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The Mechanism of the Stille Reaction Investigated by Electrospray Ionization Mass Spectrometry

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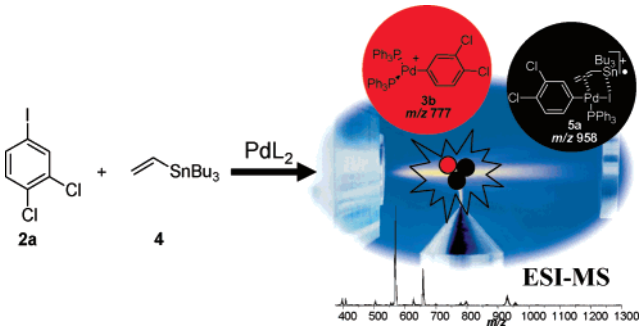

On-line monitoring of Stille reactions was performed via direct infusion electrospray ionization mass spectrometry (ESI-MS) and its tandem version (ESI-MS/MS). When operated in the positive ion mode, ESI(+)-MS was able to transfer, directly from solution to the gas phase, the species involved in all main steps of a Stille reaction, that is, the catalytically active palladium species $Pd(PPh_3)_2$, in its molecular ion form as well as the key cationic Pd(II) intermediates, including cyclic IPd-(CH_2CH)Sn species. When searching for anionic species, ESI(−)-MS monitoring showed I^- as the only anion detectable in the reaction medium. A detailed catalytic cycle for a Stille reaction was elaborated in which reaction intermediates and the previously elusive catalytically active Pd(0) species are shown in association with the respective ionic species intercepted by ESI-MS and further characterized by ESI-MS/MS.

The discovery of many palladium-catalyzed reactions has spurred intensive research on the application and mechanistic aspects of this useful synthetic methodology.[1] The Stille reaction[1b] is one of the most general, selective, and multifaceted palladium-catalyzed reactions used to construct C−C bonds.[1c] It proceeds via Pd-catalyzed coupling of organic electrophiles such as unsaturated halides, sulfonates, or triflates with functionalized organostannanes. Although it is nowadays considered a standard method in organic synthesis, recent modifications and variants of the Stille reaction have opened a multitude of new and highly attractive synthetic possibilities. Therefore, much effort has been dedicated to understand its mechanistic details so as to guide the use of Stille reactions in the most rational way.[2] The well-known working-model mechanism of the Stille[2b] reaction is based on three reaction steps: (i) oxidative addition, (ii) transmetalation, and (iii) reductive elimination (Scheme 1).

Palladium(II) species such as $Pd(OAc)_2$ are usually employed as the Pd(0) precursors. However, whereas PdL_2 is likely to be the actual catalytic species, its in situ formation has remained elusive. For the Pd intermediates, there have been several reports on their interception and characterization, but these studies have used mainly model reactions outside the real catalytic cycle.[3] Structural evidence for main intermediates in a real, complete catalytic cycle of a Stille reaction has been rare,[4] as the report by Casado and co-workers on the characterization of main Stille intermediates by ^1H, ^{19}F, and ^{31}P NMR spectroscopy.[4a]

Comprehensive mechanistic investigations usually require kinetic data based on long time scale monitoring usually provided by UV, IR, or NMR spectroscopy. However, these techniques are not often suitable to the short time scale required for investigating transient species, whereas unequivocal assignments of UV and IR bands or NMR peaks and couplings, particularly for more complex or transient structures, may be challenging and sometimes unfeasible. Electrochemical techniques have been used to monitor short-lived species, but they provide limited structural information on the detected intermediates. Using electrochemical techniques, Amatore and co-workers have obtained evidence for anionic Pd(0) and Pd(II) intermediates and then proposed a new catalytic cycle for Pd-catalyzed cross-coupling reactions in which anionic palladium species are involved.[4b,c] Recently, these authors studied the transmetalation step of the Stille reaction in DMF in the presence of $AsPh_3$ and established that it proceeds from $PhPdI(AsPh_3)$DMF species.[4d]

Direct infusion electrospray ionization[5] mass (and tandem mass) spectrometry [ESI-MS(/MS)] has recently emerged as a fast, sensitive, and selective technique able to probe reaction mechanisms[6] and to evaluate catalysts.[7] ESI-MS provides

