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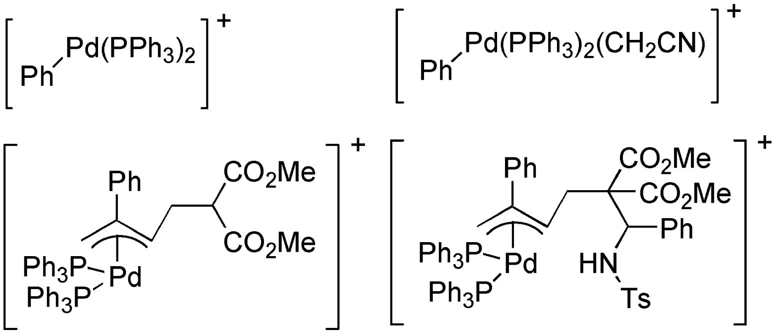

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ESI-MS Studies on the Mechanism of Pd(0)-Catalyzed Three-Component Tandem Double Addition-Cyclization Reaction

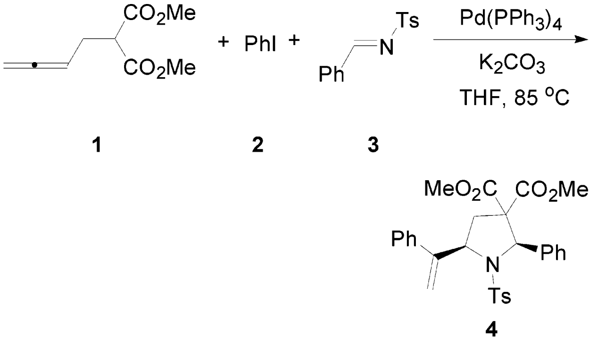
Hao Guo,[†] Rong Qian,[‡] Yuanxi Liao,[‡] Shengming Ma,*[,†] and Yinlong Guo*[,‡]

Contribution from the State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. China, and Shanghai Mass Spectrometry Center, Shanghai Institute of Organic Chemistry Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. China

Received April 21, 2005; E-mail: masm@mail.sioc.ac.cn; ylguo@mail.sioc.ac.cn

Abstract: Four cationic palladium intermediates have been characterized by the high-resolution ESI−FTMS technology, on the basis of which a mechanism was proposed for the Pd(0)-catalyzed three-component tandem double addition cyclization of organic halides, 2-(2,3-allenyl)malonates, and imines.

Recently, ESI-MS[1] has been used as an effective method for the characterization of reaction intermediates, thus providing direct evidence for the mechanism of multistep organic reactions.[2,3] During our study on the chemistry of allenes,[4,5] we have developed the Pd(0)-catalyzed three-component tandem double addition-cyclization reaction of 2-(2,3-allenyl)malonate **1**, iodobenzene **2**, and imine **3** for the stereoselective synthesis of *cis*-pyrrolidine derivative (eq 1).[6] In principle, there are two types of mechanisms: (1) carbopalladation forming π-allyl palladium species and (2) azapalladation-reductive elimination mechanism.[7] In this paper, we wish to report our recent study on the mechanism of this transformation by characterization of four organopalladium intermediates with ESI-MS technique.



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Apparatus and Methods

All MS and tandem MS experiments were performed on a Bruker Daltonics APEX III ESI-FTMS equipped with a 7.0 T shielded superconducting magnet. The vacuum was maintained by means of mechanical vacuum pumps followed by turbomolecular pumps in two different regions: ion source (maintained $\sim 3 \times 10^{-7}$ Torr) and cell region (maintained $\sim 6 \times 10^{-10}$ Torr). The ions were generated from an external electrospray ionization source. Typically, the electrospray flow rate is 10 μL·min^{-1}, which was maintained by a syringe pump. The spray was directed into a heated glass capillary drying tube with Ni-coating in both ends remaining at a temperature of about 450 K. Typically, a high voltage of about 4500 V is applied between the endplate and the spray needle. Then, the ions are accumulated in the RF-only hexapole ion storage region for 0.3 s and are focused and steered through the ion transfer region. They were finally transferred into the "infinity" cell with a "sidekick" voltage perpendicular to magnetic field for trapping and detecting. All of the parameters from the ion generation to the trapping were optimized on the tuning pars on the basis of the maximum intensity that the parent ion achieved. In tandem MS experiments, the parent ion of interest was isolated with the isolation sweep attenuation/isolation pulse length of 18 dB/2 ms and then was collided with argon gas. The collision gas argon was introduced into the cell through a pulsed valve. Mass spectra were acquired in the positive ion mode with broad-band detection (eight scans per experiment) from *m*/*z* 100 to 1500 using 256 K data points. So,

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[†] State Key Laboratory of Organometallic Chemistry.

