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Heck coupling in the gas phase: Examination of the reaction mechanism by ion/molecule reactions and mass spectrometry

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ABSTRACT

The *Heck* reaction of isoprene with (*p*-iodophenyl)-trimethylammonium iodide was conducted in the gas phase. Relevant species of the catalytic cycle including the ionic product of the Pd-catalyzed coupling reaction were reliably characterized by exact ion mass measurements and by characteristic product ions generated by tandem-MS.

1. Introduction

Homogeneous transition metal catalysis is an indispensable tool for modern organic synthesis in terms of efficiency, selectivity and atom economy [1]. A prominent example is the Pd-catalyzed *Heck* reaction which is one of the most versatile and feasible tools in C–C bond formation [2–8]. However, the *Heck* reaction awaits an exhaustive experimental elucidation of its catalytic cycle which is for many reasons a complex analytical task [8]. First and foremost, even labile and transient species have to be studied directly out of complex reaction mixtures for which electrospray ionization (ESI) [9–11] combined with tandem-MS [12] proved to be a promising approach. Using this strategy chemical reactions can be online monitored by "fishing" ionic reactants, intermediates and products directly from solution [13–22]. E.g., Eberlin and coworkers used ESI-MS to examine the *Heck* coupling reaction of an arene diazonium salt and 2,3-dihydrofuran in solution [14]. They succeeded to detect the active catalytic species and found evidence for the insertion of 2,3-dihydrofuran into the palladium arene bond. However, conclusive identification of the coupling product was impossible as it is neutral and hence not amenable to further MS analysis. To overcome this difficulty, charge tagged substrates can be applied as recently highlighted [23]. These allow investigating oxidative addition reactions to give respective ionic transition metal complexes and the MS analysis of coupling products in the gas phase. Different charge tags like quaternary ammonium or phosphonium cations and sulfonate anions are available for that purpose [21,24–28]. Furthermore, ion molecule reactions of selected ions with neutral substrate molecules executed in a tandem-MS instrument offer to follow the stepwise formation and to study intrinsic properties of reaction intermediates or test potential catalysts without the influence of solvent molecules [17].

We now report the examination of the *Heck* coupling reaction of (*p*-iodophenyl)-trimethylammonium iodide (**1**) with isoprene (**2**) in the gas phase (Scheme 1). Due to the permanently charged substrate we were able to detect a number of relevant species of the catalytic cycle including the ionic reaction product **3**. All ions were reliably characterized by exact ion mass measurements and by characteristic product ions generated by MS^n.

2. Experimental

The MS^n experiments and the gas-phase ion molecule reactions were performed on a modified *Thermo Fisher LTQ Orbitrap XL* (Bremen, Germany) hybrid instrument equipped with an ESI ion source, linear ion trap (LTQ), octapole collision cell (HCD cell) and an orbitrap mass analyzer [29,30] capable of measurements with high mass accuracy and elevated resolving power (Fig. 1). To provide

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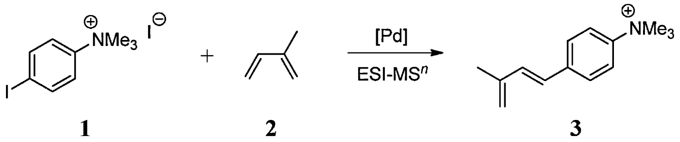


Scheme 1. *Heck* reaction of (*p*-iodophenyl)-trimethylammonium iodide (**1**) with isoprene (**2**) in the gas phase.

