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ESI-MS Detection of Proposed Reaction Intermediates in the Air-Promoted and Ligand-Modulated Oxidative Heck Reaction

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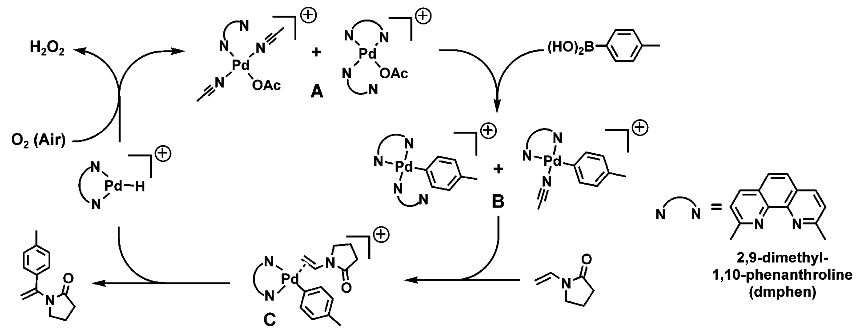

Electrospray ionization mass spectrometry (ESI-MS) and subsequent MS/MS analyses were used to directly detect palladium-containing cationic reaction intermediates in a ligand controlled palladium(II)-catalyzed oxidative Heck arylation. All potential intermediates were observed as dmphen-ligated palladium(II) species, suggesting that the dmphen bidentate ligand is attached to the metal center during the entire catalytic cycle. The study supports previous mechanistic propositions and provides new information regarding the composition of aryl-containing Pd(II) complexes in an ongoing oxidative Heck reaction. In addition, sodium acetate was found to be a useful base alternative to previously used tertiary amines.

Introduction

Since the early 1970s when R. F. Heck and T. Mizoroki independently discovered the palladium(0)-catalyzed vinylic substitution with aryl halides, a process which later came to be known as the Heck reaction,[1,2] this transformation has been a topic for extensive research.[3−5] The Heck methodology has proven to be a versatile tool for the formation of carbon−carbon bonds and has found applications, in for example, the industrial production of fine chemicals[6] and complex natural product synthesis.[7] Major advantages with this catalytic process include the high tolerance of functional groups and the possible control of both regio-[5] and stereoselectivity.[8] In the palladium(II)-catalyzed version of the Heck arylation, recently named the oxidative Heck reaction, the aryl halide is replaced as the coupling partner by an arylboronic acid[9,10] or an alternative organometallic reactant.[11−13] Importantly, arylboronic acids have a large commercial availability, are less toxic, and generate easily removable byproducts compared to alternative transmetalation substrates.[9] In order to further improve the oxidative Heck

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reaction the stable and cheap bidentate 2,9-dimethyl-1,10-phenanthroline ligand (dmphen), previously investigated by Cabri in the classical Heck reaction,[14] was found to allow vinylic substitutions with only 2 mol % of palladium catalyst.[15] The Pd(OAc)$_2$/dmphen combination provided the first examples of Pd(II)-catalyzed internal (α-) arylations of electron-rich olefins,[16] and in addition, dmphen was found to promote the essential regeneration of active Pd(II) species even under atmospheric air.[17]

The analytical technique electrospray ionization (ESI)[18,19] has, since its development in the mid-1980s, significantly increased the utility of mass spectrometry (MS).[20,21] It is considered a soft ionization technique in the sense that it yields little, if any, fragmentation products and has therefore proven to be an excellent tool for analyzing fragile biomolecules[22] and different kinds of organometallic complexes.[23−26] Electrospray ionization is not an ionization technique in the sense that neutral molecules become charged; instead, ions are transferred from solution to the gas phase in a smooth manner that is ideal for observation of short-lived molecular ions directly from a reaction medium. ESI-MS has been used previously to probe the mechanism of different palladium(0)-catalyzed reactions like the Heck[27−29] and the Suzuki[30] reaction. The tandem version, ESI-MS/MS, is a valuable tool for identification and structural assignments of charged complexes because of the possibility to use the first mass analyzer to "fish out" species with a certain *m*/*z* ratio and thereafter to subject them for fragmentation (CID) in the collision cell. The generated fragments can then be analyzed with the second mass analyzer.

This technique should also be well suited for an on-line monitoring of reaction intermediates[31] in the palladium(II)-catalyzed oxidative Heck reaction since it is believed to proceed via cationic intermediates (and only charged complexes can be observed by MS-detection). Although there is a proposed general catalytic cycle for the oxidative Heck reaction[9,32] (Figure 1), there are presently no noncomputational studies of the mechanistic aspects supporting these assumptions.

