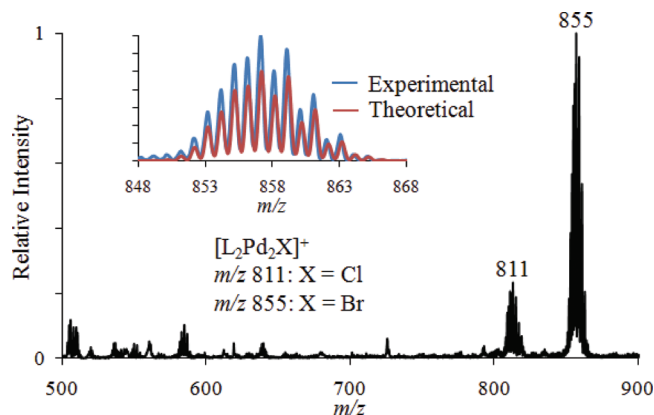
Figure 4. ESI mass spectrum obtained 1 h after the addition of phenylboronic acid to a solution of $[L_2PdC_6H_5]^+$ at 80 °C. The curve denoting the experimental isotope pattern in the inset was multiplied by a factor of 1.4 for the sake of visibility.

same reaction mixture and further stirred at 80 °C. GC-MS shows the continuation of the cross-coupling, as indicated by the detection of $C_6H_5−C_6D_5$, suggesting that the binuclear cluster is in fact still active as a catalyst in the Suzuki−Miyaura cross-coupling. The absence of $C_6D_5−C_6D_5$ at m/z 164 rules out the occurrence of homocoupling under these conditions (see Supporting Information). The binuclear cluster was detected by ESI-MS in the same reaction mixture even after 3 days and was still catalytically active, as shown by the cross-coupling product obtained after adding an equivalent amount of p-tolylboronic acid.

The results obtained are consistent with a monoaminophosphine complex LPd^0 as the catalytically active species, which forms a dimeric compound with Pd^{II} as a catalyst resting state. Alternatively, the dinuclear species may also serve as a source of colloidal palladium or a stage at the beginning of nanoparticle formation, whose involvement has been suggested in the recent literature.[3,5,38] In the "classical" mechanism with dichloro-bis-(phosphine) complexes, coordinatively unsaturated $14e^-$ Pd^0 complexes of the type $[Pd(PR_3)_2]$ are assumed to be the catalytically active species. Dissociation of one phosphine ligand from $[Pd(PR_3)_2]$ followed by oxidative addition of ArX to yield the tricoordinated Pd^{II} intermediate $[ArPd(X)(PR_3)]$ are subsequent reaction steps. Thus, the efficiency of bulky and electron-rich phosphines in the Suzuki−Miyaura reaction (and related cross-couplings) seems to be a result of their ability to generate

monophosphine−Pd^0 and −Pd^{II} complexes in the catalytic cycle. However, the CID spectrum of mass-selected $[L_2Pd_2Br]^+$ does not give rise to any monomeric species such as $[L_nPd]^+$ or $[L_nPdBr]^+$ ($n = 0-2$), but instead initial loss of cyclohexene followed by further degradation of the ligand is observed (Figure 5). Accordingly, cluster cleavage is not facile in the gas phase and cannot compete with degradation of the organic ligands.[39] In solution, however, the solvent may also act as an assisting ligand for the dissociation of the dinuclear cluster into excessively solvated mononuclear species. The association reactions of some of the fragment ions in Figure 5 with residual acetonitrile (highlighted in blue) present in the ion trap may in fact be regarded as an indication of the affinity of the coordinatively unsaturated species to add further solvent molecules.[40] This difference in the gas- and the condensed-phase behavior of such clusters as observed through collision-induced dissociation experiments is depicted in Scheme 2.