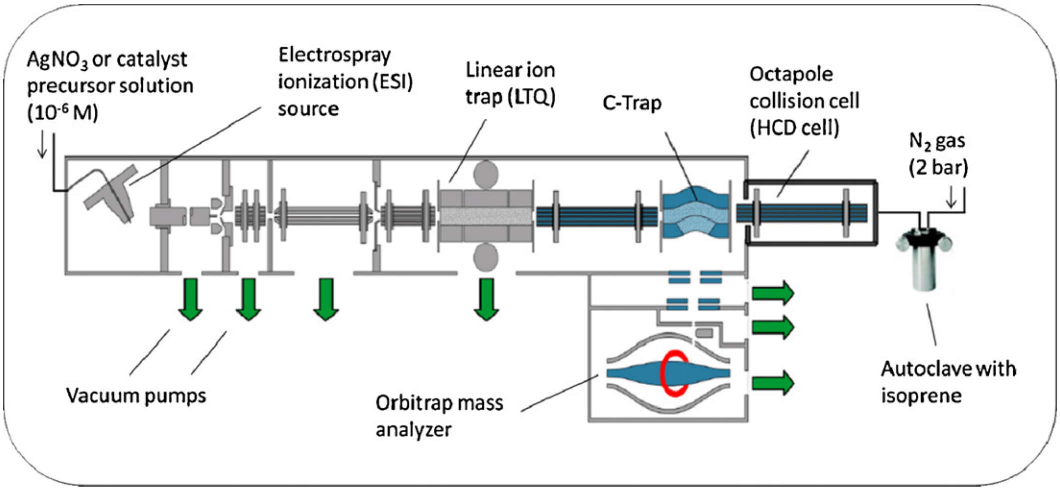


Fig. 1. Schematic view of the *Thermo Fisher LTQ Orbitrap XL* mass spectrometer upgraded with an autoclave to introduce vaporized isoprene (**2**) into the HCD cell and LTQ for ion molecule reactions.

Reproduced with permission of the manufacturer [31].

isoprene (**2**) for gas-phase ion molecule reactions the vaporized olefin was introduced via the nitrogen bath gas of the HCD cell using a stainless steel autoclave (250 ml, $P_{\max} = 200$ bar, homemade) which was furnished with the reagent and put between nitrogen source and gas inlet (nitrogen pressure 2 bar). As the partial pressure of neutral isoprene (**2**) cannot be metered in the *LTQ Orbitrap XL* instrument, the abundance of gas phase $[\mathrm{Ag(isoprene)}_n]^+$ ($n = 1$, 2) complex ions formed by ion molecule reactions of Ag^+ ions with $(\mathrm{isoprene})_g$ was used as an indirect measure for tuning and verification of reproducible experimental conditions (Fig. S1, Supporting information).

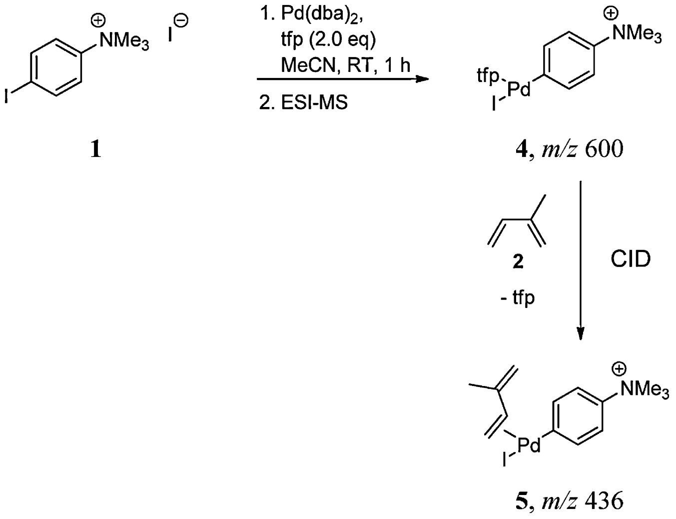
We note that the formation of isoprene adduct ions in the LTQ part of the hybrid MS-instrument is enabled by the diffusion of the volatile olefin into the LTQ. Ions of interest were characterized by sequential collision induced dissociation (CID) experiments in the LTQ and by respective exact ion masses measured in the orbitrap. All structure assignments are consistent with experimentally determined exact ion masses ($\Delta m \leq 2.2$ ppm) and theoretical isotopic patterns (e.g., Fig. S2, Supporting information). The integer nominal ion masses of Pd complex ions listed are calculated with the mass of isotope ^{106}Pd. To test our assumptions the *Heck* reaction of (*p*-iodophenyl)-trimethylammonium iodide (**1**) with isoprene (**2**) was also conducted in solution and coupling product **3** was characterized by ESI-MS^2 and by its accurate mass (Fig. S5, Supporting information).