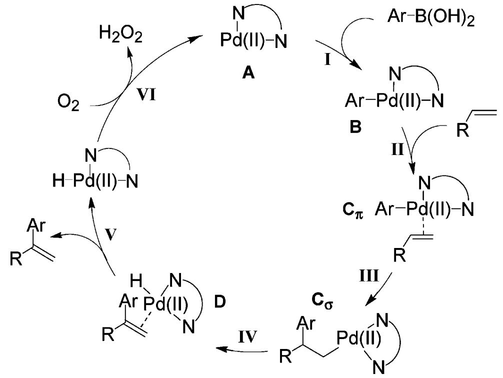

FIGURE 1. Plausible catalytic cycle of the phenanthroline ligand-modulated oxidative Heck reaction with an electron-rich olefin.[9] The different types of cationic intermediates in the catalytic cycle are assigned letters from **A**−**D** and catalytic steps are named **I**−**VI**.

Results and Discussion

The overall aim of this investigation was to detect existing cationic palladium complexes present during a productive oxidative Heck reaction between an arylboronic acid and an enamide and to explore the composition of suggested intermediates in the catalytic cycle (**A**−**D**, Figure 1). Step I in the catalytic cycle corresponds to the starting point, where different Pd(II) species of class **A** participates in a transmetalation process and arylpalladium(II) complexes of class **B** are formed. In step II, the metal center coordinates to the olefin, generating a π-complex of type **C**$_\pi$. Thereafter, the **C**$_\pi$ species undergoes a migratory insertion process forming a σ-complex (**C**$_\sigma$, step III). After the subsequent β-elimination (step IV), a palladium hydride is formed which is believed to first coordinate to the arylated olefin (**D**) before dissociating, forming free Heck product and a palladium hydride (**E**, step V). For multiple turnovers, active palladium(II) species must be regenerated (step VI). The dmphen ligand and related 1,10-phenanthroline derivatives are believed to play an important role in this process, allowing the direct use of molecular oxygen as a Pd(0) reoxidant.[33,34] A number of other bidentate ligands, such as bipyridine and dppp (1,3-bis(diphenylphosphino)propane), are also productive, although they provide slow reactions and lower yields.[17]

Regarding the exact nature of step VI in Figure 1, Stahl and co-workers recently presented an aerobic Pd(II)-catalyzed oxidation reaction where molecular oxygen is believed to directly react with a palladium hydride to generate active Pd(II) and complete the catalytic cycle.[35] Thus, the issue whether Pd(0) species are involved or not in dioxygen coupled Pd(II)-catalyzed reactions is at present not fully understood, although the essential reoxidant is commonly referred to as a "Pd(0) reoxidant". Palladium hydrides are, however, not stable under basic conditions (yielding Pd(0) and HX in the classic Heck reaction) and are very seldom detected during the course of a palladium-catalyzed reaction.[27,36]

A possible byproduct might be observed if complex **B** undergoes a competing second transmetalation with a free

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SCHEME 1. Investigated Oxidative Heck Reactions and Subsequent Hydrolysis

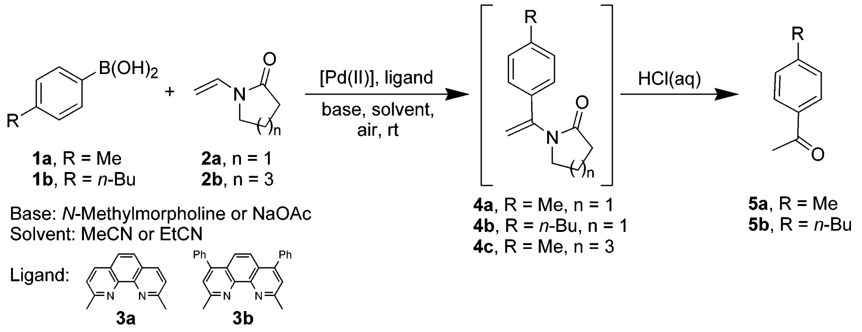

TABLE 1. Productivity from the Catalytic Systems Using Selected Reaction Components at Room Temperature[a]

no.	ArB(OH)$_2$	olefin	ligand	solvent	yield[b] (%)
1	**1a**	**2a**	**3a**	MeCN	**5a**, 63
2	**1a**	**2a**	**3a**	MeCN	**5a**, 72[c]
3	**1b**	**2a**	**3a**	MeCN	**5b**, 76
4	**1a**	**2a**	**3b**	MeCN	**5a**, 55
5	**1a**	**2b**	**3a**	MeCN	**5a**, 59[d]
6	**1a**	**2a**	**3a**	EtCN	**5a**, 69
7	**1a**	**2a**	**3a**	MeCN/H$_2$O	**5a**, 50[e]

[a] Arylboronic acid (**1**, 2 equiv), olefin (**2**, 1 mmol, 1 equiv), ligand (**3**, 0.024 equiv), NaOAc (2 equiv), Pd(II) salt (0.02 equiv) in 3 mL of solvent was stirred in an open vessel for 24 h. In all entries, except entry 4, 1−4% biaryl formation was observed. [b] Isolated yield of the corresponding aryl methyl ketone **5** after acidic hydrolysis. >95% pure according to GC−MS. [c] Palladium propionate instead of palladium acetate and increased reaction time to 30 h. [d] Increased reaction time to 7 days. [e] Acetonitrile/water, 50:50.