[‡] Shanghai Mass Spectrometry Center.

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the mass spectra reflect the dissociation process of the isolated ion in 1.0-s time window of delay. All experimental sequences, including scan accumulation and data processing, were performed with Bruker Xmass 6.1.2 software on a DELL computer with 256-MB RAM, 40-GB hard drive. The instrument was calibrated externally with PEG400 and PEG800 methanol solutions.

Results and Discussion

A solution of iodobenzene **2** (0.06 mmol) and $Pd(PPh_3)_4$ (0.0025 mmol) in THF (6 mL) was stirred at room temperature in a nitrogen atmosphere. After 30 min, 5 μL of the solution was taken and diluted with 100 μL of the mixed CH_3CN and CH_3OH (v/v = 1:1) and transferred into the ESI source by a syringe pump at a flow rate of 10 $\mu L\cdot min^{-1}$ for the MS detection. In the beginning, a CapExit voltage of 52.6 V was applied and a stable signal of ion **5** (principal ion of *m/z* 707.1263, calcd for $C_{42}H_{35}P_2Pd^+$: *m/z* 707.1259) was observed (see Figure S1 in the Supporting Information). Then, the CapExit voltages ranging from 45 to 65 V were applied, however, no obvious difference was observed. Thus, a CapExit voltage of 52.6 V was chosen for the following study. Then, the reaction temperature was raised from room temperature to 85 °C, and at this temperature, the signal of ion **5** was still clearly seen (see Figure S2 in the Supporting Information). Thus, the detection can be made with the sample from the reaction conducted at 85 °C.[6] After some study, we also observed that CH_3CN was the best solvent for diluting the sample taken from the reaction mixture (vide infra). Thus, we fixed the standard procedure for MS detection: 5 μL of the sample was taken from the reaction mixture stirred at 85 °C in a nitrogen atmosphere and was diluted with 100 μL of CH_3CN, if not otherwise stated. Then, a syringe pump was used to introduce the diluted sample into the ESI source at the rate of 10 $\mu L\cdot min^{-1}$ with a CapExit voltage of 52.6 V for the MS detection.

With the standard procedure for MS detection, we started to capture any possible intermediates in the reaction process by gradual addition of the reactants.

(1) A solution of 2-(2,3-allenyl)malonate **1** (0.05 mmol), iodobenzene **2** (0.06 mmol), and $Pd(PPh_3)_4$ (0.0025 mmol) in THF (6 mL) was stirred at 85 °C in a nitrogen atmosphere. After the standard treatment, the signals of ions **5** and **7** (principal ion of *m/z* 891.1999, calcd for $C_{51}H_{47}O_4P_2Pd^+$: *m/z* 891.1997) were detected (see Figure S3 in the Supporting Information).

(2) A solution of 2-(2,3-allenyl)malonate **1** (0.05 mmol), iodobenzene **2** (0.06 mmol), imine **3** (0.06 mmol), and $Pd(PPh_3)_4$ (0.0025 mmol) in THF (6 mL) was stirred at 85 °C in a nitrogen atmosphere. After the same treatment for the samples taken between the reaction time of 30 min and 2 h, only the signals of ions **5** and **7** were detected (see Figure S4 in the Supporting Information).