3. Results and discussion

Firstly, the oxidative addition of (*p*-iodophenyl)-trimethylammonium iodide (**1**) to bis-(dibenzylideneacetone) palladium ($\mathrm{Pd(dba)_2}$) in the presence of tri(2-furyl)-phosphine (tfp) was examined in acetonitrile solution (Scheme 2) [28]. The respective ESI mass spectrum of the reaction mixture exhibits the cation **4** of *m*/*z* 600 with prominent abundance (Fig. S2, Supporting information). This ion is selected for LTQ-MS^2-product ion experiments. The characteristic fragment ions formed upon CID clearly support the structure assignment of the precursor (Fig. 2a).

When introducing isoprene (**2**) into the instrument via the collision gas inlet of the HCD cell the mass spectrum substantially changes after a delay time of some minutes. Isoprene adduct ions **5** and **6** of complex ions **7** and **8** are formed in the gas phase by reactive collisions and are found in the respective mass spectrum at *m*/*z* 436 and *m*/*z* 474, respectively (Fig. 2b).

Precursor ion selection and CID of complex ion **6** (*m*/*z* 474) in a LTQ-MS^3 product ion experiment simply shows the loss of



Scheme 2. Oxidative addition of **1** to $\mathrm{Pd(dba)_2}$ in the presence of tfp leads to Pd complex ion **4** (*m*/*z* 600). Under CID conditions in the presence of isoprene (**2**) the isoprene adduct ion **5** of *m*/*z* 436 is formed. The arbitrary structure of Pd complex ion **5** represents an unverified illustration.

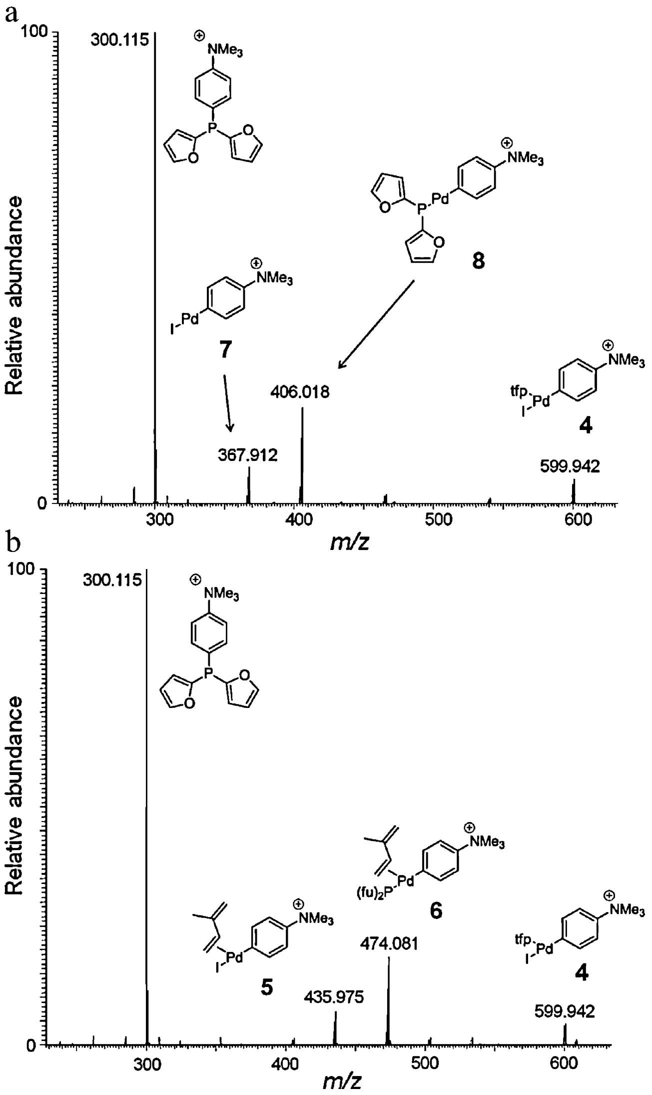
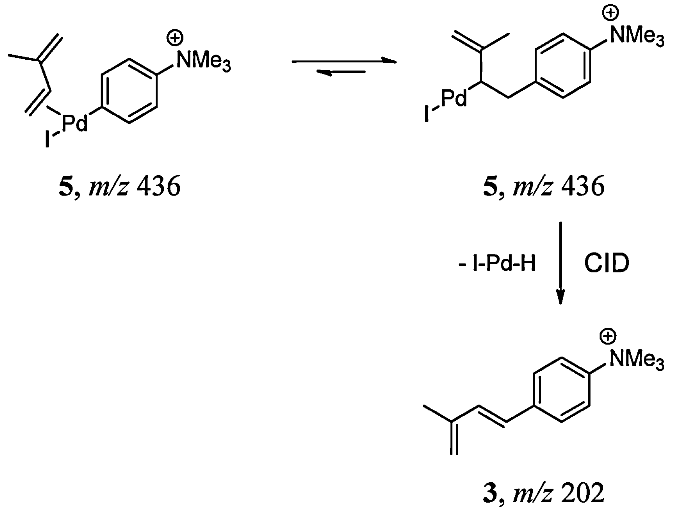


