Mass spectrometry

Probing the Mechanism of the Palladium-Catalyzed Addition of Organoboronic Acids to Allenes in the Presence of AcOH by ESI-FTMS**

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The products of transition-metal-catalyzed reactions are usually explained and predicted in terms of four elementary reactions.[1] However, deduction of the real mechanism

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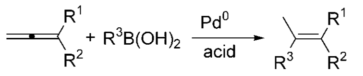
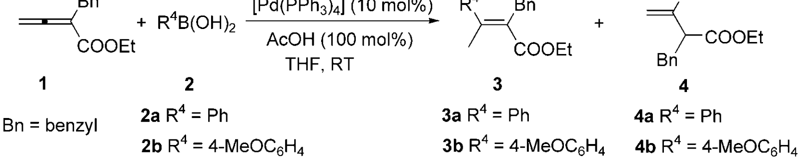
usually requires the isolation and characterization of organometallic species, which is usually not easy and is often time-consuming.[2] Thus, the interception and detection of reaction intermediates by instrumental analysis is a facile and reliable alternative method.[3–5] Molecular analysis by mass spectrometry (MS) has greatly benefited from the development of electrospray ionization (ESI) techniques,[6,7] since molecules and supramolecules of high polarity and molecular complexity can be easily ionized by ESI for investigation by MS.[4,5] ESI-MS is a technique that allows the ions present in solution to be transferred into the gas phase, where they can be analyzed and eventually characterized, with minimal fragmentation. Thus, straightforward analytical applications of ESI-MS to the characterization of organometallic intermediates have started to catch the attention of chemists.[8] Here we report our recent observation of the high resolution and high-mass-accuracy MS characterization of several organometallic species, which leads to a better understanding of the reaction mechanism of the palladium-catalyzed highly regio- and stereoselective addition of organoboronic acids to allenes in the presence of AcOH.

Although allenes have been considered as highly unstable,[9] recent studies show that they demonstrate useful reactivities and selectivities.[9–11] During our systematic study on the chemistry of allenes,[12] we have developed a palladium-catalyzed highly regio- and stereoselective hydroarylation or hydroalkenylation of allenes with organic boronic acids that gives tri- or tetrasubstituted alkenes (Scheme 1).[13] Despite the importance of its synthetic utility this reaction still has a number of unaccountable features, including the mechanistic details.



Scheme 1. The Pd-catalyzed addition reaction of allenes with organoboronic acids in the presence of an acid.

After some preliminary studies, we successfully found that the ESI-FTMS monitoring of the [Pd(PPh$_3$)$_4$]-catalyzed reaction of 2,3-allenoate with two organoboronic acids (**2a** and **2b**, Scheme 2) in the presence of AcOH in THF yielded some interesting information about the reaction intermediates. A solution of allenoate **1**[14] (0.05 mmol), organoboronic acid (0.1 mmol), [Pd(PPh$_3$)$_4$] (0.005 mmol), and AcOH (0.05 mmol) in THF (6 mL) was stirred at room temperature under N$_2$ atmosphere for the time indicated in Figure 1.[13] Then, 20 µL of this solution was diluted with 80 µL of methanol and transferred into the ESI source at a flow rate of 10 µL min^{-1} for the MS detection.



Scheme 2. The reaction of a 2,3-allenoate with two organoboronic acids, as monitored by ESI-FTMS.

The palladium intermediates involved in the catalytic cycle were intercepted, detected, and characterized by high resolution accurate mass measurements of their corresponding ions with the ESI-FTMS instrument in the positive-ion mode. After three minutes of the reaction with organoboronic acid **2a**, ions assigned to intermediate **5** (principal ion of *m/z* 689.1004; calcd. for $C_{38}H_{33}O_2P_2{}^{106}Pd^+$: *m/z* 689.1003; Figure 1 a) and the by-product **6** (principal ion of *m/z* 465.2276; calcd. for $C_{28}H_{33}O_6{}^+$: *m/z* 465.2277; Figure 1 a) were detected.