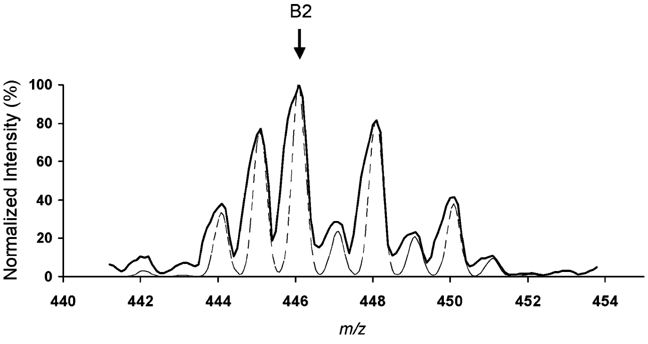

FIGURE 2. ESI-MS-(+) spectrum of palladium complex **B2** ($C_{23}H_{22}N_3$-Pd, *m/z* 446), solid line, and theoretical isotopic pattern, dotted line.

arylboronic acid before the migratory insertion takes place (step III).[37] According to this competing Suzuki-like reaction pathway, a symmetric biaryl product (**G**, not shown in Figure 1) will be formed after an aryl−aryl reductive elimination process.

The ligand-mediated oxidative Heck protocol previously developed in our laboratory proceeds under air at room temperature with a base (2.0 equiv) and dmphen (**3a**, 0.024 equiv) as the ligand.[17] *p*-Tolylboronic acid (**1a**, 2.0 equiv) and the electron-rich enamide **2a** (1.0 equiv) with Pd(OAc)$_2$ (0.02 equiv) as palladium(II) source were chosen as the standard reaction system for ESI-MS analysis (Scheme 1). The rationale behind the employment of an electron-rich olefin was that if an internally arylated product was isolated, the regioselective outcome would support a Heck process proceeding via cationic Pd(II) σ- and π-intermediates.[5] After full conversion, intermediate α-arylated products (**4a**−**c**) were hydrolyzed with HCl (aq) and isolated as the corresponding aryl methyl ketones (**5a**,**b**). Acetonitrile is a polar solvent that also works well in ESI-MS analysis. Accordingly, the labile organometallic reaction intermediates, which might only exist under specific conditions, were believed to remain unaffected when removed from the reaction mixture and injected into the ESI-MS for analysis. In order to improve the signal-to-noise ratio in the ESI-MS-(+) detection, sodium acetate was evaluated as an alternative base to *N*-methylmorpholine. Unexpectedly, this weak inorganic base furnished a faster reaction, with full internal selectivity but with a slightly reduced yield (63% of product **5a** after 24 h, Table 1, entry 1) compared to the corresponding reaction with *N*-methylmorpholine (71% **5a** after 48 h).[16] Additional reactions with arylboronic acid **1b**, enamide **2b**, ligand **3b**, and propionitrile as solvent also proceed smoothly with sodium acetate (entries 2−6). In order to test whether or not water had an impact on the reaction outcome, the solvent in the standard reaction was changed to a 50:50 acetonitrile/water solution, furnishing only slightly lower yield of isolated **5a** (50% instead of 63%, entries 7 and 1). The amount of biaryl, formed through a competing Suzuki-like pathway varied between 1 and 4%. Competing protodeboronation and phenol formation were also found to consume arylating agents **1a**,**b**, although these processes did not affect the yield of the oxidative Heck reaction because of the excess (2 equiv) of arylboronic acid.[38−40]

Next, we decided to initiate the mechanistic investigation, attempting to probe the plausible catalytic cycle of the reaction presented in Scheme 1 with **1a**, **2a**, and **3a** through the use of ESI-MS analysis. An aliquot was withdrawn from the reaction mixture after 3 h and was directly diluted 10 times with acetonitrile.[41−43] After sample injection, ESI-MS-(+) traces were

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(41) All reported ESI-MS and ESI-MS/MS signals were obtained after 3 h based on an investigation at different time intervals (see Figure 5 or the Supporting Information, S33−36). Interestingly, in the standard reaction between **1a** and **2a** using dmphen and Pd(OAc)$_2$, all detected palladium complexes were already present after 10 min. To allow the detected palladium(II) species to describe a productive catalytic cycle, the selected time of analysis was set to 3 h, corresponding to around 50% conversion of the yield-determining starting material (**2a**) in the standard reaction. Two additional graphs are included on pp S39−40 (Supporting Information). In the first graph, the plotted intensity of the standard reaction is corrected for detector saturation by utilizing isotopic peak intensity. In the second graph, accumulated ion intensities from detected adducts are presented.