Fig. 2. (a) LTQ-MS^2 product ion spectrum of Pd complex ion **4** (m/z 600) in the absence of gaseous isoprene (**2**). (b) LTQ-MS^2 product ion spectrum of complex ion **4** in the presence of gaseous isoprene (**2**). Isoprene adduct ions **5** (m/z 436) and **6** (m/z 474) are formed by ion/molecule reactions of respective ions **7** and **8** with isoprene (**2**) (characteristic mass shift $\Delta m = 68$ Da; fu = furyl).

isoprene (**2**) (Fig. S3, Supporting information). When activating complex ion **5** (m/z 436) in a similar LTQ-MS^3 product ion experiment fragment ion **3** (m/z 202) is delivered which represents the *Heck* coupling product of (p-iodophenyl)-trimethylammonium iodide (**1**) with isoprene (**2**) (Scheme 3 and Fig. 3). We note that the reversed addition reaction i.e., the loss of isoprene (**2**) (68 Da) from ion **5** is not observed under collision activation conditions pointing towards the formation of the respective σ-complex as illustrated in Scheme 3. The depicted structure of the *Heck* coupling product **3** is derived from results of the reaction of iodobenzene with isoprene (**2**) in solution reported in the literature [32] and by now not fully verified (Scheme 3).

Collision activation of ion **3** in a MS^4 product ion experiment shows the repeated loss of methyl radicals (15 Da), yielding fragment ions of m/z 187 and m/z 172 (Fig. S4, Supporting information). This remarkable fragmentation pattern i.e., the loss of a methyl radical from an even electron number precursor ion ($m/z\ 202 \rightarrow m/z$ 187), is certainly enabled by the substantial stabilization capability of the extended π-system of **3** as Scheme 4 illustrates [33].



Scheme 3. Collision activation of the Pd isoprene adduct ion **5** yielding the *Heck* coupling product ion **3** of m/z 202 [32].

To further probe our structure assignment we synthesized **3** in solution by *Heck* coupling of (p-iodophenyl)-trimethylammonium iodide (**1**) with isoprene (**2**). The ESI-MS analysis of the respective reaction mixture delivers an abundant ion of m/z 202 representing the main reaction product **3** which also exhibits the characteristic losses of 15 Da upon CID (Fig. S5, Supporting information) clearly supporting the assumptions presented above. Complete work-up of the solution phase *Heck* reaction including isolation, purification and conclusive structure elucidation of **3** by NMR-spectroscopy are currently underway.