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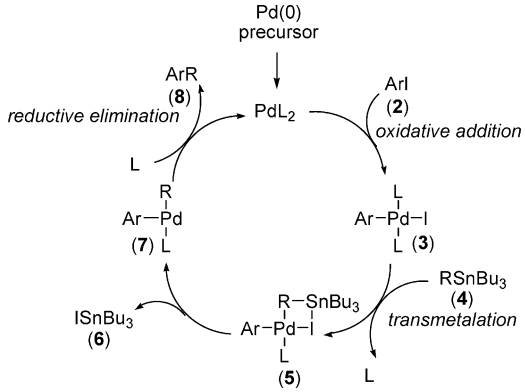
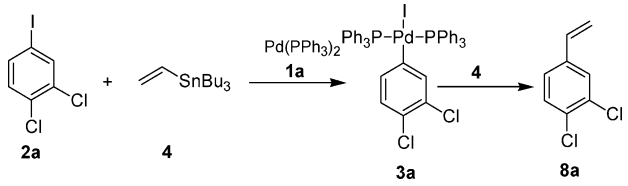
SCHEME 1



SCHEME 2



continuous "snapshots" of the ionic composition (anions and cations) of the reaction medium since it gently[8] transfers reagents and products, but most particularly reaction intermediates (ionic species or ionized forms of neutral species) directly from solution to the gas phase in which MS and MS/MS characterization can be performed.[6j] Herein we report a ESI-MS(/MS) investigation in which key Pd intermediates involved in the major steps of a real catalytic cycle of a Stille reaction have been intercepted and characterized.

The Catalytically Active Pd(0) Species. We initiated our investigation by the Stille coupling reaction of vinyltributyltin (**4**) with 3,4-dichloroiodobenzene (**2a**) promoted by Pd(0) precursors that is expected to form styrene derivative **8a** (Scheme 2). We searched first for the catalytically active Pd(0) species, supposedly **1a**, involved in the oxidative addition step (Scheme 1). In Stille reactions, coordinatively unsaturated 14π-electron PdL_2 species **1**, usually coordinated with weak donor ligands such as tertiary phosphanes, are reasonably assumed to constitute the catalytically active complex. $Pd(PPh_3)_4$,[9a,b] which occurs as a $Pd(PPh_3)_3$ complex in solution, is the most common Stille precatalyst.[9c] After the endergonic loss of a second phosphane ligand,[9d,e] the catalytically active species $Pd(PPh_3)_2$ is generated. It is proposed that phosphanes and water reduce the Pd(II) from the $Pd(OAc)_2$ precatalyst to generate the catalytically active species $Pd(PPh_3)_n$, but the in situ formation of such species has remained elusive.

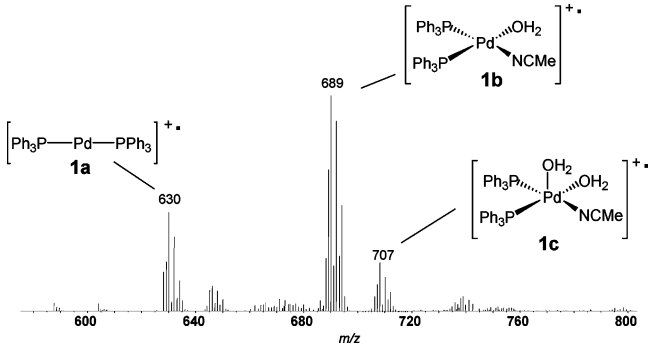


FIGURE 1. ESI(+)-MS of an acetonitrile solution of $Pd(OAc)_2/PPh_3$. The spectrum is shown across a narrow *m*/*z* range in which major Pd species were detected.

To investigate therefore the in situ formation of $Pd(PPh_3)_2$ (**1a**), we used either $Pd(OAc)_2/Ph_3P$ or $Pd(PPh_3)_4$ as precatalyst. Acetonitrile solutions of these precatalysts were directly infused into the ESI source operated in the positive ion mode so as to monitor, via ESI(+)-MS, the cationic species formed in solution (or during ESI) and eventually transferred to the gas phase. As Figure 1 exemplifies, for both $Pd(PPh_3)_4$ and $Pd(OAc)_2/PPh_3$ solutions, very similar spectra were acquired.