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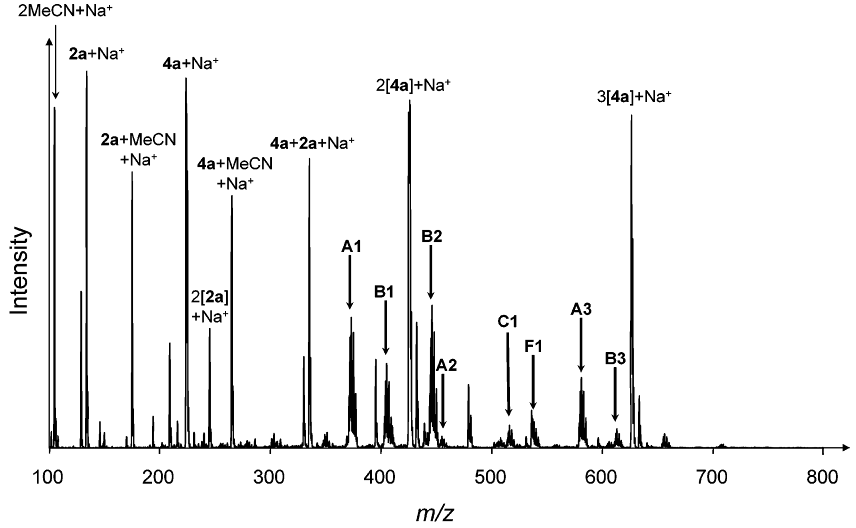

FIGURE 3. ESI-MS-(+) spectrum for the standard reaction, using **1a**, **2a**, **3a**, NaOAc, and MeCN under air at room temperature after 3 h (entry 1, Table 1). Palladium complexes depicted according to Table 2.

recorded by scanning the first quadrupole of an API III+ triple-quadrupole instrument. Various groups of *m*/*z* signals corresponding to the characteristic isotopic distribution pattern of palladium-containing complexes were detected (Figure 2). The *m*/*z* separation between adjacent peaks revealed that only monocharged cationic species were observed. The full ESI-MS scan of the reaction mixture from the standard reaction is depicted in Figure 3. The largest peaks came from sodium adducts of arylated olefins (monomers, dimers, and even trimers), but also olefin adducts or even solvent species could be observed. By utilizing the power of tandem mass spectrometry (MS/MS), a structural proposition of each of the palladium complexes could be deduced. The ion with strongest intensity in each complex (the ion from ^{106}Pd, which is the palladium isotope with highest natural abundance) was selected for further MS/MS-(+) analysis. A daughter ion spectrum was recorded with the collision energy and collision gas thickness set to 20 eV and 200 × 10^{13} molecules·cm^{-2}, respectively (see the Supporting Information).

Table 2. Starting Pd(II) Complexes (A). Three different dmphen-coordinated single-charged cationic complexes were detected. Of those, derivative **A1** was the predominant type **A** species, according to the ESI-MS intensity. The 16-electron bis-dmphen complex **A3** is thought to provide **A1** by up-front fragmentation.[20] MS/MS-(+) data supported the assigned composition of **A3** by establishing loss of monocoordinated dmphen from the coordination sphere of the metal. A clear difference between species of class **A** compared to all other detected organopalladium compounds are that they all have acetate associated to the Pd(II) center. Clearly, after transmetalation (step I, Figure 1) monocharged aryl containing moieties cannot bind yet another counterion like the acetate anion and still be visible in ESI-MS-(+). To assess if the metal still carried one of its two originally bonded acetate ions in complex **A1**−**3**, Pd(OAc)$_2$ from the standard reaction was replaced with palladium propionate. The reaction with palladium propionate proceeded somewhat slower, although providing a 72% yield of **3a** after 30 h (Table 1, entry 2). In the presence of the sodium acetate anion, ions of **A1**−**3** were again observed, supporting the role of the acetate as a palladium(II) ligand and not as a sole proton scavenger. An intriguing feature of the MS/MS spectrum of complex **A1** (Supporting Information) is that the dissociation of an acetate ion should render a +2 charged palladium−ligand species and consequently not gives a fragment with a *m*/*z* ratio of 314. The recording of the *m*/*z* = 314 signal suggests a single-electron transfer. Such unexpected charge transfers are, however, not unheard of. Reduction processes can occur in the collision cell for transition metals in higher oxidation states (M^{z+} with $z > 1$) when colliding with residual gas molecules.[44]

Table 2. Aryl−Pd(II) Complexes (B). The principal transmetalation product recorded was the fully ligated **B2**. Importantly, MS/MS-(+) experiments afforded further support to the suggested structures, confirming the presence of the chelating dmphen in **B1**−**3** (see the Supporting Information). In the MS/MS spectrum for, e.g., potential intermediate **B2** (Figure 4), the neutral dissociation of acetonitrile and toluene could be established and a relatively large signal (*m*/*z* 313), matching the mass of a charged Pd−dmphen complex, was also observed. The elimination of toluene from tolyl-containing **B**-type ions is not a surprising process with benzylic hydrogens in the near proximity of the metal center.[21] The fragmentation of complex **B1** was almost identical to **B2** with the difference that the solvent molecule (MeCN) first dissociated from the mother ion **B2** when exposed to MS/MS-(+) analysis.[45]

