

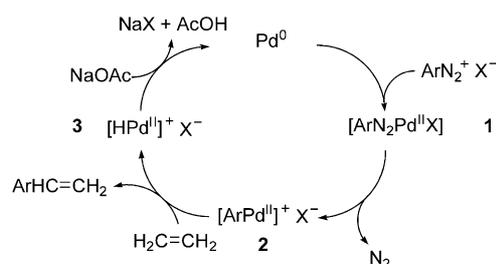
Probing the Mechanism of the Heck Reaction with Arene Diazonium Salts by Electrospray Mass and Tandem Mass Spectrometry**

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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.

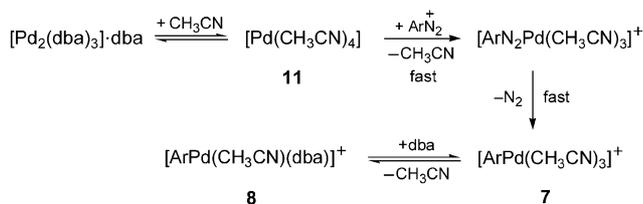
In their initial work,^[4] Matsuda and co-workers proposed the catalytic cycle outlined in Scheme 1 for the Heck reaction with arene diazonium salts. The palladium/aryl diazenide complex **1** was postulated to form from the reaction of arene diazonium salts and $[\text{Pd}(\text{PPh}_3)_4]$ (Scheme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



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

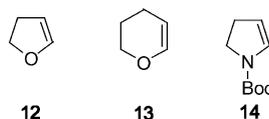
has been proposed to give the palladium/aryl diazenide complex **4**, which undergoes spontaneous nitrogen extrusion to furnish the aryl palladium species **5**.^[7]

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 3. The time-dependent exchange process for conversion of $[\text{Pd}_2(\text{dba})_3]\text{-dba}$ into intermediate **8**.

involving intermediate **8**. However, after 90 minutes of mixing, olefin insertion products were clearly detected, now with relatively high abundances, and again involving only **8**. For example, three new Pd-containing species were detected



for olefin **12**: **15** (m/z 324), **16** (m/z 517), and **17** (m/z 558; Figure 2). All of these three species correspond to association of **8** with the olefin and are the likely key catalytic intermediates in the Heck reaction (with no loss or loss of one ligand), with the palladium atom bound to the β position of the olefin and the aryl group transferred from the Pd center to the α position of the olefin. Similar results were observed for olefins **13** and **14**. Intermediate **8** is probably the most reactive one and the key intermediate in the olefin-insertion step of the Heck catalytic cycle investigated herein. All the other Pd cations **7**, **9**, and **10** appear to be much less reactive toward olefin insertion.

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 3 a 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

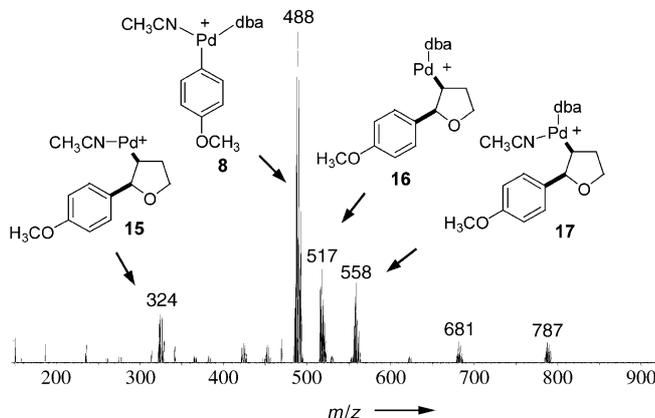


Figure 2. ESI(+)-MS spectrum for a solution (2 nmol L^{-1}) of the arene diazonium salt $4\text{-MeOPhN}_2^+\text{BF}_4^-$ and $[\text{Pd}_2(\text{dba})_3]\text{-dba}$ in acetonitrile after 90 min of mixing and subsequent addition of the olefin **12**.

from the coordination sphere of palladium forms the fragment ion of m/z 517, while further loss of dba forms the main fragment ion of m/z 283. Also enlightening is the fragment ion of m/z 341: its m/z ratio and Pd-isotopic distribution indicates the composition $[\text{HPd}(\text{dba})]^+$, which suggests that a hydride ion has been transferred from the olefin to Pd! This