Variation of the Reaction Conditions. In a series of experiments, ESI-MS was used for monitoring the progress of the reactions at various temperatures with and without omission of some components. Table 2 summarizes the fractions of the precatalyst complex $[L_2PdCl]^+$, the oxidative addition products with the aryl halide ArX, and the transmetalation product with the arylboronic acid Ar′B(OH)$_2$, respectively, under various reaction conditions. As can be seen from the fraction of the oxidative addition product $[ArPdL_2]^+$, at high temperature
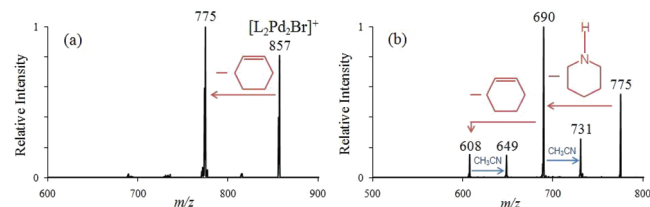
the addition of boronic acid has a small effect on the rate of oxidative addition (entries 11 and 12). At low temperature, the otherwise slow oxidative addition (entry 13) increases considerably in rate after the addition of boronic acid concomitant with a notable increase of the "wrong" insertion product $[Ar′PdL_2]^+$, which would lead to a homocoupling of the boronic acid (entry 14). In the absence of bromobenzene and a doubled amount of base, $[Ar′PdL_2]^+$ is formed even at room temperature (entry 15). These findings are corroborated by inverse experiments using p-bromotoluene and phenylboronic acid (entries 16−18).

The results are fully consistent with condensed-phase studies of Lloyd-Jones and co-workers, who found that arylboronic acids promote the formation of the catalytically active species at low temperature.[41] As sketched in Scheme 3, at high temperature (80 °C) the direct reduction of Pd^{II} to Pd^0 is fast and leads to the rapid formation of the insertion product. However, at lower temperature (40 °C), the base-assisted reduction is slower than the otherwise steady rate of the indirect, boronic acid-assisted pathway of reduction and therefore leads to the dramatic increase in the contribution of the reduction via boronic acid. However, this increase in activity proceeds at an expense of selectivity, in that the amount of the unwanted transmetalation product $[Ar′PdL_2]^+$ increases significantly as compared to the reaction at 80 °C. These findings suggest that at low temperature the base-assisted oxidative addition is slow and the transmetalation can

Figure 5. (a) MS/MS spectrum of the signal at m/z 857 and (b) MS^3 spectrum of the resulting signal at m/z 775.

Scheme 2. Possible Differences in the Gas- and Condensed-Phase Behavior of the Binuclear Cluster $[L_2Pd_2X]^+$

Scheme 3. Schematic Representation of the Possible Pathways for the Reductive Activation of Pd^{II} at High and Low Temperatures, Respectively
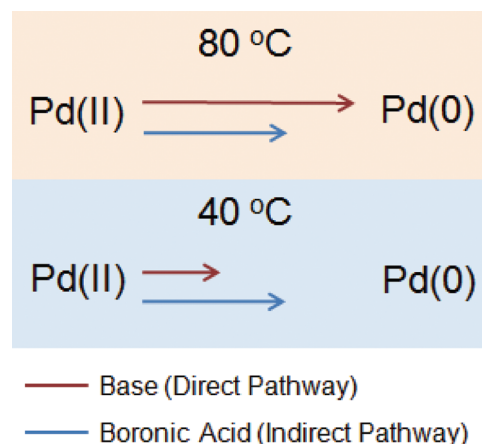
Table 2. Fractional Abundances of the Precatalyst Complex $[L_2PdCl]^+$ and of the Oxidative Addition Products with the Aryl Halide ArX (represented by the $[ArPdL_2]^+$ signal) versus the Transmetalation Product with the Arylboronic Acid (represented by the $[Ar′PdL_2]^+$ signal) upon ESI-MS Monitoring of the Suzuki−Miyaura Coupling under Various Reaction Conditions

no.[a]	ArBr (1.0 equiv)	Ar′B(OH)$_2$ (equiv)	K$_3$PO$_4$ (equiv)	time (min)	temp (°C)	$[L_2PdCl(CH_3CN)]^+$	$[ArPdL_2]^+$	$[Ar′PdL_2]^+$
11	C$_6$H$_5$		0.5	30	80	0.15	0.85	
12	C$_6$H$_5$	p-CH$_3$C$_6$H$_4$ (0.15)	0.5	30	80	0.05	0.87	0.08
13	C$_6$H$_5$		0.5	30	40	0.82	0.18	
14	C$_6$H$_5$	p-CH$_3$C$_6$H$_4$ (0.15)	0.5	30	40	0.05	0.70	0.25
15		p-CH$_3$C$_6$H$_4$ (0.3)	1.0	40	rt	0.35		0.65
16	p-CH$_3$C$_6$H$_4$		0.5	10	40	0.99	0.01	
17	p-CH$_3$C$_6$H$_4$	C$_6$H$_5$ (0.15)	0.5	30	40	0.02	0.68	0.30
18	p-CH$_3$C$_6$H$_4$	C$_6$H$_5$ (0.15)	0.5	60	40	0.00	0.70	0.30

[a] In order to avoid a possible confusion with the entries in Table 1, the numbering is continued.

