

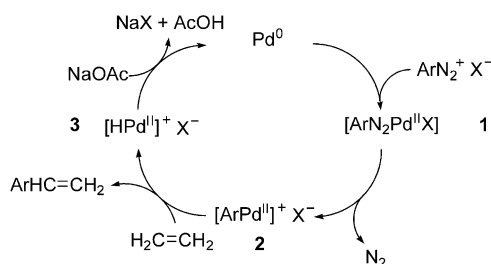
Probing the Mechanism of the Heck Reaction with Arene Diazonium Salts by Electrospray Mass and Tandem Mass Spectrometry**

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The Heck reaction, with its many creative and effective variations, finds a prominent place among the synthetic tools available in organic synthesis for the construction of C–C bonds.^[1] The Heck reaction has found growing applications mainly because of its rather mild conditions and versatility, and some highly enantioselective versions have been reported.^[2] Despite some impressive demonstrations of its synthetic capability, the Heck reaction still has a number of unaccountable features and unverified mechanistic details.

The phosphane-free version of the Heck reaction also holds great synthetic potential, and is usually more economical, practical, and experimentally simpler than the phosphane version.^[3] One example of the phosphane-free protocol is that in which arene diazonium salts are used as the arylating partner instead of the traditional aryl halides and triflates. This version of the Heck arylation, initially used by Heck and further developed by Matsuda and co-workers,^[4] has been finding increasing application in the synthesis of natural products^[5] and biologically active compounds^[6] but, in contrast to the main-stream halides and triflates, less attention has been given to the understanding of its mechanistic aspects.

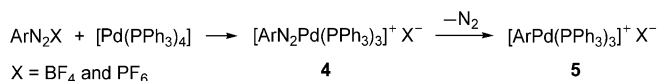
In their initial work,^[4] Matsuda and co-workers proposed the catalytic cycle outlined in Scheme 1 for the Heck reaction with arene diazonium salts. The palladium/aryl diazenide complex **1** was postulated to form from the reaction of arene diazonium salts and $[\text{Pd}(\text{PPh}_3)_4]$ (Scheme 2). Such a reaction



Scheme 1. The catalytic cycle proposed by Matsuda and co-workers for the Heck reaction with arene diazonium salts.

has been proposed to give the palladium/aryl diazenide complex **4**, which undergoes spontaneous nitrogen extrusion to furnish the aryl palladium species **5**.^[7]

The development of electrospray ionization (ESI)^[8,9] has greatly expanded the range of molecules that can be analyzed by mass spectrometry, including those of high polarity, molecular complexity, and mass. ESI is characterized by the gentleness by which gaseous ions are formed, and even



Scheme 2. Oxidative addition pathway to form palladium(II) complex 5.

loosely bonded, supramolecular ionic species survive intact.^[9c,10] ESI-MS is also rapidly becoming the technique of choice for mechanistic studies and high-throughput screening of homogeneous catalysis.^[11] Having recognized the pivotal importance of characterizing the cationic palladium intermediates involved in the catalytic cycle proposed by Matsuda and co-workers (Scheme 1),^[12] we decided to take advantage of the ability of ESI to smoothly transfer ionic species to the gas phase, and to use our experience in the investigation of reaction mechanisms by mass spectrometry,^[13] to probe the mechanism of the Heck reaction. ESI-MS/MS was used to “fish” the palladium intermediates directly from solution to the gas phase, and also to perform their unprecedented structural characterization.

