

COMMUNICATION

"Dba-free" palladium intermediates of the Heck–Matsuda reaction†

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The "dba-free" Heck–Matsuda reaction was investigated *via* direct ESI-MS(/MS) monitoring. Palladium species involved in the reduction of Pd(II) during a Wacker type reaction and several "dba-free" arylpalladium transient complexes were detected and characterized. Based on these findings, a more comprehensible catalytic cycle for this pivotal reaction is suggested.

The Heck reaction is recognized as one of the most important synthetic tools for construction of C–C bonds.¹ This pivotal reaction has found numerous applications due to its rather mild reaction conditions and versatility. Despite several impressive demonstrations of its synthetic utility, the reaction is still under mechanistic investigation.²

Phosphane-free versions of the Heck reaction have also been attracting interest due to its superior economy, practicability, and experimentally simpler protocols.³ An illustrative case of the phosphane-free protocols is that in which arenediazonium salts are used as the arylating partner instead of the more conventional aryl halides and aryl triflates.⁴ This version is known as the Heck–Matsuda arylation and has been finding increasing application in the synthesis of natural products and biologically active molecules.⁵ Contrary to the mainstream Heck reactions, less attention has however been paid to the understanding of the mechanistic aspects of the Heck reaction using arenediazonium salts.

To get broad knowledge of a reaction mechanism, it is critical to fully intercept and characterize most, ideally all intermediates and catalytic species, including even the most transient species present in the reaction solution at different periods during its course. Mass spectrometry with direct

infusion of reaction solutions *via* electrospray ionization (ESI),^{6,7} or more recently, *via* ambient desorption/ionization techniques⁸ has been providing a solid bridge between solution and gas phase chemistries for comprehensive mechanism investigations.¹⁰ These techniques allow rapid and efficient "fishing" of reactants, intermediates and/or products in their intact ionic forms, or in protonated or deprotonated forms or in charge-tagged forms directly to the gas phase. MS and MS/MS characterization can therefore be performed on the gaseous ions *via* the measurement of their *m/z* values and/or the structural information provided by their collision induced dissociation (CID) products.⁹

We have previously applied ESI-MS(/MS) to investigate the Heck–Matsuda reaction with arenediazonium salts using Pd₂(dba)₃·dba as the catalyst¹¹ as well as other palladium mediated reactions.¹² Several cationic Pd species present in the reaction medium were intercepted and characterized, and a detailed catalytic cycle for this reaction was proposed (Scheme 1). Complex **4** with dibenzylideneacetone (dba) as a ligand was assigned as the key catalytically active Pd(II) species in the olefin insertion step. The catalytic role of the Pd(II) species such as **2** and **3** in this step has however not been investigated in "dba-free" media.

Here we report on the ESI-MS(/MS) monitoring of the Heck–Matsuda reactions with arenediazonium salts using Pd(OAc)₂ as the sole Pd source instead of Pd₂(dba)₃·dba. An investigation was therefore undertaken to find the actual catalytic species present in a "dba-free" medium, and to compare these results with those obtained when dba is present. These findings provided the basis for an expanded mechanistic view of this pivotal reaction.

For the Heck–Matsuda reaction with arenediazonium salts, we have observed that the arylated adducts **8** are obtained in good yields only when Pd(OAc)₂ is pre-mixed in wet acetonitrile with 2,3-dihydrofuran (DHF) prior to the addition of the remaining DHF, the arenediazonium salt, and the base (NaOAc).^{4f} In this step, probably the reduction of Pd(II) to Pd(0) occurs in a way similar to that of the Wacker olefin oxidation.^{2b} Fig. 1a shows the ESI(+)-MS for the reaction between Pd(OAc)₂

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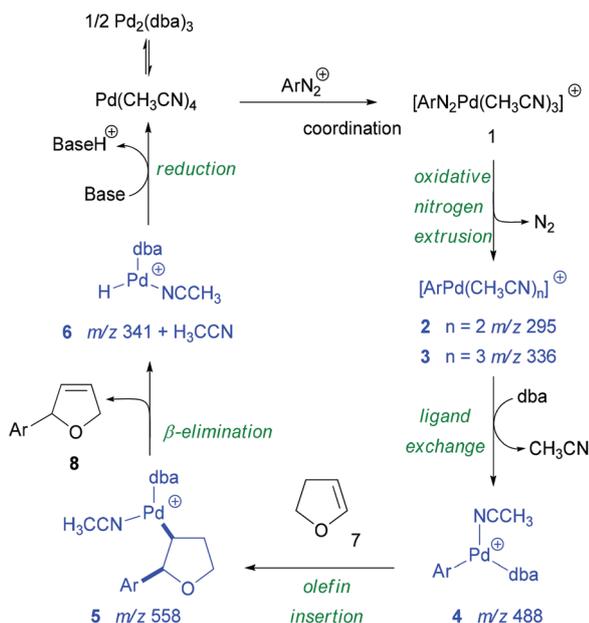
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Scheme 1 Previously reported catalytic cycle for the Heck–Matsuda reaction based on ESI-(+)-MS/MS monitoring. (Structures highlighted in blue correspond to intermediates characterized by ESI-(+)-MS/MS experiments.)