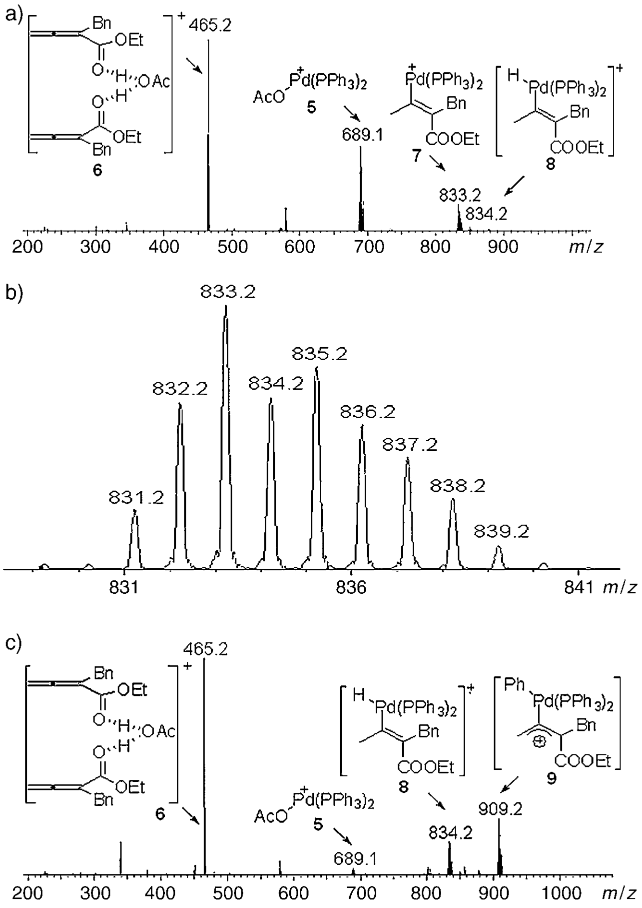
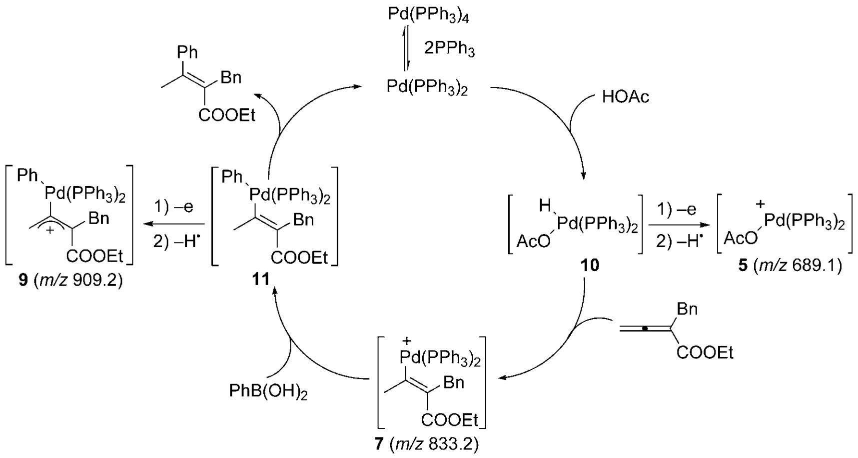


Figure 1. ESI-(+)-MS of the sample taken at a) 3 min and c) 2 h after mixing allenoate **1** and organoboronic acid **2a**. b) Experimental isotopic distribution of the mixture of **7** and **8**.

The composition of the major cationic intermediates changes dramatically with time. Continuous monitoring of these intermediates by ESI-FTMS also allowed us to detect three other ions: the palladium cation **7** (principal ion of *m/z* 833.1993; calcd. for $C_{49}H_{45}O_2P_2{}^{106}Pd^+$: *m/z* 833.1945; Figure 1 a), which usually disappeared five minutes after initiation of the reaction, the palladium cation **8** (principal ion of *m/z* 834.2025; calcd. for $C_{49}H_{46}O_2P_2{}^{106}Pd^{\cdot+}$: *m/z* 834.2023; Figure 1 a and Figure 1 c), which might result from the oxidation of the neutral intermediate HPd(PPh$_3$)$_2$–vinyl species during the ESI process,[15,16] and the cationic π-allyl intermediate **9** (principal ion of *m/z* 909.2265; calcd. for $C_{55}H_{49}O_2P_2{}^{106}Pd^+$: *m/z* 909.2259; Figure 1c), which may be formed by sequential oxidation during the ESI process and elimination of H$^\bullet$ from the (η^3-allyl)palladium complex in the gas phase.[8,17,18] Similar results were observed for organoboronic acid **2b** (see the Supporting Information). All the experimental isotopic distributions of the palladium-containing species matched the theoretical isotopic distributions, as simulated with the Bruker Xmass 6.1.2 program.



Scheme 3. Proposed catalytic cycle for the palladium-catalyzed addition of an organoboronic acid to an allene in the presence of AcOH based on the MS study.