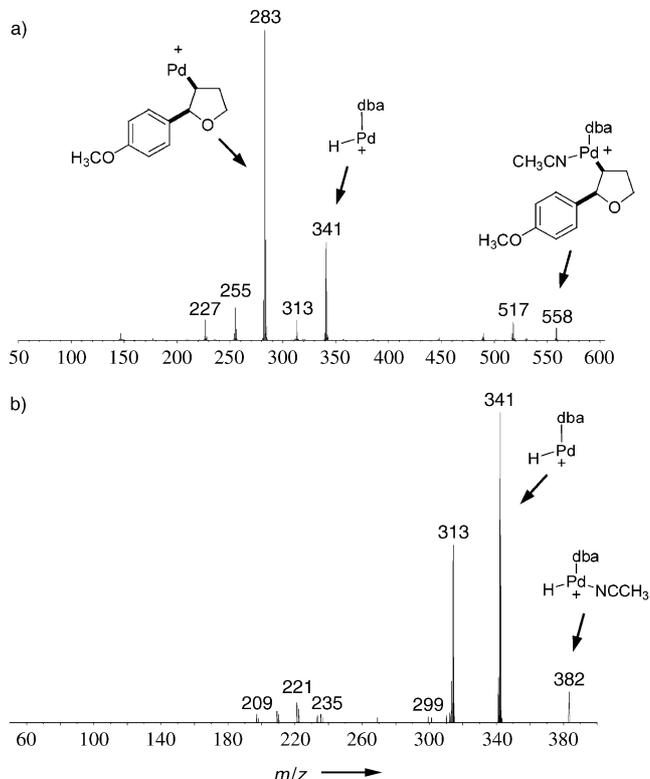


Figure 3. ESI(+)-MS/MS for a) the Heck ionic intermediate **17** (m/z 558) and b) the H-abstraction intermediate $[\text{HPd}(\text{CH}_3\text{CN})(\text{dba})]^+$ (m/z 382).

interesting CID-induced process is equivalent to the last step proposed for the catalytic cycle of the Heck reaction—the hydride elimination step (Scheme 1). The other intermediates **15** and **16** display similar dissociation chemistry as discussed for **17**, including the formation of gaseous $[\text{HPd}(\text{dba})]^+$. Detection of the H-abstraction intermediate $[\text{HPd}(\text{dba})]^+$ in solution was more challenging. However, this intermediate could be detected for olefins **13** and **14** as minor ions associated with acetonitrile and the olefin. One such complex, $[\text{HPd}(\text{CH}_3\text{CN})(\text{dba})]^+$, when mass-selected and subjected to CID (Figure 3b), displayed a characteristic dissociation by loss of acetonitrile that yields $[\text{HPd}(\text{dba})]^+$ (m/z 341) and further loss of CO (m/z 313) from the dba ligand.

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 $4\text{-MeOPhN}_2^+\text{BF}_4^-$ and $[\text{Pd}_2(\text{dba})_3]\text{-dba}$ for 90 minutes. Hence, $[\text{Pd}_2(\text{dba})_3]\text{-dba}$ 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.

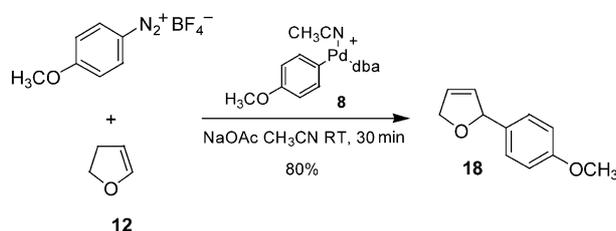
For the first time, therefore, several cationic intermediates of the oxidative addition step of the Heck reaction involving arene diazonium salts have been detected by ESI-MS monitoring and structurally characterized by ESI-MS/MS. A dynamic, time-dependent process with ligand equilibria between several 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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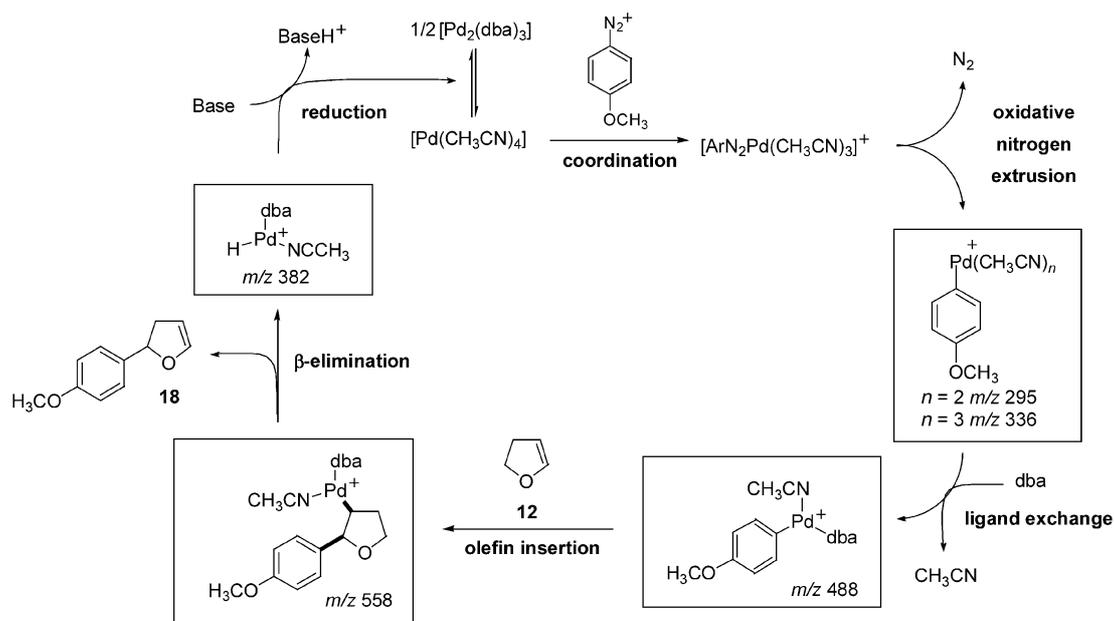
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Scheme 4. Heck reaction of **12** with arene diazonium salt 4-MeOPhN₂⁺BF₄⁻ promoted by intermediate **8**.

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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