(3) A solution of 2-(2,3-allenyl)malonate **1** (0.05 mmol), iodobenzene **2** (0.06 mmol), imine **3** (0.06 mmol), $Pd(PPh_3)_4$ (0.0025 mmol), and K_2CO_3 (0.05 mmol) in THF (6 mL) was stirred at 85 °C in a nitrogen atmosphere. In the first 5 min, ions **5** and **6** (principal ion of *m/z* 748.1527, calcd for $C_{44}H_{38}NP_2Pd^+$: *m/z* 748.1525) were detected (Figure 1a);[3e] at 20 min, ions **5**−**7** were detected (Figure 1b); at 40 min, ions **5**−**8** (principal ion of *m/z* 1150.2657, calcd for $C_{65}H_{60}NO_6P_2SPd^+$: *m/z* 1150.2666) were detected. Meanwhile, the signals of ions **9** (*m/z* 223.0366, calcd for $C_9H_{12}O_4K^+$: *m/z* 223.0369) generated from 2-(2,3-allenyl)malonate **1**, **10** (*m/z* 298.0297, calcd for $C_{14}H_{13}NO_2SK^+$: *m/z* 298.0301) generated from imine **3**, **11** (*m/z* 558.1348, calcd for $C_{29}H_{29}NO_6SK^+$: *m/z* 558.1351) formed from the product **4**, and **12** (*m/z* 1077.3075, calcd for $C_{58}H_{58}N_2O_{12}S_2K^+$: *m/z* 1077.3070, the K^+-bound dimmer of **4**) started to appear (Figure 1c).[8] After 5 h, the signal of ion **5** obviously became weaker while that of ion **6** disappeared (see Figure S5a in the Supporting Information). After 15 h, the signals of ions **5**, **8,** and **9** also disappeared (see Figure S5b in the Supporting Information). After 24 h, the signal of ion **7** became very weak (see Figure S5c in the Supporting Information). After 36 h, the signal of ion **7** disappeared, and only very strong signals of ions **10**−**12** could be detected (see Figure S5d in the Supporting Information).

At the begining, it was observed that the lifetime of ion **8** is very short and that its signal can only be detected occasionally. Then, the influence of the solvent used for diluting the sample such as CH_3OH, CH_3OH/H_2O (v/v = 10:1), CH_3CN, or CH_3CN/H_2O (v/v = 10:1) was studied, which indicated that CH_3CN is the best one. However, the lifetime of the ion **8** was still very short, that is, when a syringe pump was used to introduce the 100 μL of the diluted sample into the ESI source at the rate of 10 $\mu L\cdot min^{-1}$ for the MS detection, the signal of ion **8** could only be detected for the first 50 μL of the diluted sample, while for the rest 50 μL the signal became weaker and weaker. To observe a stable signal of ion **8**, the effect of the concentration of the sample was studied. When 25, 50, 200, and 400 μL of CH_3CN were applied for diluting the 5 μL sample, no better signal was observed. The best signal of ion **8** was observed when 5 μL of the sample was diluted with 100 μL of CH_3CN.

We also analyzed each individual reaction component by ESI−FTMS. No MS data was observed for the reactants **1**−**3** under the standard procedure for MS detection. Then, we used a solution of CH_3CN saturated with K_2CO_3 to prepare the sample, and the signals of ion **9** derived from **1** (see Figure S6a in the Supporting Information) and the signals of ion **10** derived from **3** (see Figure S6b in the Supporting Information) were observed while **2** still could not be detected in any form.

Furthermore, all the experimental isotopic distributions of the palladium-containing species **5**−**8** matched the theoretical isotopic distributions, which were simulated by Bruker Xmass 6.1.2 software (see Tables 1−4 in the Supporting Information).

For further structural characterization of these intermediates, all isotopologue ions forming the isotopic clusters of **5**−**7** were isolated for SORI-CAD (sustained off-resonance irradiation collision activated dissociation) experiment with argon in tandem mass spectrometric analysis. Figure 2a−c shows that (1) intermediate **5** yielded **5A** (*m/z* 339.1301, calcd for $C_{24}H_{20}P^+$: *m/z* 339.1297, Figure 2a); (2) the intermediate **6** displayed similar dissociation chemistry of **5** by the loss of acetonitrile at the first step to yield **5** and **5A** (Figure 2b); (3) intermediate **7** yielded **7A** (*m/z* 629.1088, calcd for $C_{33}H_{32}O_4PPd^+$: *m/z* 629.1084, Figure 2c) by the loss of one PPh_3 ligand.

For further structural assignment of the fragment **5A**, it was isolated for MS/MS/MS. Figure 3 shows that **5A** could yield