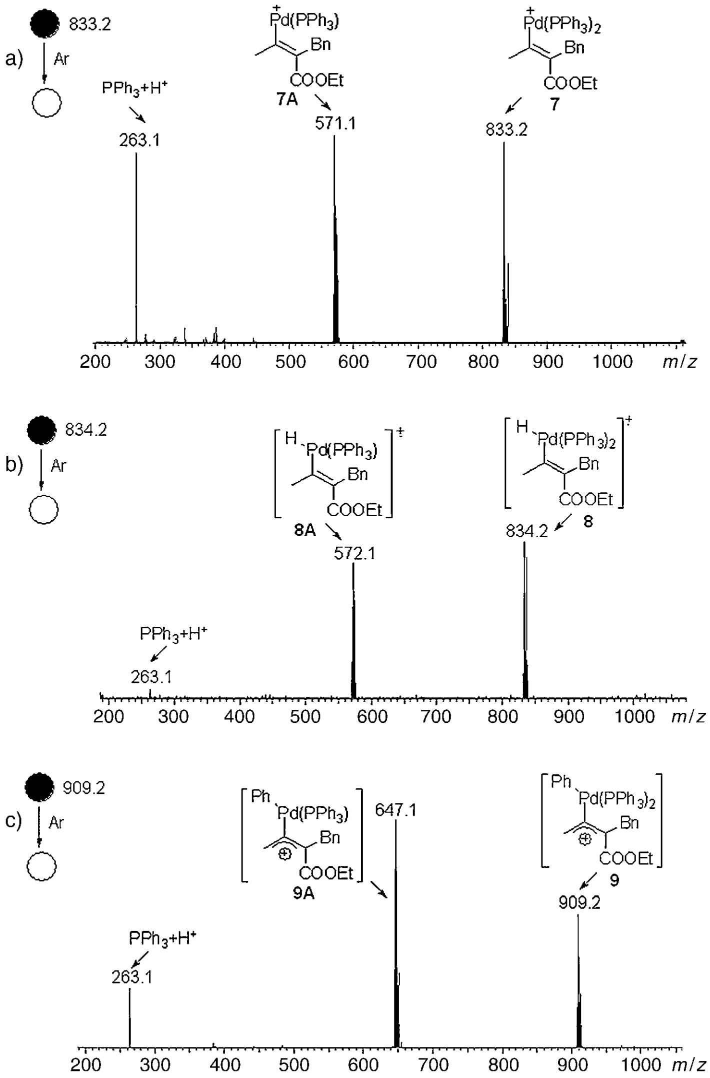


Figure 2. ESI-(+)-MS/MS of a) intermediate **7** (principal ion of *m/z* 833.1993), b) intermediate **8** (principal ion of *m/z* 834.2025), and c) intermediate **9** (principal ion of *m/z* 909.2265).

For further structural characterization of the intermediates of this reaction, all isotopolog ions forming the isotopic clusters of **7**, **8**, and **9** were isolated for a SORI-CAD (sustained off-resonance irradiation collision-activated dissociation) experiment with argon in a tandem mass spectrometric analysis.[19] Figure 2a–c show that intermediates **7** (principal ion of *m/z* 833.1993), **8** (principal ion of *m/z* 834.2025), and **9** (principal ion of *m/z* 909.2265) yield palladium cations **7A** (principal ion of *m/z* 571.1046; calcd. for $C_{31}H_{30}O_2P^{106}Pd^+$: *m/z* 571.1029; Figure 2a), **8A** (principal ion of *m/z* 572.1105; calcd. for $C_{31}H_{31}O_2P^{106}Pd^{\bullet+}$: *m/z* 572.1107; Figure 2b), and **9A** (principal ion of *m/z* 647.1342; calcd. for $C_{37}H_{34}O_2P^{106}Pd^+$: *m/z* 647.1344; Figure 2c) by loss of one PPh_3 ligand. The above results allow us to propose a mechanism for the reaction, which is shown in Scheme 3 with organoboronic acid **2a** as an example. Firstly, the oxidative addition reaction between AcOH and Pd^0 affords the palladium hydride species **10**, which may undergo hydropalladation with the less-sterically hindered terminal C=C bond in the allene moiety, with elimination of OAc^-, to afford alkenylpalladium intermediate **7**.[20] Transfer of the aryl group from the arylboronic acid to **7** gives **11**, which affords the final product by reductive elimination.[21]

In conclusion, we have successfully characterized some key intermediates in the Pd^0-catalyzed addition reaction of allenes with boronic acids in the presence of AcOH by ESI-FTMS, and this has led to the mechanism shown in Scheme 3. Further studies in this area are being carried out in our laboratory.

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