As shown in Figure 1, we found that indeed the catalytically active species we were "fishing" for, that is, $Pd(PPh_3)_2$ (PdL_2 in Scheme 1), were efficiently intercepted and characterized by ESI(+)-MS mainly as a typical cluster of isotopologue $[Pd(PPh_3)_2]^{+\bullet}$ ions ($\mathbf{1a}^{+\bullet}$), the most abundant of those being that of *m*/*z* 630. Besides $\mathbf{1a}^{+\bullet}$, its acetonitrile and water adducts $[Pd(PPh_3)_2(MeCN)(H_2O)]^{+\bullet}$ ($\mathbf{1b}^{+\bullet}$) of *m*/*z* 689 and $[Pd(PPh_3)_2(MeCN)(H_2O)_2]^{+\bullet}$ ($\mathbf{1c}^{+\bullet}$) of *m*/*z* 707 were also detected with characteristic *m*/*z* ratios and distributions of Pd isotopologue ions. Species **1a** is suggested therefore to be present in its neutral form in solution and to be oxidized to its respective molecular ion during the ESI process.[10] The solvent adducts $\mathbf{1b}^{+\bullet}$ and $\mathbf{1c}^{+\bullet}$ are most likely formed from $\mathbf{1a}^{+\bullet}$ during the ESI process.

The ^{106}Pd isotopologue ion of $\mathbf{1a}^{+\bullet}$ of *m*/*z* 630 was selected for ESI(+)-MS/MS characterization via collision-induced dissociation (CID). It dissociates mainly via a structurally diagnostic pathway that proceeds by the loss of PPh_3 to give $Ph_3PPd^{+\bullet}$ of *m*/*z* 368 followed by the loss of Pd to give $PPh_3^{+\bullet}$ of *m*/*z* 262. The somewhat uncommon loss of atomic palladium (^{106}Pd)[11] was confirmed via ESI(+)-MS/MS/MS[12] of the ion of *m*/*z* 368 ($Ph_3PPd^{+\bullet}$), which shows that the ion dissociates nearly exclusively by ^{106}Pd loss. The loss of Pd is likely governed by the thermochemistry associated with competition

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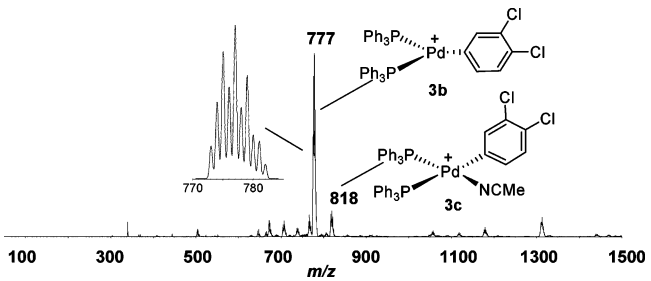
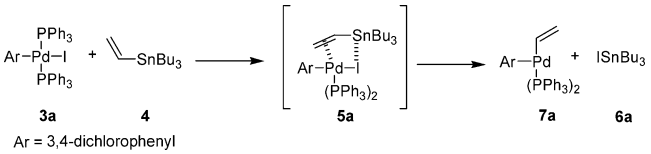


FIGURE 2. ESI(+)-MS of an acetonitrile solution of $Pd(PPh_3)_4$ after the addition of 3,4-dichloroiodobenzene **2a**.

SCHEME 3



for the electron (the IE of Ph_3P is much lower than Pd, that is, IE Pd = 8.3369 eV versus IE Ph_3P = 7.44 eV). Species $\mathbf{1a}^{+\bullet}$, that is $[Pd^0(PPh_3)_2]^{+\bullet}$, also dissociates by the loss of a neutral benzene molecule to form the minor fragment ion of *m*/*z* 552 (see Supporting Information Figures S1 and S2).