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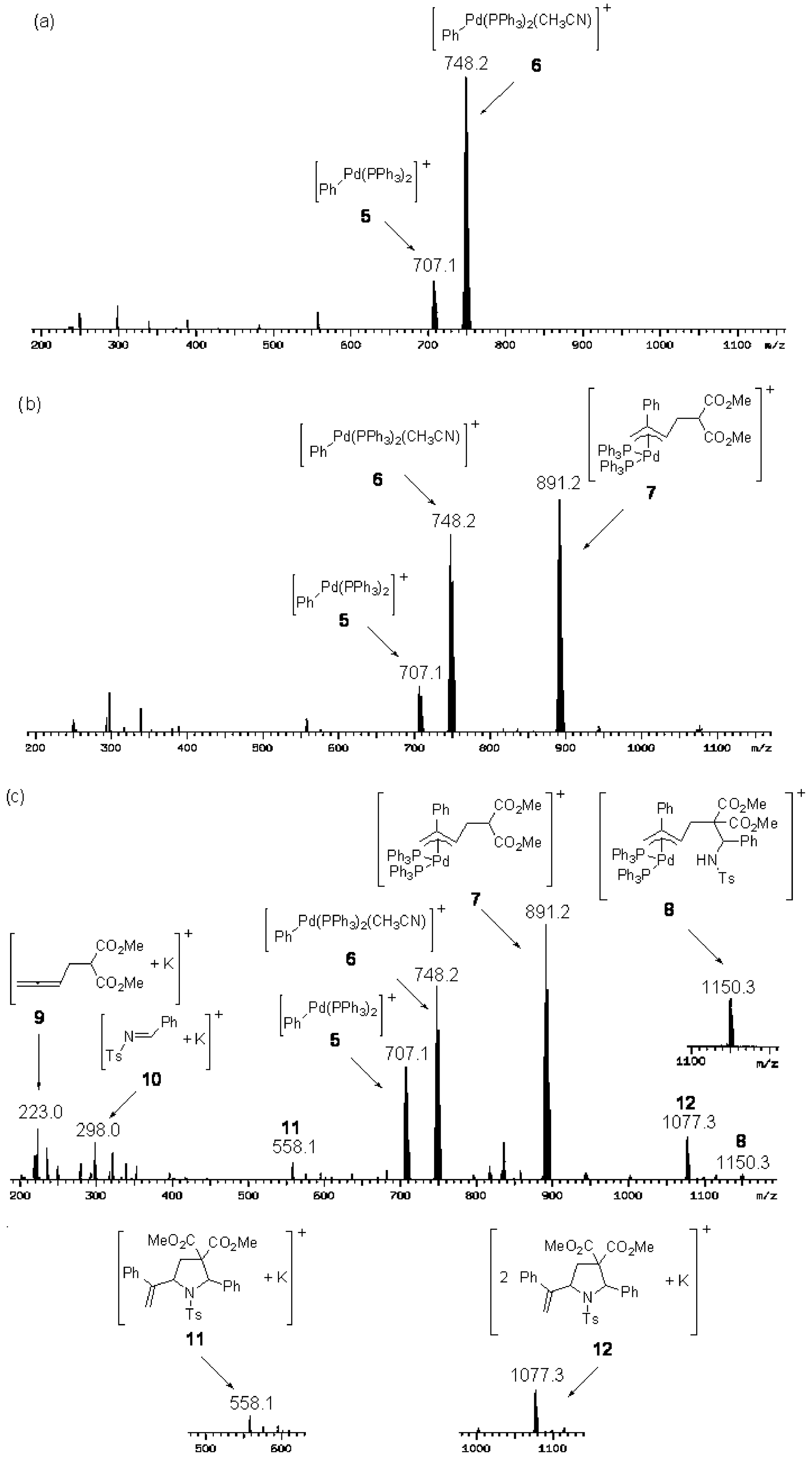

Figure 1. ESI(+)-MS carried out with the standard procedure for MS detection for the sample taken from the reaction mixture of 2-(2,3-allenyl)malonate **1** (0.05 mmol), iodobenzene **2** (0.06 mmol), imine **3** (0.06 mmol), $Pd(PPh_3)_4$ (0.0025 mmol), and K_2CO_3 (0.05 mmol) in THF (6 mL) stirred at 85 °C in a nitrogen atmosphere at the reaction time of (a) 5 min, (b) 20 min, and (c) 40 min.