Table 2. Pd(II) Complexes (C). In the case of **C1**, a structural assignment by MS/MS-(+) was ambiguous. The *m*/*z* ratio (516) corresponds either to an aryl-Pd(II) species π-bonded to the olefin (**C**$_\pi$) or the corresponding 1,2-inserted σ-complex (**C**$_\sigma$). The observation of dissociation of both free enamide **2a** (*m*/*z* 405) and β-elimination product **4a** (*m*/*z* 315), from the **C1** complex, suggest an equilibrium between the π-complex and the σ-complex, but since the conditions in Q2 are quite different from actual oxidative Heck reaction conditions, no definite conclusions can be made. Although the *m*/*z* ratio 516 also fits a π-complex of class **D** (Figure 1), the information from MS/

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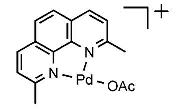
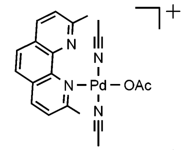
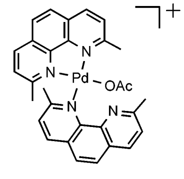
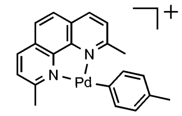
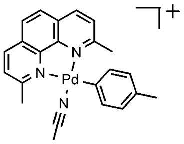
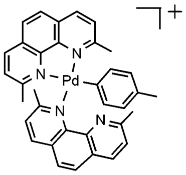
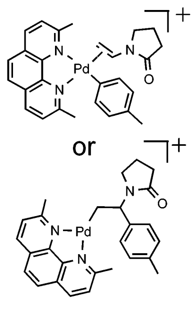
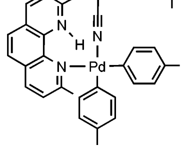
TABLE 2. Single Charged Cationic Palladium(II) Complexes Detected in the Standard Oxidative Heck Reaction with 1a, 2a, and 3a Using ESI-MS-(+) Analysis

no.	m/z^a	Pd(II)-complex^b
1	373	 **A1**
2	455	 **A2**
3	581	 **A3**
4	405	 **B1**
5	446	 **B2**
6	613	 **B3**
7	516	 **C1**
8	538	 **F1**

^{a} Reported m/z values are based on ^{106}Pd. ^{b} Structures supported by MS-MS-(+) analysis.

MS-(+) reduces that possibility by detecting elimination of non-arylated **2a** (the insertion-elimination, step III−IV in Figure 1, is considered irreversible).[4,46] Another interesting observation in the MS/MS-(+) spectrum of **C1** was that the signal of *m*/*z* 315 points toward a dmphen−Pd(II)−hydride complex (see the Supporting Information, p S26) probably formed via a CID-induced β-elimination from the σ-bonded **C1** complex and loss of product **4a**. The intensive **C1** MS/MS fragment ion *m*/*z* 355 was a more bothersome discovery. We have at present no explanation for this signal (see the Supporting Information, p S26).

Table 2. Pd(II) Complex (F). Detection of the biaryl intermediate **F1** was challenging because of overlapping peaks. Rewardingly, via mass-selection and CID-induced fragmentation, the spectrum, after loss of a toluene fragment, displayed dissociation chemistry very similar to **B2**, supporting the presented cis structure or the alternative trans isomer.

Importantly, all potential intermediates listed in Table 2 do not necessarily originate from the reaction cocktail. This holds especially true for electronically unsaturated complex **A1** and **B1**, which are most likely formed during the desolvation step in the ion source and/or by up-front collision-induced dissociation from intermediates **A3** and **B2−3**, respectively.[27,45] Alternatively, they might function as reactive intermediates in dissociative catalytic processes.

An interesting feature during the investigation at different time intervals (Figure 5) was how the intensity of the proposed intermediates varied between the different sampling times, e.g., complexes **A1** and **A3** were increasing over the whole reaction, while all three complexes of class **B** were showing decreased intensity. A possible explanation for this behavior could be that the transmetalation step (step I, in Figure 1) becomes slower with time due to the continuous consumption of arylboronic acid **1a**, yielding not only product **4a** but also side products, such as bitolyl,[38] *p*-methylphenol,[39] and toluene[40] (from protodeboronation). However, interpretation of the different ion intensities is somewhat hampered as the response factor for the detected Pd complexes probably varies depending on the degree of competition for excess charge between different species in the generated ESI droplets.[42,43] Even in cases where intensities can be directly correlated to concentrations, caution should be exerted when drawing conclusions based on a specific species concentration. The resting state for Ar−Pd species may be altered when the relative concentration of a substrate is changed during a reaction.[47]

The proposed identity of the observed complexes in the standard reaction (Table 2) was further supported by a series of additional reactions where the reaction components, one at a time, were exchanged to deliver analogous and chemically equivalent palladium(II) intermediates (Table 1). For each homologous replacement, an electrospray mass spectrum was recorded for the specific reaction. Novel palladium-containing cations were further analyzed by MS/MS (Table 3).