and DHF in CH₃CN 5 min after the reagents were mixed in stoichiometric amounts. Five major ions were characterized as key reaction species: **9** of *m/z* 247 (note that all *m/z* values are given for the most abundant ¹⁰⁶Pd isotopologue ion), **14** of *m/z* 275, **15** of *m/z* 234, **16** of *m/z* 327 and **17** of *m/z* 286. The proposed structures are supported by the characteristic isotopologue distribution of these Pd species and by the dissociation chemistries observed *via* ESI-MS/MS experiments (see ESI† for details).

The dissociation observed for **9** (Fig. S1†) indicates that this intermediate is formed by ligand exchange between AcO[−] and MeCN on Pd(OAc)₂. This is probably the first step of the

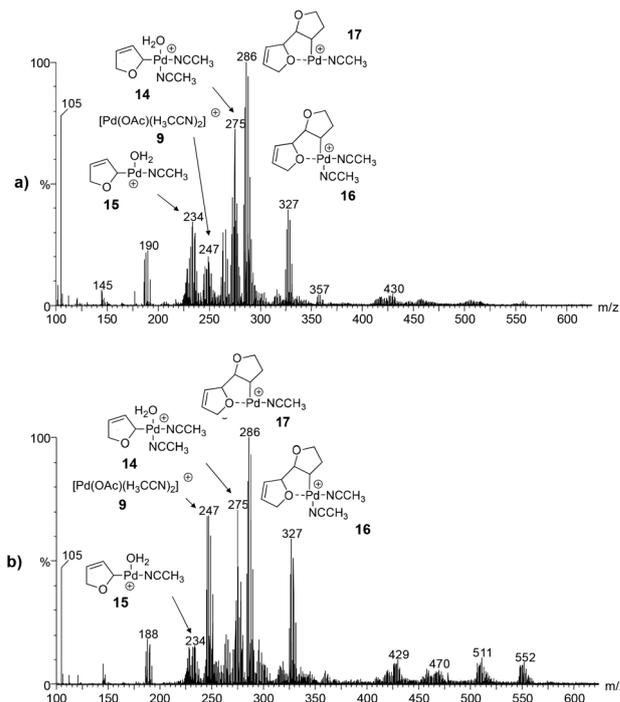
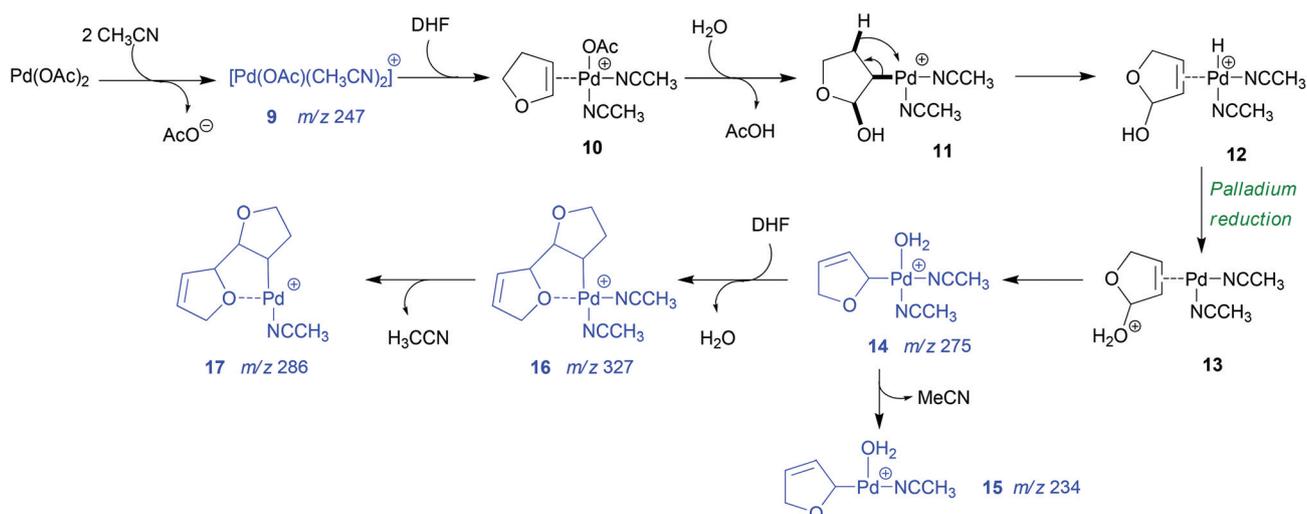


Fig. 1 ESI(+)-MS of the reaction solution of the Wacker type palladium reduction after (a) 5 min and (b) 30 min.