This study shows that the combination of ESI-MS^n, charge tagged substrates and gas-phase ion/molecule reactions in an instrument capable to determine accurate ion masses of product and precursor ions can be very useful for the detailed examination of complex reaction mechanisms [17,23]. Since even labile ionic intermediates and coupling products can individually be formed

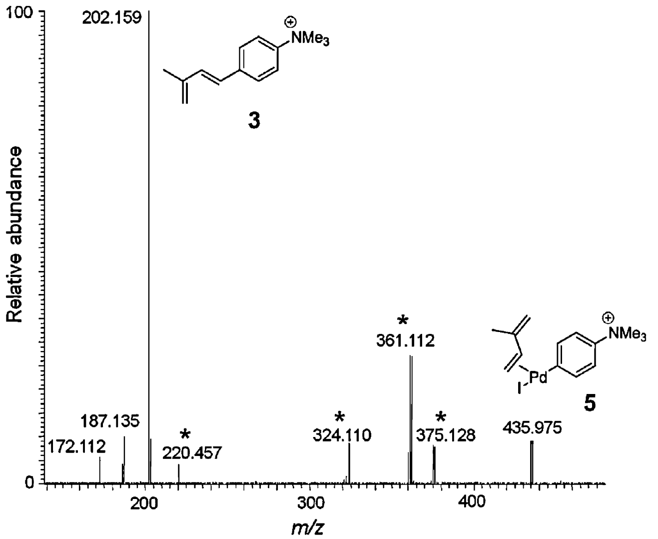
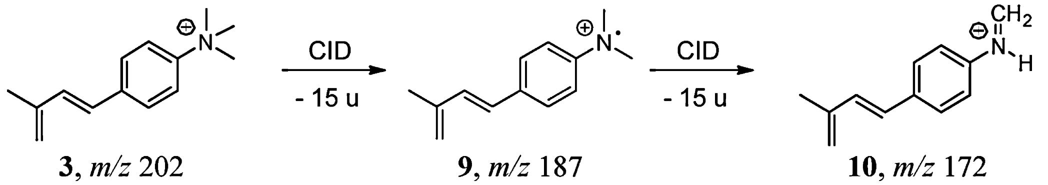


Fig. 3. LTQ-MS^3 product ion spectrum of isoprene adduct ion **5** (m/z 436). The dominant fragment ion at m/z 202 represents the *Heck* coupling product **3**. The ions of m/z 187 and m/z 172 are fragment ions of the *Heck* coupling product **3** of m/z 202, formed after loss of one or two methyl radicals (Scheme 4 and Fig. S4, Supporting information). The formation of the low abundant ions marked with asterisks cannot be explained by CID of precursor ion **5**. We speculate that these ions are products of unspecific fragmentation reactions or formed by adduct formation of isoprene (**2**) with background species present in the LTQ.



Scheme 4. Fragmentation pattern of ion **3**, i.e., the *Heck* coupling product, in a LTQ-MS^4 product ion experiment: the sequential loss of one, respectively of two methyl radicals (15 Da = CH_3) is noted and can be explained by the substantial stabilization by the extended π-system of **3**. Besides the depicted structure of product ion **10** the second loss of a methyl radical can also involve the isoprene methyl group after radical delocalization via the conjugated system.

by either ion/molecule reactions of ionic precursors with neutral substrate molecules or by collision activation of complex adduct ions a stepwise examination of a reaction mechanism is possible. To the best of our knowledge this is the first time that the major species involved in an ionic *Heck* coupling are monitored in the gas phase. In doing so, we find ample experimental evidence verifying the generally accepted text book mechanism of the *solution-phase Heck* reaction [3]. Finally, the presented results encourage using this approach to examine mechanisms of other transition metal catalyzed reactions in the gas phase.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijms.2011.07.013.

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