Table 3. Starting Pd(II) Complexes (A). The presented structure of complex **A1** was validated by using the related but 152 g/mol heavier bathocuproine (**3b**) instead of **3a** as ligand. Both **3a** and **3b** furnished product **4a** in similar yields (Table 1, 63% (entry 1) and 55% (entry 4), respectively) with more than 99% internal selectivity (GC−MS). The MS patterns were almost identical except that the trace from **A1′**, as expected, had its peaks positioned 152 *m*/*z* units higher. Intermediate **A2**, containing a monoligated bidentate ligand, could not be observed among the derivatized ions in the MS-spectrum when ligand or solvent was exchanged to **3b** or propionitrile (Table 1, entries 4 and 6). The presence of **A3′** was detected in the ESI-MS-(+) scan. The subsequent MS/MS-(+) fragmentation process started

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(46) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066.

(47) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527−2571.

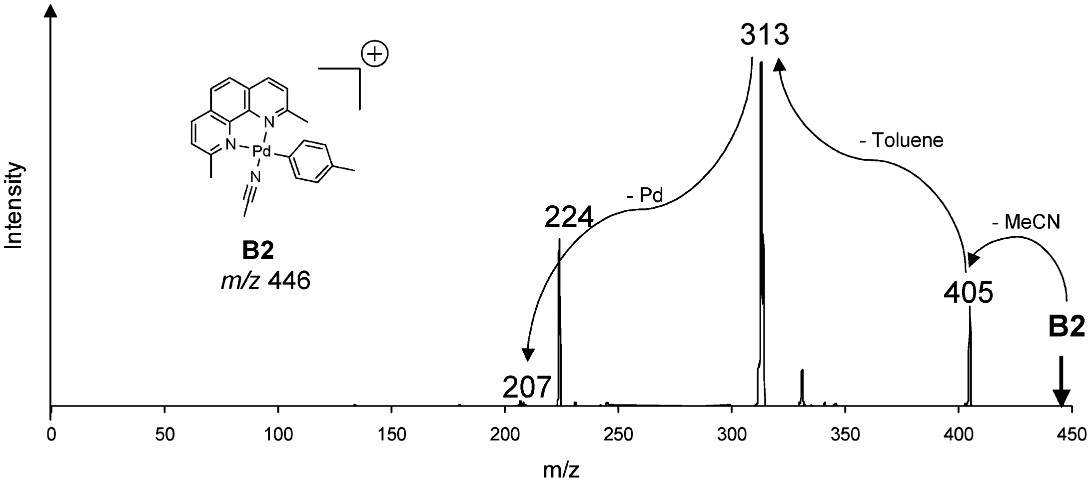


FIGURE 4. MS/MS-(+) spectrum for palladium complex **B2** *m*/*z* 446, (**B2**−MeCN) *m*/*z* 405, (**B2**−[toluene + MeCN]) *m*/*z* 313. The large signal at *m*/*z* 224 is not believed to originate from the **B2** mother ion since when the MS/MS spectrum was recorded for other palladium isotopes than ^{106}Pd, it was not observed.

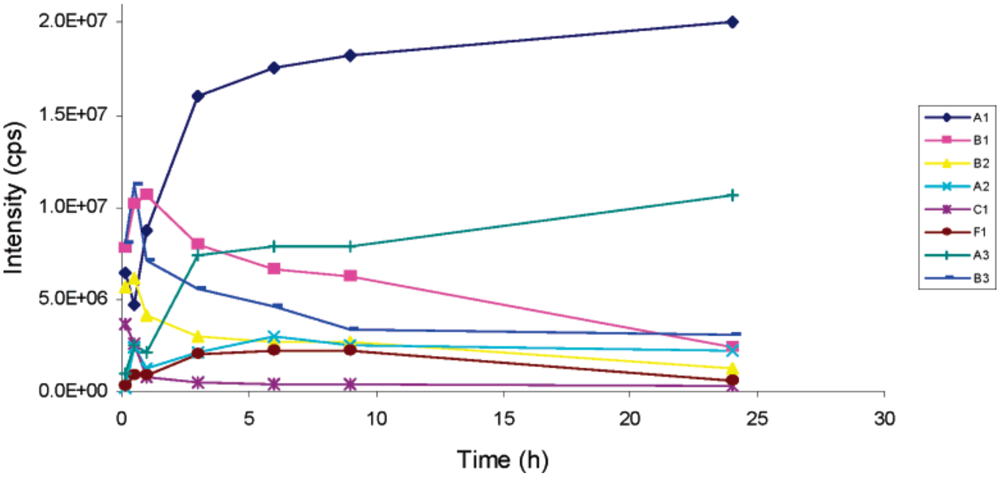


FIGURE 5. Intensity vs reaction time for ESI-MS detected palladium complexes in the standard reaction using **1a**, **2a**, **3a**, NaOAc, and MeCN (entry 1, Table 1).

with a loss of the extra nitrogen ligand and thereafter followed the same dissociation pattern as for **A1** and **A1′**.