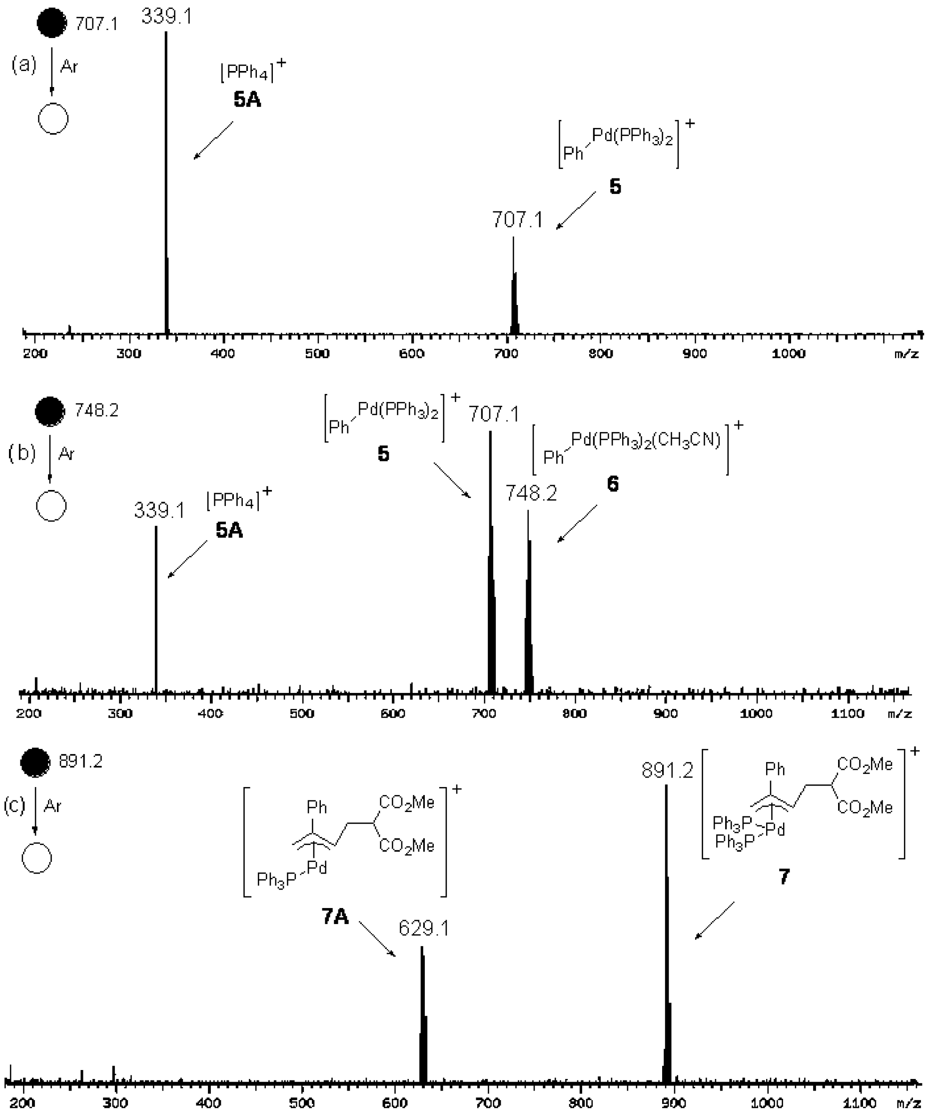

Figure 2. MS/MS for (a) the intermediate **5**, (b) the intermediate **6**, and (c) the intermediate **7**.

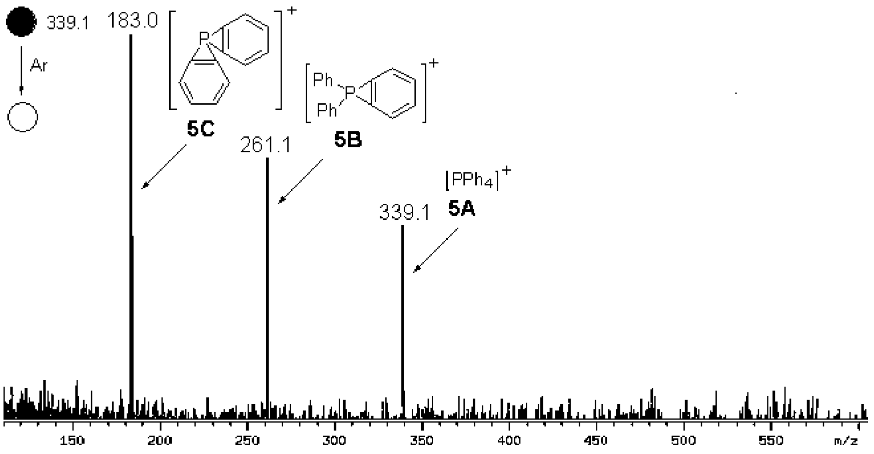

Figure 3. MS/MS/MS for the fragment **5A**.

5B (*m*/*z* 261.0831, calcd for $C_{18}H_{14}P^+$: *m*/*z* 261.0828) and **5C** (*m*/*z* 183.0360, calcd for $C_{12}H_8P^+$: *m*/*z* 183.0358) by loss of one molecule of benzene or two molecules of benzene.

Through accurate mass determinations, all the ions have been fully characterized (Table 1).

