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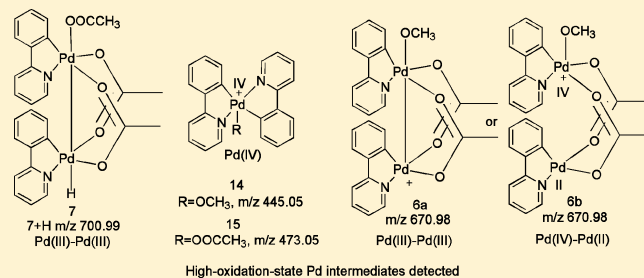
Investigation of the Mechanisms of Palladium-Catalyzed C–H Acetoxylation and Methoxylation by Electrospray Ionization Mass Spectrometry

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Supporting Information

ABSTRACT: Electrospray ionization mass spectrometry (ESI-MS) was used to monitor the progress of the Pd-catalyzed acetoxylation and methoxylation of carbon–hydrogen bonds with $\text{PhI}(\text{OAc})_2$ as an oxidant. The reaction intermediates were characterized by high-resolution ESI-MS. The reaction mechanisms are proposed to be $\text{Pd}(\text{II})$ – $\text{Pd}(\text{IV})$ or $\text{Pd}(\text{II})$ – $\text{Pd}(\text{III})$ redox cycles depending on the σ -donor ligand and the solvent polarity.



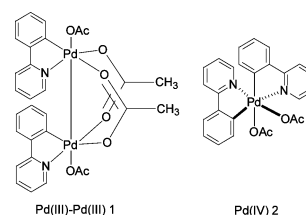
During the past several years Pd-catalyzed ligand-directed C–H functionalization has advanced rapidly.¹ The oxidative functionalization of sp^2 C–H bonds in particular has been the subject of much research.² The groups of Sanford and Ritter have reported on the Pd-catalyzed oxygenation of organic substrates using $\text{PhI}(\text{OAc})_2$ as the oxidant.^{2a,c,3} Their works describe the development of the methods and the investigation of the involved mechanisms, and in those studies, the structures of the reaction intermediates were characterized by ^1H nuclear magnetic resonance (NMR) spectroscopy or low-temperature X-ray diffraction due to the high reactivity of these compounds.^{2a,c,3b} There are some discrepancies between these reports with respect to the reaction mechanism, and we hoped to capture the reaction intermediates by electrospray ionization mass spectrometry (ESI-MS) and ^1H NMR spectrometry under different reaction conditions and to further explore the mechanism of Pd-catalyzed oxidation reactions in this study.

Recently, ESI-MS has been used to characterize reaction intermediates, affording direct evidence for the mechanisms of multistep organic reactions, and it has particular advantages which have been reported in the investigation of mechanisms of organic reactions.⁴ However, ESI-MS has some drawbacks for studying the metal-mediated reaction mechanism, such as (i) solvent molecules combine with or are dissociated from the metal center and (ii) a reaction intermediate may be formed during the ionization process that is not present in the solution (for example, electron transfer can occur during the electrospray process).⁵ The ESI-MS technique has also been used to study the mechanism of palladium-mediated reactions universally.⁶ However, the mechanism of Pd-catalyzed oxidation reactions has not been systematically explored by ESI-MS. In this study, we investigated the reaction mechanism by ESI-MS

and ^1H NMR and, moreover, explored the electronic effects on the reaction when using acetic acid and methanol as cosolvents.

This study focused on the $\text{Pd}(\text{OAc})_2$ -catalyzed acetoxylation or methoxylation of 2-phenylpyridine (**3**) with $\text{PhI}(\text{OAc})_2$ as oxidant. The results of previous mechanistic research suggest that high-oxidation-state palladium intermediates^{2a,c,7} exist in this reaction, involving bimetallic $\text{Pd}(\text{III})$ complex **1** and monomeric $\text{Pd}(\text{IV})$ complex **2** (Scheme 1). However, we

Scheme 1. Reported High-Oxidation-State Pd Intermediates



detected a new complex by ESI-MS during the progress of the reaction. The mechanism of this type of reaction has three steps: (i) the direct C–H activation of substrate **3** to generate a cyclopalladated intermediate, (ii) the oxidation of $\text{Pd}(\text{II})$ complexes to afford high-oxidation-state $\text{Pd}(\text{III})$ or $\text{Pd}(\text{IV})$ intermediates, and (iii) the reductive elimination of $\text{Pd}(\text{III})$ or $\text{Pd}(\text{IV})$ intermediates to form the C–O products.

The structure of the cyclopalladated intermediate depends on the mole ratio of substrate **3** to $\text{Pd}(\text{OAc})_2$. When the mole ratio was 1:1, 10 μL of the reaction solution was dissolved in 1

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mL of methanol and analyzed by ESI-MS after a reaction time of 4 h (Figure 1).