Wacker type Pd reduction reaction (Scheme 2). Complexes **14** and **15** (Fig. S2 and S3†) differ only by the number of MeCN ligands (Scheme 2), and were identified as the oxidative addition product between Pd(0) solvated species and DHF, the product of the Wacker oxidation of DHF. Although the isomeric **13** and **14** intermediates would be undistinguishable by ESI-MS, the fragment of *m/z* 206 – detected due to the loss of the 2*H*-furyl radical from the ion of *m/z* 275 – supports structure **14**. We rationalize that **14** is connected to **9** by the complexes shown in Scheme 2, which could not be detected by



Scheme 2 Proposed mechanism for the Wacker type Pd(II) reduction mediated by DHF.

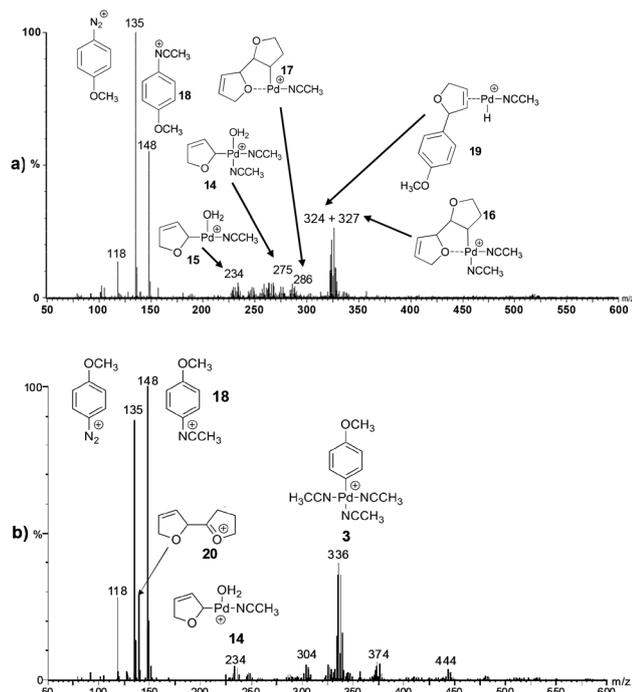


Fig. 2 ESI(+)-MS of dba-free arylpalladium complexes and its olefin insertion with DHF.

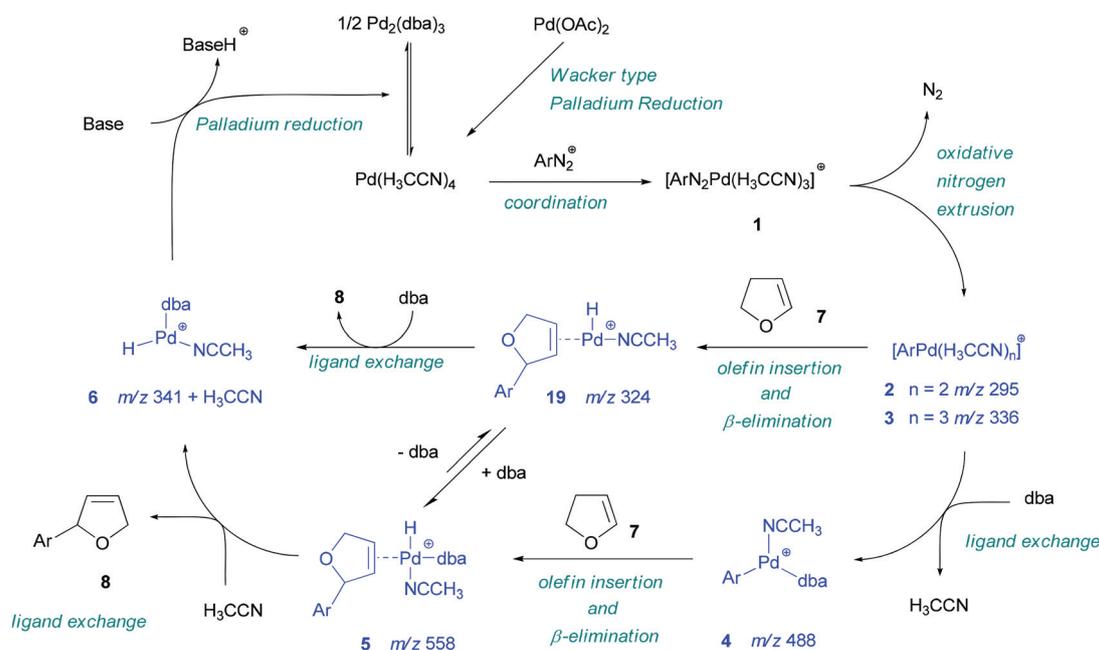
ESI(+)-MS. The failure to detect **13** suggests that reductive elimination is faster than oxidative addition which forms **14**.¹³ Complexes **16** and **17** seem to be formed by ligand exchange promoted by DHF in complexes **14** and **15**, followed by insertion of DHF into the bond between Pd and π -allyl (Scheme 2).