With the accurate characterization of all these intermediates by ESI−FTMS, we excluded the azapalladation-reductive elimination pathway.[7] Thus, a mechanism is proposed as shown in Scheme 1. Oxidative addition of PhI with $Pd(PPh_3)_2$, formed through the disassociation of two molecules of PPh_3 from

Scheme 1. The Mechanism of Pd(0)-Catalyzed Three-Component Tandem Double Addition-Cyclization Reaction Based on the Study of ESI−FTMS

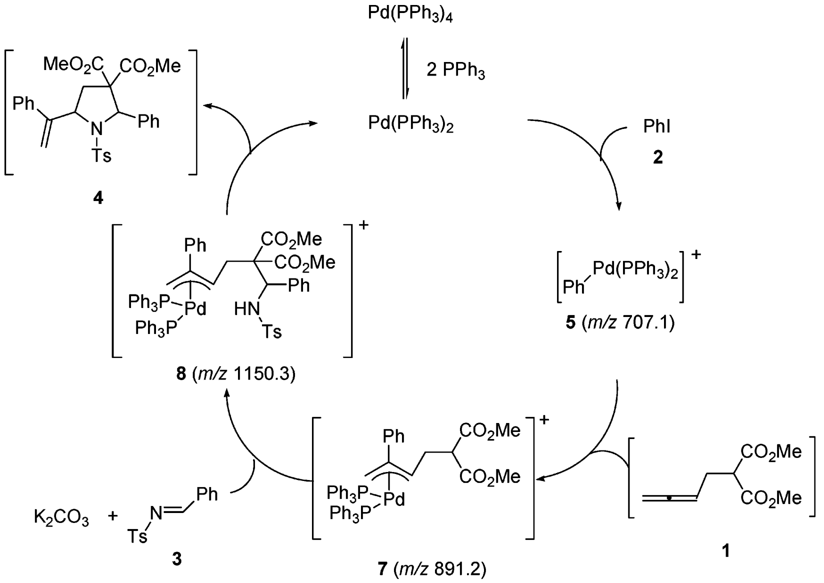

Table 1. The Results of Accurate Mass Determinations of Main Intermediates or Fragment Ions by ESI−FTMS[a]

compounds	Ions' elemental composition	experimental mass	theoretical mass	relative error (ppm)
5	$C_{42}H_{35}P_2Pd^+$	707.1263	707.1259	0.6
5A	$C_{24}H_{20}P^+$	339.1301	339.1297	1.2
5B	$C_{18}H_{14}P^+$	261.0831	261.0828	1.1
5C	$C_{12}H_8P^+$	183.0360	183.0358	1.1
6	$C_{44}H_{38}NP_2Pd^+$	748.1527	748.1525	0.3
7	$C_{51}H_{47}O_4P_2Pd^+$	891.1999	891.1997	0.2
7A	$C_{33}H_{32}O_4PPd^+$	629.1088	629.1084	0.6
8	$C_{65}H_{60}NO_6P_2SPd^+$	1150.2657	1150.2666	−0.8
9	$C_9H_{12}O_4K^+$	223.0366	223.0369	−1.3
10	$C_{14}H_{13}NO_2SK^+$	298.0297	298.0301	−1.3
11	$C_{29}H_{29}NO_6SK^+$	558.1348	558.1351	−0.5
12	$C_{58}H_{58}N_2O_{12}S_2K^+$	1077.3075	1077.3070	0.5

[a] The values with ^{106}Pd are reported.

$Pd(PPh_3)_4$, would yield intermediate **5**,[9,10] which can undergo carbopalladation[10] with 2-(2,3-allenyl)malonate **1** yielding the π-allyl palladium intermediate **7**. Deprotonation of the malonate moiety in **7** and the subsequent addition with imine **3** would yield intermediate **8**.[11] Subsequent intramolecular allylic amination[12] would yield the product **4** and regenerate the catalytically active $Pd(PPh_3)_2$.

In conclusion, ESI−FTMS has been successfully applied to characterize four cationic palladium intermediates in the palladium(0)-catalyzed three-component tandem double addition cyclization of 2-(2,3-allenyl)malonate **1**, iodobenzene **2**, and imine **3**. With this information, a mechanism was proposed. Further studies in this area are being pursued in our laboratory.

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Supporting Information Available: Experimental data not listed in the text and theoretical isotopic distribution of the palladium intermediate ions. This material is available free of charge via the Internet at http://pubs.acs.org.

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