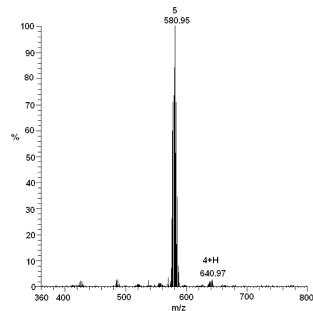
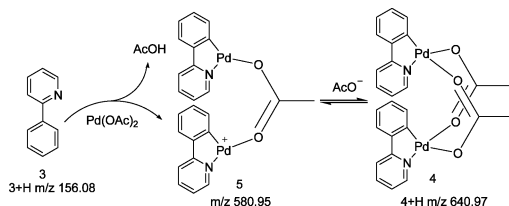


Figure 1. ESI(+)-MS spectrum acquired 4 h after the addition of 2-phenylpyridine to a solution of $\text{Pd}(\text{OAc})_2$ with a mole ratio of 1:1 at 40 °C.

The spectrum in Figure 1 suggests that the intermediates were bimetallic Pd(II) complexes 4 and 5. An equilibrium exists between 4 and 5 during the reaction process, as shown in Scheme 2, and bimetallic complex 5 is the primary

Scheme 2. Proposed Mechanism for the C–H Activation of 2-Phenylpyridine with a Mole Ratio of 1:1



intermediate, having the greatest abundance in the reaction mixture. We propose that bimetallic complex 5 is most likely the catalyst's resting state during C–H functionalization. On the other hand, complex 5 may be formed from complex 4 during the ionization process by loss of an acetate ion. Using the optimal conditions for the acetoxylation of 3,^{2a} we monitored the oxidation of 4 and 5 with $\text{PhI}(\text{OAc})_2$ as an oxidant. A 10 μL aliquot of the resulting solution was dissolved in 1 mL of methanol and subjected to ESI-MS analysis after a reaction time of 15 min at –10 °C (Figure 2). Figure 2 shows the appearance of some new signals, which were attributed to the oxidation and reductive elimination of bimetallic Pd

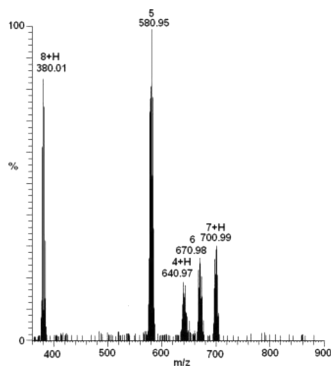
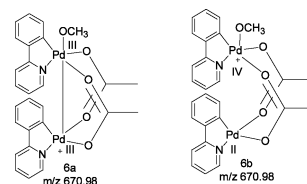


Figure 2. ESI(+)-MS spectrum obtained 15 min after the addition of $\text{PhI}(\text{OAc})_2$ to a solution of 4 and 5 at –10 °C.

complexes. The bimetallic Pd(III) intermediate 6 and protonated intermediate 7 were observed at m/z 670.98 and 700.99, respectively, and were formed by the addition reaction of methanol and acetic acid to bimetallic Pd(II) complexes using the iodine(III) reagent $\text{PhI}(\text{OAc})_2$ as an oxidant. Due to the difference in the σ -donating abilities of the methoxy and acetoxy groups,⁷ there are some differences between complexes 6 and 7. Intermediate 6 is most likely a bimetallic cationic species that has two possible formulations. This dimer can be viewed as a Pd(III) dimer with an effective bond between the two Pd centers (6a) or as a Pd(IV) species attached to a bridging Pd(II) complex (6b) (Scheme 3). In contrast,

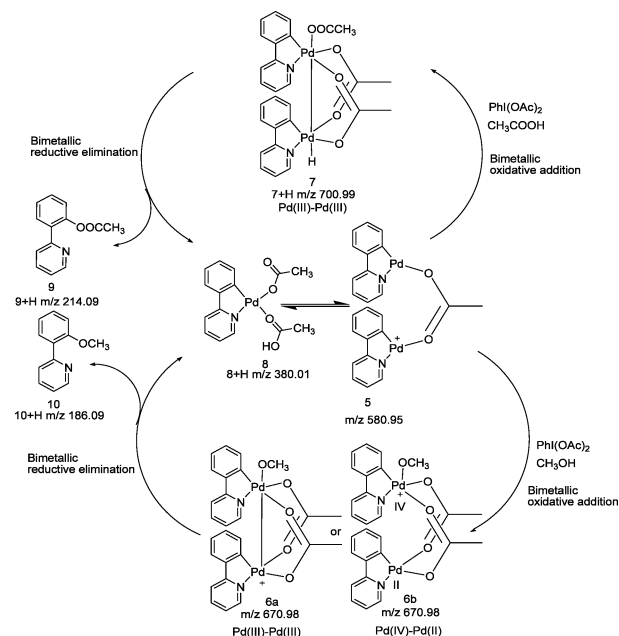
Scheme 3. Two Possible Formulations for Intermediate 6: Pd(III)–Pd(III) (6a) versus Pd(IV)–Pd(II) (6b)