Stille Pd(II) Intermediates. After we succeeded in intercepting the main catalytic species $Pd(PPh_3)_2$ (**1a**), we searched next for species **3a** (Scheme 2) to be formed in the second step of the Stille reaction, that is, the oxidative addition of **1a** to 3,4-dichloroiodobenzene (**2a**). Figure 2 shows a typical ESI(+)-MS of the reaction mixture. Note the detection of a main Pd-containing ion that corresponds to the Pd(II) species $[(Ph_3P)_2Pd-C_5H_3Cl_2]^+$ (**3b**, $ArPdL_2^+I^-$) for which the ion of *m*/*z* 777 is the most abundant isotopologue. Note also the detection of the acetonitrile adduct $\mathbf{3c}^+$ of *m*/*z* 818. ESI-MS/MS characterization of $\mathbf{3b}^+$ was performed by selecting its isotopologue ion of *m*/*z* 777 for CID. As easily rationalized from its putative structure, $\mathbf{3b}^+$ was found to dissociate by the loss of a neutral PPh_3 molecule giving the fragment ion of *m*/*z* 515, whereas the phenyl cation rearrangement is likely to precede the dissociation that forms another major fragment ion: PPh_4^+ of *m*/*z* 339. Note that the loss of benzene from $\mathbf{1a}^{+\bullet}$ and the formation of Ph_4P^+ from $\mathbf{3b}^+$ as well as the loss of Ph_3P^+ from $\mathbf{7b}^+$ (see below) are all examples of P−C bond activation, for which there has been precedent in the literature.[13] The acetonitrile complex of $\mathbf{3b}^+$, that is $\mathbf{3c}^+$ of *m*/*z* 818, dissociates mainly by the loss of the CH_3CN ligand to give $\mathbf{3b}^+$ of *m*/*z* 777, as expected by the relative weakness of the Pd−L bond (see Supporting Information Figure S3). Next, we investigated the formation of intermediates **5a**, **6a**, and **7a** of the Stille reaction involved in the transmetalation and reductive elimination steps that occur after the addition of the vinylstannane **4a** (Scheme 3). Note that the use of a faster microreactor[14] was in this case unnecessary, actually inconvenient, since vinylstannane addition to the Pd(II) species required several minutes to proceed. We monitored

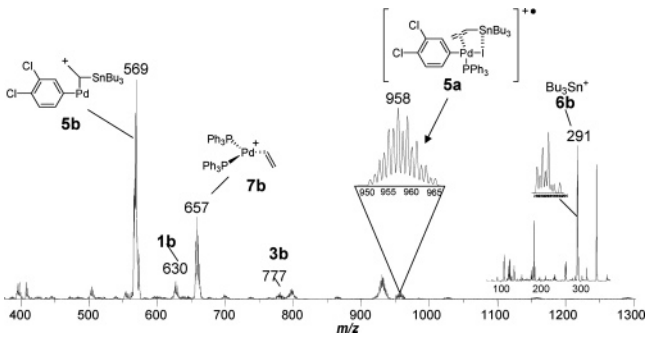
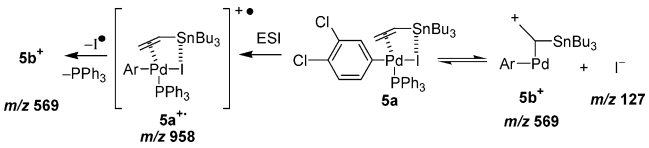


FIGURE 3. ESI(+)-MS of the Stille reaction of 3,4-dichloroiodobenzene (**2a**) and vinyltributyltin (**4a**) in acetonitrile mediated by $Pd(PPh_3)_4$.

SCHEME 4



the reaction occurring in an acetonitrile solution containing vinyltributyltin, $[Pd(PPh_3)_4]$, and **2a** by ESI(+)-MS from 30 s up to 2 h.

Initially, ESI(+)-MS data similar to those depicted in Figure 2 were acquired, but after 15 min, as Figure 3 illustrates, species **5a** involved in the transmetalation step was intercepted in the form of its molecular ion $\mathbf{5a}^{+\bullet}$ ($[Cl_2C_6H_3(PPh_3)IPd-CH(CH_2)-SnBu_3]^{+\bullet}$ of *m*/*z* 958) and mainly as the cationic $\mathbf{5b}^+$ of *m*/*z* 569. We rationalize that $\mathbf{5b}^+$ could have been sampled either directly from the reaction solution due to the ionization equilibrium of **5a** or be formed in the gas phase via dissociation of $\mathbf{5a}^{+\bullet}$ by the loss of both an iodide radical and neutral PPh_3, or from both processes (Scheme 4). As shown by an inset in Figure 3, another interesting ion of *m*/*z* 291 was intercepted. This ion corresponds probably to the interception of one of the transmetalation products **6a** (Scheme 1) as Bu_3Sn^+ ($\mathbf{6b}^+$), and this cation is again rationalized to be sampled either directly from the reaction solution (owing to equilibrium with I^-) or from ESI ionization followed by iodine radical loss, or from both processes. Note that the solution equilibria with I^- may be considerably disfavored but would be shifted toward the ionic species as ESI(+) continuously removes I^- from the solution.