Figure 6. Changes of the relative intensities of representative signals with reaction time using catalyst **1**, phenylboronic acid, K$_3$PO$_4$, and (a) bromobenzene and (b) [D$_5$]-bromobenzene.

Scheme 4. Proposed Mechanistic Pathway for Suzuki–Miyaura Cross-Coupling by Dichloro-bis-(aminophosphine) Complex 1[a]

[a] The species not observed during ESI-MS analysis (including the corresponding neutral intermediates) are depicted in gray.

compete effectively. However, at typical operating conditions of 80 °C in the Suzuki–Miyaura cross-coupling, the insertion proceeds much faster, suggesting occurrence of a direct pathway for the efficient reduction of Pd^{II} species to the catalytically active Pd^0 species, followed by oxidative addition to afford the desired [ArPdL$_2$]$^+$ cation. Transmetalation to [Ar′PdL$_2$]$^+$ is still possible, but not enhanced to a similar extent.

Finally, we briefly address the reaction kinetics as qualitatively monitored via ESI-MS.[42] Figure 6 shows the time–behavior of the most significant ions for the cross-coupling reaction with unlabeled and deuterated bromobenzene. To this end, we consider the signals of [C$_6$H$_5$PdL$_2$]$^+$ (m/z 747) and [C$_6$D$_5$-PdL$_2$]$^+$ (m/z 752), respectively, as representatives for the insertion products and those of [L$_2$Pd$_2$X]$^+$ (m/z 811 and 855 for X = Cl and Br, respectively) as the putative resting state of the catalyst. In both cases, the relative amount of the insertion species remains constant for about an hour and then decreases in favor of the binuclear [L$_2$Pd$_2$X]$^+$ species, which are, however, already observed at the early stages of the reaction. The plateau behavior at the beginning is assigned to the completion of the oxidative addition of the aryl halide to the catalytically active species, which further undergoes cross-coupling and gradually releases the cross-coupling product. When the reagents are consumed,

the cycle terminates and the palladium accumulates in the binuclear species. These findings are summarized in the form of Scheme 4, which shows the major intermediates observed using ESI-MS as well as the assumed neutral species involved that escape detection.

■ CONCLUSIONS

The present study demonstrates the potential of ESI-MS for the direct monitoring of the Suzuki–Miyaura cross-coupling reaction, which allows the identification of some new mechanistic features and possible reaction intermediates. Most significant is the observed accumulation of binuclear Pd^0–Pd^{II} halide clusters at the end of the reaction, which may be the catalyst's resting state, but still is catalytically active. The observation of this dinuclear cluster allows several interpretations: (i) It could indicate a molecular mechanism to be operative, which acts as a source of mononuclear aminophosphine complexes (even though such species were not observed via ESI-MS), which would be in accordance with the classical mechanism and, hence, the most probable interpretation. (ii) Although seemingly less likely, the appearance of L$_2$Pd$_2$X$^+$ could also indicate the involvement of palladium nanoparticles in the catalytic cycle, in that the dinuclear clusters may serve as precursors of (solvated) palladium nanoparticles catalyzing the cross-coupling. (iii) The cluster itself could act as a catalytically active species, which seems least likely of the three alternatives, given that the largest amounts of the dinuclear cluster are observed at the end of the reaction. In this context, we also point out a recently observed stabilizing effect of halide ligands in the Stille reaction, which had been attributed to mononuclear species, but could also be associated with the role of halide ligands in stabilizing palladium clusters formed in the course of the reaction.[43] Furthermore, the ESI experiments confirm the role of the arylboronic acid in catalyst activation at low reaction temperature and demonstrate that the enhanced reactivity is outbalanced by a loss in selectivity. In a more general perspective, application of ESI-MS for monitoring reactions occurring in the condensed phase may help in quickly finding optimal reaction conditions with respect to the formation of the desired products in maximum yields. In this respect, the results documented in Tables 1 and 2 demonstrate that ESI-MS might potentially be used for the optimization of reaction conditions in synthetic transformations without any additional workup and at the smallest scales.[8,44]

■ ASSOCIATED CONTENT

■ AUTHOR INFORMATION

Corresponding Author
*Phone: ++420 220 183 463. Fax: ++420 220 183 462. E-mail: schroeder@uochb.cas.cz.

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