complex 7 was a neutral bimetallic species. Notably, 7 underwent direct C–O bond-forming reductive elimination rather than disproportionation to Pd(IV) and Pd(II) species. At the same time, palladium complex 8 formed directly after reductive elimination from bimetallic Pd(III) complexes was detected at m/z 380.01. We examined the mixture with ^1H NMR spectroscopy at –30 °C, and the chemical shift of the aromatic region of the reaction mixture with $\text{PhI}(\text{OAc})_2$ (Figure S1a, Supporting Information) moved downfield relative to that of the starting material (Figure S1b, Supporting Information), which indicates the changes in binding interaction. One possible mechanism for this transformation is presented in Scheme 4.

We next used ESI-MS to investigate the resting state of [Pd] using excess 3 under the same reaction conditions. The results

Scheme 4. Proposed Catalytic Cycle for Pd(II)/Pd(III)



acquired with a 2:1 mole ratio of **3** to $\text{Pd}(\text{OAc})_2$ differed from those when using a 1:1 mole ratio (Figure 3). The abundant signal due to **11** at m/z 415.04 in Figure 3 indicates that monomer **11** acted as the dominant resting state of Pd during the catalytic cycle.

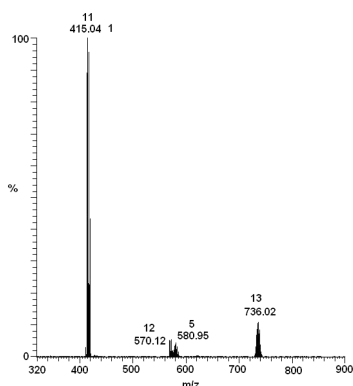


Figure 3. ESI(+)-MS spectrum obtained 4 h after the addition of 2-phenylpyridine to a solution of $\text{Pd}(\text{OAc})_2$ with a mole ratio of 2:1 at 40 °C.

In addition, bimetallic Pd(II) complex **5** and mononuclear Pd(II) complex **11** coexist under these conditions (Scheme S1, Supporting Information). Because the coordination ability of nitrogen is stronger than that of oxygen, complex **11** was afforded as the predominant product, which is consistent with the previously reported results. The reaction mixture was monitored by ^1H NMR spectroscopy at -30 °C (Figure S2a, Supporting Information), and the ^1H NMR spectrum showed that monomer **11** was the main product, which is consistent with the literature reported by Sanford.⁸ Next, we analyzed the high-oxidation-state Pd intermediates when using $\text{PhI}(\text{OAc})_2$ as an oxidant. Similarly, the oxidation reaction mixture was analyzed by ESI-MS under optimal conditions (Figure 4).

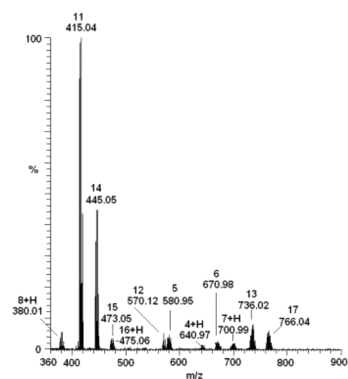


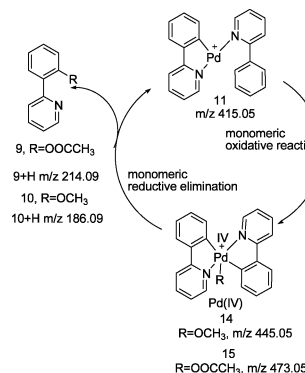
Figure 4. ESI(+)-MS spectrum obtained 30 min after the addition of $\text{PhI}(\text{OAc})_2$ to a solution of 2-phenylpyridine and $\text{Pd}(\text{OAc})_2$ at a ratio of 2:1 at -10 °C.

Some new signals not found in the spectrum in Figure 3 appeared, including signals for high-oxidation-state Pd intermediates and palladium complexes formed from the reductive elimination of bimetallic Pd(III) or monomeric Pd(IV) intermediates. These results indicate that Pd(II)–Pd(III) and Pd(II)–Pd(IV) catalytic cycles maybe coexist under these conditions. Meanwhile, the binding interaction was monitored by changes in the chemical shift. The chemical shift of the

aromatic region (Figure S2b, Supporting Information) moved downfield in comparison to that of the starting material (Figure S2a, Supporting Information).