Our investigation began with the oxidative addition step using the arene diazonium salt 4-MeOPhN₂⁺BF₄⁻ and [Pd₂(dba)₃]-dba (dba = dibenzylideneacetone) as the source of palladium. We used ESI-MS to monitor the reaction of 4-MeOPhN₂⁺BF₄⁻ and [Pd₂(dba)₃]-dba in acetonitrile by scanning the first quadrupole (Q1) of a hybrid triple quadrupole linear ion-trap mass spectrometer (Qtrap from Applied Biosystem). The reactant diazonium ion (*m/z* 135) together with four ionic species could be detected by ESI-MS after one to five minutes of reaction: **6** (*m/z* 295; all *m/z* values are reported for ¹⁰⁶Pd), **7** (*m/z* 336), **8** (*m/z* 488), and **9** (*m/z* 681; Figure 1 a). All the ions display the characteristic isotopic distribution of palladium-containing species.^[14] These species correspond to the proposed ionic intermediate **2** formed by the oxidative addition of the Pd catalyst to the arene diazonium salt (Scheme 1), and differ only in the type and number of ligands coordinated to the central Pd atom. They are, therefore, likely to be present in solution (except **6** which is likely formed by in-source collision-induced dissociation (CID) of **7**) and thus potential intermediates in the catalytic cycle. We also attempted to detect **1** (Scheme 1, Ar = 4-MeOPh) as its cation [4-MeOPhN₂Pd]⁺ (*m/z* 241) or corresponding acetonitrile complexes. Intermediate **1** is probably too short lived and could not be detected even when using a microreactor for the effective mixing of reactants and fastest possible ESI-MS analysis.^[15]

Interestingly, the composition of the cationic intermediates changes drastically with time: by continuously monitoring these intermediates by ESI-MS we noticed that the ionic composition varies considerably with time. The ionic composition stabilizes after 90 minutes of mixing, with ions **7** and **6** converting almost completely into **8** (Figure 1b), which became by far the most prominent species. Intermediate **9** remained, and a new Pd₂-containing species **10** (*m/z* 787) was formed. All these intermediates were then mass-selected for MS/MS structural characterization, and their dissociation chemistry matched their proposed structures. For example, **7** dissociates by three consecutive losses of acetonitrile, fol-

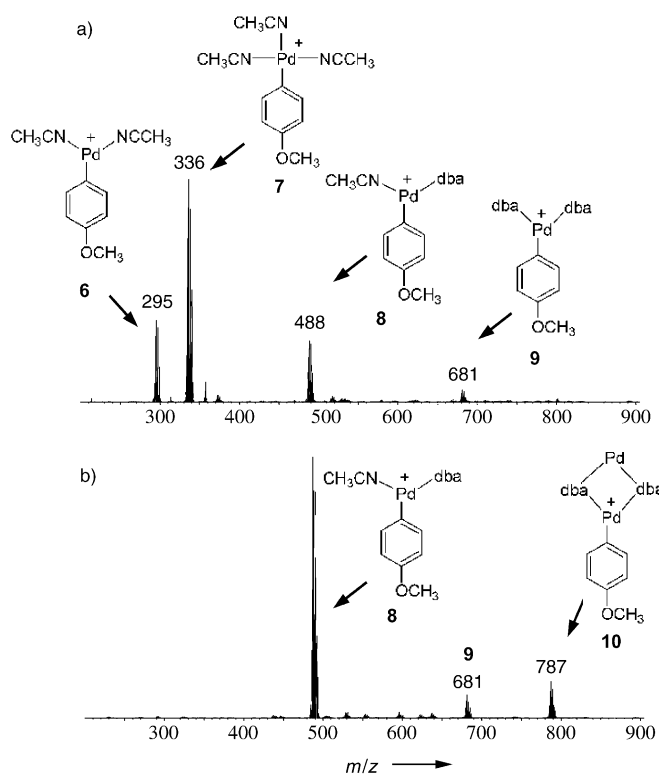


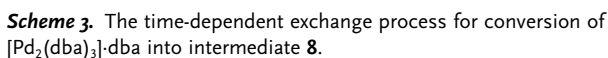
Figure 1. ESI(+)-MS spectrum of a solution (2 nmol L⁻¹) of the arene diazonium salt 4-MeOPhN₂⁺BF₄⁻ and [Pd₂(dba)₃]-dba in acetonitrile after mixing for: a) 5 min and b) 90 min. The reactant diazonium ion (*m/z* 135) was also detected as the most abundant ion, but spectra were scanned from *m/z* 200 for clarity.




lowed by loss of formaldehyde. Intermediate **8** dissociates by loss of acetonitrile followed by loss of CO and a neutral loss of a species with mass m/z 102, most probably phenylacetylene from dba.