Table 3. Aryl−Pd(II) Complexes (B). The previously utilized ligand **3b** was again used to directly validate the proposed structures in Table 2. As expected, when ligand **3b** was used, the corresponding *m*/*z* ratios for the new cationic complexes of type **B** could be observed in the mother scan (Table 3). The following MS/MS-(+) analysis of the ions further supported the structures by illustrating a dissociation pattern matching that of the parent **B** complexes (see the Supporting Information). Complex **B2′**, for example, possesses some specific MS/MS-(+) easily distinguished features like toluene and acetonitrile dissociations and a dominating palladium−bathocuproine signal. The applicability of the chemical verification process of complex **B3** through **B3′** was a bit more demanding since the signal was weak in the ESI-MS-(+) scan and the presence of isobaric ions complicated the task when ligand **3b** was used. In any case, the cleavage of the neutral ligand and the dissociation of toluene, leaving the charged palladium center bonded to bidentate **3b**, was distinguishable by MS/MS-(+) analysis, manifesting the proposed structure. To further establish the structure for the reaction intermediates of class **B**, a different arylpalladium precursor was needed. The choice fell on homologous *p*-(*n*-butyl)phenylboronic acid (**1b**), an arylating agent with similar properties as *p*-tolylboronic acid (**1a**) but with a higher molecular weight (Table 1, entry 3). When **1a** was exchanged to **1b** and the reaction mixture analyzed with mass spectrometry, the *m*/*z* ratio of the mother ions **B1″**, **B2″**, and **B3″** agreed with expectation. Subsequent dissociation of daughter ions in MS/MS-(+) of mass-selected ions also followed the anticipated pattern.

Table 3. Pd(II) Complexes (C). The intriguing complex **C1** was investigated in a similar way as described above. Arylating agent **1b** and ligand **3b** were successfully exploited as chemical equivalents, but an olefin analogue of *N*-vinylpyrrolidinone (**2a**) was needed. Thus, the slightly larger enamide *N*-vinylcaprolactam (**2b**) was selected. This reactant furnished **5a** via **4c** with almost identical yield and selectivity in the oxidative Heck reaction as with **2a** (Table 1, entry 5). Even though there was a large difference in reaction time, it did not prevent the detection of intermediates and the ESI-MS-(+) analysis produced anticipated results, including a complex of type **C1″** (Table 3).

TABLE 3. ESI-MS-(+)-Detected Single Charged Cationic Complexes in Oxidative Heck Reactions Using Homologous Reaction Components

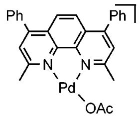
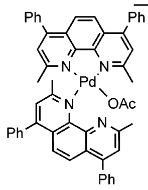
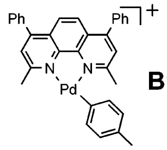
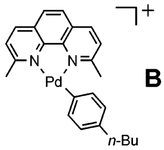
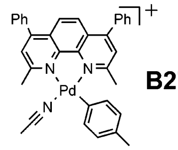
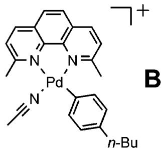
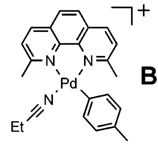
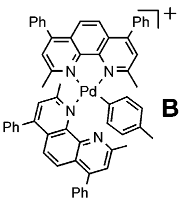
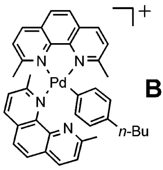
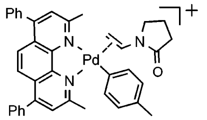
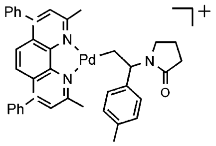
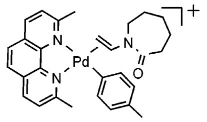
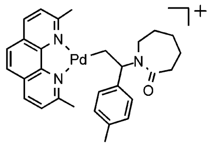
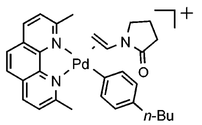
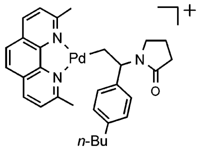
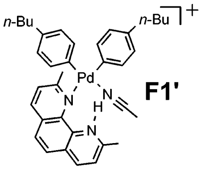
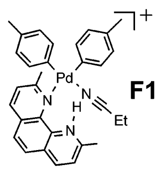
no.	standard Pd(II) complex	homolog	Pd(II) complex		*m/z*
1	**A1**	**3b**		**A1'**	525
2	**A3**	**3b**		**A3'**	885
3	**B1**	**3b**		**B1'**	557
4	**B1**	**1b**		**B1''**	447
5	**B2**	**3b**		**B2'**	598
6	**B2**	**1b**		**B2''**	488
7	**B2**	EtCN		**B2'''**	460
8	**B3**	**3b**		**B3'**	917
9	**B3**	**1b**		**B3''**	655
10	**C1**	**3b**	 **or** 	**C1'**	668
11	**C1**	**2b**	 **or** 	**C1''**	544
12	**C1**	**1b**	 **or** 	**C1'''**	558
13	**F1**	**1b**		**F1'**	622
14	**F1**	EtCN		**F1''**	552