Another key species that arises from transmetalation, that is **7a**, was also intercepted by ESI(+)-MS via $\mathbf{7b}^+$ of *m*/*z* 657 (Figure 3). This ion is rationalized to arise via a (disfavored) solution equilibrium between **7a** and $\mathbf{7b}^+$ plus $PhCl_2^-$. We rationalize that, despite its low concentration in solution, $\mathbf{7b}^+$ is detected due to the outstanding sensibility of ESI(+)-MS, whereas the more abundant but neutral **7a** escapes detection.

ESI-MS/MS Characterization of the Pd(II) Intermediates. To further characterize via ESI(+)-MS/MS the important cationic Stille intermediates, the most abundant isotopologues of *m*/*z* 958 ($\mathbf{5a}^{+\bullet}$), 569 ($\mathbf{5c}^+$), and 657 ($\mathbf{7b}^+$) were selected and subjected to CID (see Supporting Information Figure S4). Species $\mathbf{5a}^{+\bullet}$ of *m*/*z* 958 dissociates by a structurally diagnostic fashion, that is, by $I^\bullet$ loss to form the fragment ion of *m*/*z* 831, and then by PPh_3 loss to form $\mathbf{5b}^+$ of *m*/*z* 569.

Interestingly, gaseous $\mathbf{5b}^+$ of *m*/*z* 569 dissociates by a gas-phase process analogous to the last reductive elimination step of the Stille reaction (Scheme 1), yielding both the *final Stille*

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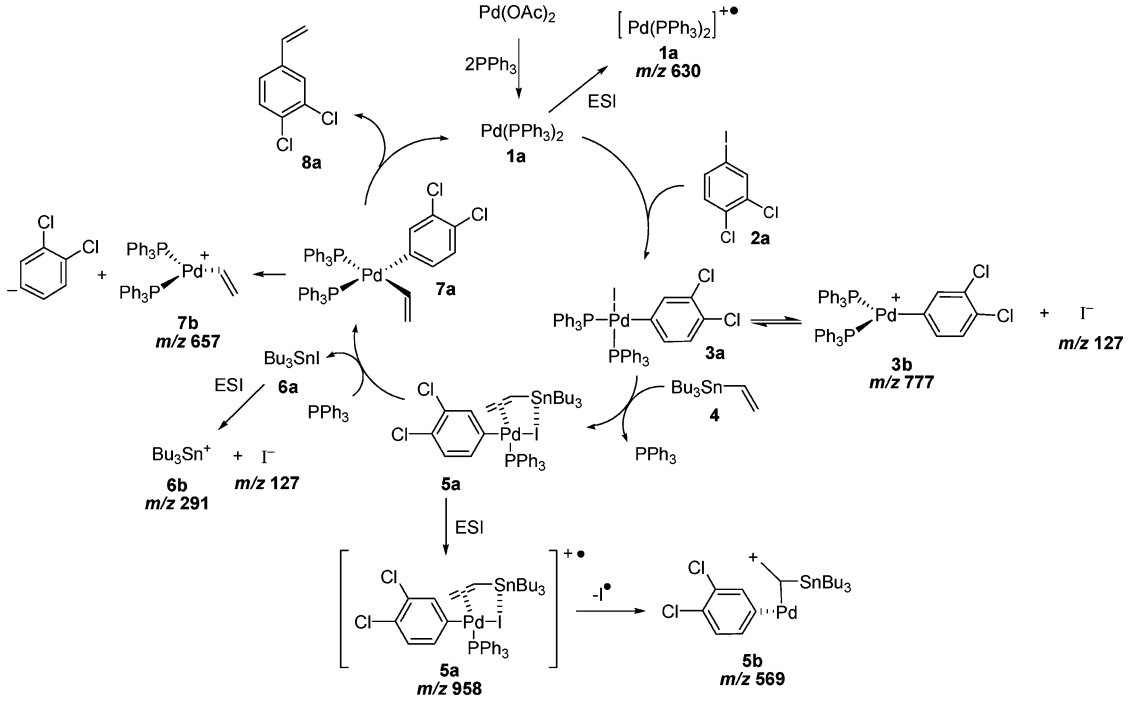
SCHEME 5