Thus, an interesting dynamic and time-dependent process involving ligand exchange in **7–10** has been detected, which can be rationalized through a series of equilibrium reactions (Scheme 3). Initially the acetonitrile solvent molecules rapidly replace dba from $[\text{Pd}_2(\text{dba})_3]\cdot\text{dba}$ to form $[\text{Pd}(\text{CH}_3\text{CN})_4]$ (**11**). This palladium(0) complex undergoes an oxidative addition with the arene diazonium salt to form a very unstable intermediate which rapidly forms intermediate **7** (m/z 336) by oxidative extrusion of N_2 .^[7] In the presence of dba complex **7** is slowly converted into **8** (m/z 488), which appears to be the most stable of the cationic Pd intermediates.

All of the Pd cations **7–10** are potential candidates for the intermediates which add to the olefin in the Heck catalytic cycle (**2** in Scheme 1). However, as the composition of **7–10** varies with time, and to verify which of these intermediates would undergo insertion more efficiently, the model olefins **12**, **13**, and **14** (Boc = *tert*-butoxycarbonyl) were added to the solution of the arene diazonium salt and [Pd₂(dba)₃] \cdot dba in acetonitrile after mixing for 5 or 90 minutes.

In the first set of experiments, the olefins were added after mixing $[\text{Pd}_2(\text{dba})_3]\cdot\text{dba}$ and the arene diazonium salt for five minutes. Insertion species were detected in the ESI mass spectrum, but in very low relative abundances and generally



12 **13** **14**

For structural assignments, **15–17** were mass-selected with Q1 and then submitted to 10 eV CID with nitrogen in q2 in tandem mass spectrometric (MS/MS) experiments. As an example, Figure 3a shows the product-ion mass spectrum for **17** (m/z 558). The dissociation chemistry of **17** is fully consistent with its expected structure: loss of acetonitrile

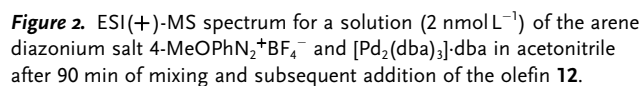


Figure 3 displays two ESI(+)-MS/MS spectra, (a) and (b), showing the fragmentation patterns of different intermediates.

(a) Heck ionic intermediate 17 (m/z 558) and **(b) the H-abstraction intermediate** $[\text{HPd}(\text{CH}_3\text{CN})(\text{dba})]^+$ (m/z 382).

The spectra show the mass-to-charge ratio (m/z) on the x-axis and relative intensity on the y-axis. The base peak is at m/z 341 in both spectra.

(a) Heck ionic intermediate 17 (m/z 558):

- Base peak: m/z 341.
- Other significant peaks: m/z 227, 255, 283, 313, 517, 558.
- Chemical structures shown: A precursor (4-methoxyphenyl) and the Heck ionic intermediate 17.

(b) H-abstraction intermediate $[\text{HPd}(\text{CH}_3\text{CN})(\text{dba})]^+$ (m/z 382):

- Base peak: m/z 341.
- Other significant peaks: m/z 209, 221, 235, 299, 313, 382.
- Chemical structures shown: A precursor (4-methoxyphenyl) and the H-abstraction intermediate $[\text{HPd}(\text{CH}_3\text{CN})(\text{dba})]^+$.

The discovery of **8** as the most reactive intermediate suggests that a stepwise addition of reagents in the Heck reaction with diazonium salts would be beneficial, since **8** dominates after mixing 4-MeO-PhN₂⁺BF₄⁻ and [Pd₂(dba)₃].dba for 90 minutes. Hence, [Pd₂(dba)₃].dba and the arene diazonium salt were pre-mixed in catalytic amounts

(in respect to the olefin) in acetonitrile, stirred for 90 minutes to favor formation of **8** followed by addition of stoichiometric amounts of olefin **12** and the arene diazonium salt.^[16] The final Heck product, 2-(4-methoxyphenyl)-2,5-dihydrofuran, was obtained in 80% yield as the only regioisomer after 30 minutes of nitrogen evolution (Scheme 4). This protocol, which features a delay of 90 minutes before addition of the olefin, has become the standard and most-efficient protocol in our laboratory for Heck arylations using arene diazonium salts.