Since palladium black forms in the reaction solution, the behavior of the Pd species was monitored in the reaction

solution by ESI(+)-MS during the first 30 min. A continuous increase in the abundance of **9** (relative to intermediates **14**, **15**, **16** and **17**, Fig. 1b) as well as the detection of Pd species of higher m/z values in smaller abundances (m/z 429, 470, 511 and 552) were observed. These new species were selected for ESI(+)-MS/MS characterization, and their dissociation was found to converge to the ion of m/z 429 by MeCN losses (Fig. S6–S9[†]). The spectra for the ion of m/z 429 suggested its connection with **17** (m/z 327) due to the loss of both MeCN (41 Da) and, most probably, carbamic acid (61 Da).

Next, the crucial oxidative addition step between 4-MeOPhN₂⁺BF₄⁻ and the Pd(0) species was further investigated by the addition of 0.5 eq. of the arenediazonium salt to the initial reaction solution. As Fig. 2a shows, the population of the Pd-ions **14**, **15**, **16** and **17** decreased and the most relevant ions detected were 4-MeOPhN₂⁺ of m/z 135, **18** of m/z 148 (nucleophilic substitution of N₂ by MeCN) and **19** of m/z 324, which appears to represent a key reaction intermediate. Intermediate **19** was therefore selected and dissociated. Its dissociation chemistry supports a route for formation of **19** involving complexation between the Heck adduct and the palladium hydride solvated by MeCN (Fig. S13[†]).

The ESI(+)-MS for the reaction solution after addition of the remaining 0.5 eq. of 4-MeOPhN₂⁺BF₄⁻ (Fig. 2b) showed a decrease in the abundance of **19** with the respective increase of that for **3**. This dynamic change in the ionic composition of the reaction solution snapshotted by ESI(+)-MS can be rationalized by the oxidative addition of 4-MeOPhN₂⁺ to the Pd(0) species formed by palladium hydride decomposition promoted by BF₄⁻. The addition of the arenediazonium salt avoids formation of the palladium black observed in the initial Pd(OAc)₂ and DHF dissolution in MeCN. Another interesting trend was the decreasing of **16** of m/z 327 and **17** of m/z 286



Scheme 3 Updated catalytic cycle for the Heck–Matsuda reaction.

and the detection and characterization of **20** of m/z 139. The structure of **20** is supported by its CID chemistry (Fig. S14†) and its formation likely proceeds *via* nucleophilic addition of DHF to the π -allyl complex **14**. The detection of **20** also corroborates with the proposed structure of the Pd intermediates **16** and **17**.

Notable was also the detection of the oxidative addition complex **3** and the palladium hydride complex **19**, which demonstrates the participation of “dba-free” species in the catalytic cycle of the Heck–Matsuda reaction. Therefore, “dba-free” species may also be catalytically active even when Pd₂(dba)₃ is applied as a Pd source. These results prompted us to redraw our earlier proposed catalytic cycle¹¹ in a way that “dba-free” arylpalladium complexes could bypass the dba/MeCN ligand exchange to promote the carbopalladation step that forms the final Heck–Matsuda adduct **8** (Scheme 3).

The previously observed stability of the dba-containing complex **4** as compared to those of **2** and **3** can provide a qualitative measurement of the relative reactivity between these species.¹¹ Assuming that the olefin insertion step to dba-free arylpalladium complexes **2** and **3** is fast, the concentration of **2** and **3** tends to decrease when compared to that of **4**. The probability of dba-free Pd to collapse and precipitate as palladium black is therefore higher when compared to those bonded to dba. This scenario suggests an important reservoir role for **4**, which is responsible to deliver Pd(0) slowly to the reaction pathway by arylation of dba followed by π -elimination and basic palladium hydride decomposition to yield “naked” Pd(0) species such as Pd(CH₃CN)₄.¹⁴

Conclusions

Reaction monitoring *via* ESI(+)-MS(/MS) has provided evidence for the participation of “dba-free” arylpalladium intermediates in the olefin insertion step of the Heck–Matsuda reaction with arenediazonium salts using Pd(OAc)₂ as the palladium source. This new mechanistic information prompted us to redraw an expanded view of the Heck catalytic cycle, bringing new insights into this pivotal Pd mediated transformation.

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