Table 3. Pd(II) Complex (F). Last, we investigated the proposed structure of byproduct intermediate **F1** by the same replacing strategy. The variable components in the complex were one-at-a-time switched to equivalent replacements, such as ligand **3b**, aryl group **1b** and propionitrile as solvent. Interestingly, no bitolyl product or bitolyl complex of type **F1** was observed when bulky ligand **3b** was used (Table 1, entry 4). Unfortunately, this did not increase the yield of **4a** (Table 1, entries 1 and 4) since the olefin and not the arylboronic acid was yield determining. The MS/MS-(+) dissociation pattern of the **F**

complexes was easily interpreted due to the quick loss of coordinating aryl and solvent molecule, leaving the characteristic daughter ion of Pd(II)−*N*,*N*-ligand.

Conclusion

Potential oxidative Heck intermediates including starting palladium(II) catalysts, transmetalation complexes, and insertion intermediates were observed directly in the reaction mixture by ESI-MS-(+) analysis. The detected organopalladium intermediates were found to be in good agreement with the generally suggested catalytic cycle of an oxidative Heck reaction. The structures of the detected ions were validated by MS/MS and by stepwise replacement of reaction components. The bidentate nitrogen ligand 2,9-dimethyl-1,10-phenanthroline (dmphen) was ubiquitous in all detected complexes and appeared to play an essential role not only for regeneration of active Pd(II) but for the whole reaction process. The sensitivity, speed, direct assay, and versatility of the ESI-MS methodology suggest applications as a tool for mechanistic studies also in related reaction systems.

Experimental Section

General Procedure of Reaction Preparation. Oxidative Heck reactions were run under air in room temperature from arylboronic acid (**1a**,**b**, 2 equiv), olefin (**2a**,**b**, 1.00 mmol, 1 equiv), sodium acetate (2 equiv, 164 mg) as base, ligand (**3a**,**b**, 0.024 equiv), and palladium(II) precursor (0.020 mol) in 2 mL of solvent. Acetonitrile, propionitrile, or a 50:50 acetonitrile/water system served as solvent. The reaction mixture was vigorously stirred for 1−7 days. After completion, the reaction mixture was interrupted, and intermediate α-arylated enamides **4a**−**c** were hydrolyzed in situ using 5 mL of 2 M HCl, generating the corresponding aryl methyl ketones (**5a**,**b**). The crude product was extracted from the reaction mixture with CH_2Cl_2, concentrated and purified on silica gel using a mixture of iso-hexane and ethylacetate (20:1) to give the pure aryl methyl ketones **5a**,**b** in 50−76% yield.

Mass Spectrometry. An API III+ triple-quadrupole mass spectrometer equipped with an articulated IonSpray interface was used in this study. The reaction mixture was diluted 10 times with acetonitrile after 3 h of stirring in an open vessel at room temperature and introduced by continuous infusion with the aid of a syringe pump at a flow-rate of 5 μL/min through a fused silica capillary (50 μm inner diameter and 184 μm outer diameter). The fused silica capillary was centered in a stainless steel capillary counter assembly, which also served as the ESI high voltage contact. The nebulizer gas flow was set to 0.5 L/min. The flow rate of dry nitrogen counter-current curtain gas (heated to 60 °C) was 1.2 L/min over the sampling orifice. The mass spectrometric parameters were as follows: ion spray voltage (ISV) 3500 V, interface plate voltage (IN) 650 V, orifice lens voltage (OR) 50 V, and AC entrance rod (R0) 30 V. Mass spectral data were typically recorded by scanning the 100−800 u region with a dwell time of 1−2 ms and a step size of 0.1 u in multichannel acquisition mode (MCA summation of 10−20 scans). Mass scale calibration was performed using a polypropylene glycol solution (PPG). During the MS/MS experiments the collision energy was set to 20 eV. The collision gas was argon with 99.9999% purity. The collision gas thickness was 2×10^{15} molecules·cm^{-2}.

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Supporting Information Available: Text giving full details of experimental procedures, spectrometric data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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