product **8a** (detected by GC−MS) and $[Bu_3Sn-Pd]^+$ of *m*/*z* 397. This structurally diagnostic loss for a gaseous and isolated ion is evidence that Pd is able, intrinsically, to transfer the vinyl group from Sn to the aryl group. Intermediate **7b**$^+$ dissociates mainly via two interesting routes involving either vinyl cation or phenyl cation migration to phosphorus with formation of the respective phosphonium ions $Ph_3PCH{=}CH_2^+$ of *m*/*z* 289 and PPh_4^+ of *m*/*z* 339.

ESI(−)-MS Monitoring of Anionic Intermediates. We also monitored by ESI(−)-MS the same Stille reaction depicted in Scheme 2. We were particularly interested in the interception of major anionic complexes such as those proposed by Amatore and co-workers to be the effective Stille catalysts, that is, $PdL_2(OAc)^-$ and $ArPdI(OAc)L_2^-$.[8] Despite its superior sensitivity and speed, continuous ESI(−)-MS monitoring was able to detect only the raising, leveling off, and fading of I^- of *m*/*z* 127, that is, the counterpart anion of several solution salts postulated for the interception of **3**, **5**, and **6** (see Scheme 5 and Supporting Information Figure S5).

Scheme 5 depicts a detailed catalytic cycle for the Stille reaction. Reaction steps and intermediates are basically similar to the working model proposed in the Stille reaction (Scheme 1), but now the reaction intermediates **3a**, **5a**, **6a**, and **7a** including the previously elusive catalytically active Pd(0) species **1a** are shown in association with their respective ionic species intercepted by ESI-MS and further characterized by ESI-MS/MS.

For a Stille reaction, on-line ESI(+)-MS(/MS) monitoring have allowed us to intercept and characterize (a) the actual catalytically active species $Pd(PPh_3)_2$, (b) the oxidative addition product **3a** as the corresponding ionic species **3b**, and (c) the transmetalation intermediate **5a** and two products of this process **6a** and **7a**. Gas phase reductive elimination (for **7b**$^+$) has also been observed. Therefore, for the first time, most of the major intermediates of a Stille reaction have been intercepted, isolated, and characterized. Using ESI(−)-MS, the counteranion I^- was the single species detected. Such straightforward experiments further illustrate the applicability of direct infusion ESI-MS(/MS) in revealing, elucidating, and helping to consolidate mechanisms of organic reactions.

Experimental Section

General Procedure of Stille Reaction Screening. In a dry N_2 inert atmosphere glovebox, aryl iodide **2a** (0.057 mmol) and the vinylstannane **4** (0.063 mmol, 1.1 equiv) were placed in a 2.0 mL vial, and the vessel was charged with 1.5 mL of previously dry and degassed MeCN. To this solution was added $Pd(PPh_3)_4$ (0.0062 mmol, 10 mol %) and stirred vigorously. The system was taken at once with a Teflon-sealed microsyringe and analyzed on-line by ESI-MS for 3 h.

ESI-MS and ESI-MS/MS. All experiments were performed on a hybrid triple quadrupole linear ion-trap mass spectrometer (2000 QTrap MDS mass spectrometer, Applied Biosystems). For typical electrospray ionization (ESI) conditions, the Teflon-sealed microsyringe was put in a pump that delivered the reagent solution into the ESI source at a flow rate of 10 μL min^{-1}. ESI and the QqQ (linear trap) mass spectrometer was operated in the positive ion mode. Main conditions were curtain gas nitrogen flow, 20 mL min^{-1}; ion spray voltage, 4500 eV; declustering potential, 21 eV; entrance potential, 10 eV; collision cell exit potential, 12 eV. The cationic species were subjected to collision-induced dissociation (CID) with nitrogen by using collision energies ranging from 5 to 45 eV.

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Supporting Information Available: Full details of spectrometric data of **1a** (Figure S1), **3b**,**c** (Figure S3), **5a**,**b**, and **7a**,**b** (Figure S4). This material is available free of charge via the Internet at http://pubs.acs.org.

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