There were several Pd(II) complexes formed via reductive elimination from Pd(III) and Pd(IV) mixed methoxide/acetate intermediates, and complex **11** was afforded as the predominant intermediate. A possible mechanism is proposed for the Pd(IV)–Pd(II) transformation (Scheme 5) and the Pd(III)–

Scheme 5. Proposed Catalytic Cycle for Pd(II)–Pd(IV)



Pd(II) transformation (Scheme 4). The mechanisms proposed in Schemes 4 and 5 revealed that the structure of the high-oxidation-state Pd intermediates was controlled by the steric/electronic characteristics of **3** and solvents.

The accurate masses of all the palladium ions determined by LTQ Orbitrap XL MS and the theoretical masses are shown in Table 1. None of the relative errors of detection were greater

Table 1. Comparison of the Results of Accurate Mass Determination by LTQ Orbitrap XL MS and the Masses Calculated for the Proposed Ion Structures^a

| compd | ion elemental composition | measd m/z | calcd m/z | rel error (ppm) |
|--------|---|-------------|-------------|-----------------|
| 4 + H | $\text{C}_{26}\text{H}_{23}\text{N}_2\text{O}_4\text{Pd}_2^+$ | 640.9725 | 640.9726 | −0.16 |
| 5 | $\text{C}_{24}\text{H}_{19}\text{N}_2\text{O}_2\text{Pd}_2^+$ | 580.9515 | 580.9515 | 0.00 |
| 6 | $\text{C}_{27}\text{H}_{25}\text{N}_2\text{O}_3\text{Pd}_2^+$ | 670.9833 | 670.9832 | 0.15 |
| 7 + H | $\text{C}_{28}\text{H}_{27}\text{N}_2\text{O}_6\text{Pd}_2^+$ | 700.9934 | 700.9937 | −0.43 |
| 8 + H | $\text{C}_{15}\text{H}_{16}\text{NO}_4\text{Pd}^+$ | 380.0109 | 380.0109 | 0.00 |
| 11 | $\text{C}_{22}\text{H}_{17}\text{N}_2\text{Pd}^+$ | 415.0422 | 415.0421 | 0.24 |
| 12 | $\text{C}_{33}\text{H}_{26}\text{N}_3\text{Pd}^+$ | 570.1157 | 570.1156 | 0.18 |
| 13 | $\text{C}_{35}\text{H}_{28}\text{N}_3\text{O}_2\text{Pd}_2^+$ | 736.0249 | 736.0250 | −0.14 |
| 14 | $\text{C}_{23}\text{H}_{19}\text{N}_2\text{OPd}^+$ | 445.0527 | 445.0527 | 0.00 |
| 15 | $\text{C}_{24}\text{H}_{19}\text{N}_2\text{O}_2\text{Pd}^+$ | 473.0472 | 473.0476 | −0.85 |
| 16 + H | $\text{C}_{24}\text{H}_{21}\text{N}_2\text{O}_2\text{Pd}^+$ | 475.0627 | 475.0632 | −1.05 |
| 17 | $\text{C}_{36}\text{H}_{30}\text{N}_3\text{O}_3\text{Pd}_2^+$ | 766.0354 | 766.0355 | −0.13 |

^aThe values are reported for ^{106}Pd for monomeric Pd complexes and ^{106}Pd and ^{108}Pd for bimetallic Pd complexes.

than 2 ppm, and all of the experimental isotopic distributions of the Pd species matched the theoretical isotopic distributions (Figure S3a–k, Supporting Information).

In summary, this study used ESI-MS and ^1H NMR to identify the mechanism of the Pd-catalyzed ligand-directed C–H methoxylation and acetoxylation of phenylpyridine under different conditions. The reaction produces dimeric high-oxidation-state Pd intermediates **6** and **7** when using a 1:1 mole ratio of **3** to $\text{Pd}(\text{OAc})_2$. Complex **7** is a dimeric Pd(III)–Pd(III) species, in which the Pd–Pd center inserts into an O–

H bond. Intermediate **6** can be viewed as a mixed-valence Pd(IV)–Pd(II) complex or as a Pd(III)–Pd(III) dimer due to the electronic effects of the methoxyl group. When using excess 2-phenylpyridine, Pd(IV) methoxide and acetate are afforded as the primary intermediates, a result that is attributed to the steric/electronic characteristics of **3**. The binding interaction was monitored by ^1H NMR spectroscopy to help in understanding the mechanism of this reaction. We hope that this mechanistic investigation will afford important insight into Pd-catalyzed oxidative reactions.

■ ASSOCIATED CONTENT

📄 Supporting Information

Text, schemes, and figures giving full experimental procedures and additional characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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