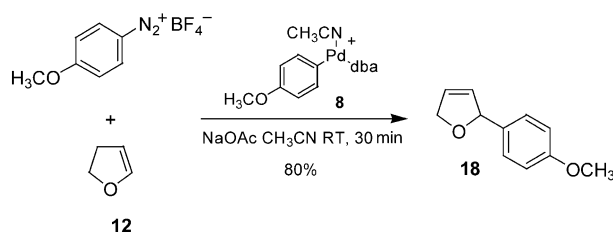
For the first time, therefore, several cationic intermediates of the oxidative addition step of the Heck reaction involving arene diazonium salts have been detected by ESI-MS monitoring and structurally characterized by ESI-MS/MS. A dynamic, time-dependent process with ligand equilibria between several ionic intermediates was also observed for the oxidative addition step. Our results suggest that the most-reactive intermediate for olefin addition is **8**, which dominates

A detailed catalytic cycle for the Heck reaction with arene diazonium salts can be proposed on the basis of the ESI-MS/MS results (Scheme 5, olefin **12** is used as an example).^[16] New aspects of the Heck reaction, such as the role of different solvents and the use of different Pd sources, is currently being investigated by ESI-MS/MS. We are also using tandem mass spectrometric experiments in the Qtrap mass spectrometer^[17] to mass-select ionic intermediates and to explore and compare their intrinsic gas-phase reactivities by performing reactions to probe which of the five ionic intermediates detected in the oxidative addition (**6–10**) are indeed the most reactive toward olefin insertion.

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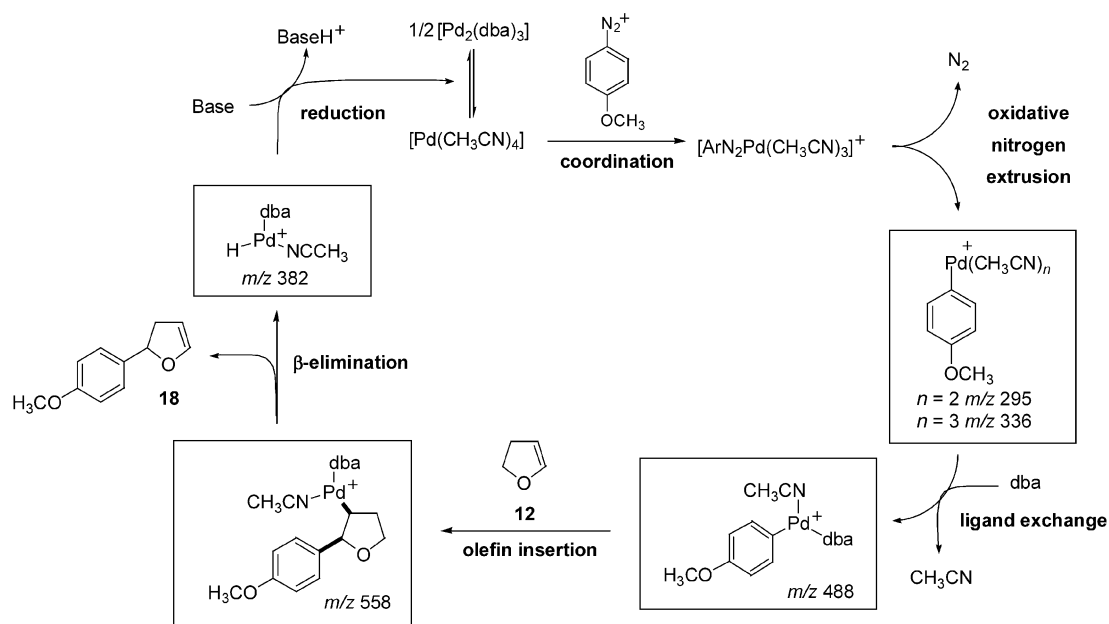
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Keywords: Heck reaction · homogeneous catalysis · mass spectrometry · reaction mechanisms · reactive intermediates



Scheme 4. Heck reaction of **12** with arene diazonium salt 4-MeOPhN₂⁺BF₄[−] promoted by intermediate **8**.

after mixing the arene diazonium salt and [Pd₂(dba)₃]-dba for approximately 90 minutes. Therefore, a delay of 90 minutes before addition of the olefin is beneficial for maximum yield.



Scheme 5. Proposed catalytic cycle for the Heck reaction with arene diazonium salts.

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