COMMUNICATION

Diazo Compounds and Palladium-Aryl Complexes: Trapping the Elusive Carbene Migratory Insertion Organometallic Products

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The reactions of Pd-aryl complexes with diazo compounds N_2CH-$CH=CHPh$ and N_2CHPh allowed us to isolate the organometallic products formed right after the migratory insertion of a non-stabilized CHR carbene into the Pd-aryl bond. η^3-Allylic and η^3-benzylic palladium complexes were formed respectively. This is a compelling experimental evidence for the key step in the palladium-catalyzed cascade transformations of diazo derivatives leading to multiple C-C or C-X bond formation.

A large number of palladium catalyzed C-C and C-X coupling reactions use carbene precursors as reagents. These transformations are extremely interesting since the carbene fragment is amenable to a double functionalization that leads to cascade reactions and therefore to a more efficient building up of molecular complexity. Following the pioneer work of Van Vranken et al.,[1] a lot of progress has been made and this type of reaction has now a prominent position among the Pd-catalyzed cross coupling processes.[2,3] These reactions use non-stabilized carbenes (CHR or CRR') as coupling partners and the most common carbene precursors are diazo compounds and tosylhydrazones as shown in Scheme 1.[4-6] The latter decompose in basic medium via the Bamford–Stevens reaction to the reactant diazo compound.[7] The proposed general mechanism for these reactions involves the formation of a palladium carbene from the diazoalkane, followed by a migratory insertion of the carbene fragment into the Pd-R bond, the R group being previously installed on palladium (Scheme 1). This is a plausible route, supported by DFT calculations, but very few experimental studies have been done to probe and support the steps of the reaction, in particular, the key bond-forming migratory insertion step.
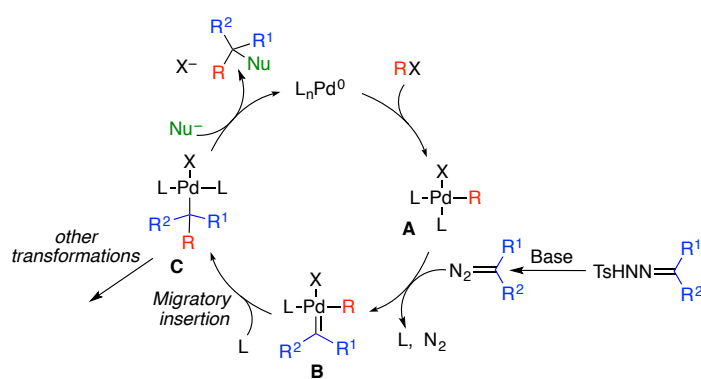
Scheme 1. General catalytic cycle proposed for Pd-catalyzed coupling reactions with hydrazones or diazo compounds as carbene precursors (the formation of Pd-R is shown here as the results of oxidative addition to a Pd(0) complex).

The feasibility of the carbene migratory insertion on palladium organometallic complexes has been shown for stabilized carbenes, rarely used in catalysis as reactants, i.e. monoamino or monoalkoxo Fisher-type carbenes,[8] and one N-heterocyclic carbene (NHC).[9] The evolution of some palladium haloalkyl derivatives leads to complexes whose formation could be explained via dehalogenation, formation of a putative Pd-carbene and a migratory insertion reaction.[10] However, to our knowledge, there is only one example of the insertion of a non-stabilized CRR' carbene fragment from a diazoalkane in a palladium chelating metalacycle, resulting in a new palladium complex.[11] A couple of examples of the decomposition of a palladium aryl complex in the presence of a diazoalkane have been reported, but no organometallic intermediates were detected and just the organic products derived from a putative migratory insertion process were found.[12] We report here the isolation of the complexes derived from the migratory insertion of a non-stabilized carbene (CHR, R = hydrocarbyl) into a Pd-Aryl bond, i.e. the intermediate **C** in Scheme 1.

Complexes [PdArBr(dppe)] (**1**) and [PdAr(dppe)(NCMe)]BF_4 (**2**) (Ar = C_6F_5, Ph; dppe = bis(diphenylphosphino)ethane) were used as models of intermediate **A** in Scheme 1, and tested in the reactions with diazo compounds. Pentafluorophenyl was

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used because of its advantageous spectroscopic features in ^{19}F NMR. However, since the strong Pd-C bond for this aryl makes the reactions that require the Pd-C cleavage generally slower, reactions of the analogous phenyl complexes were also carried out. Intermediate **A** can be formed in a catalytic process by an oxidative addition process, as it is very common and it is shown in Scheme 1, but it could also arise from a transmetalation reaction from a main group organometallic or even by a C-H activation process.[2] By selecting diazoalkanes N_2CHR with R = CH=CHPh, Ph, we provide a way to stabilize the expected alkyl intermediate (**C**, Scheme 1) by coordination of the unsaturation (double bond or aryl) to the metal. Both diazo compounds are common reagents in Pd-catalyzed processes.[2c,13,14]

The reaction of the solvento acetonitrile complexes **2** with the diazoalkane **3** at room temperature in acetonitrile leads immediately to the formation of the η^3-allylic derivatives **4** (Scheme 2). The formation of a new Ar-C bond is very clear for Ar = C_6F_5 since the signals for the *ortho* fluorine atoms in ^{19}F NMR shift about 20 ppm when a Pd-C_6F_5 moiety (about -120 ppm) is transformed into a C-C_6F_5 bond (about -142 ppm) (Figure 1).
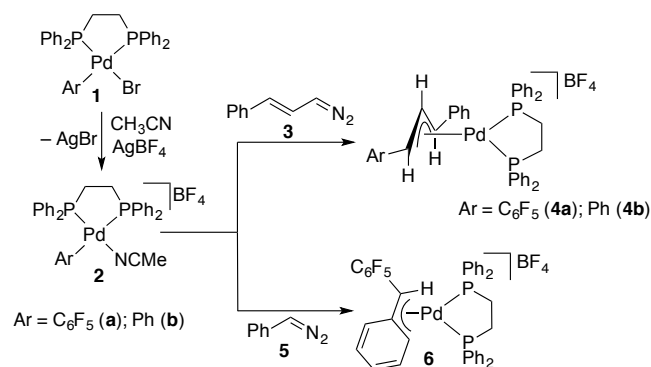
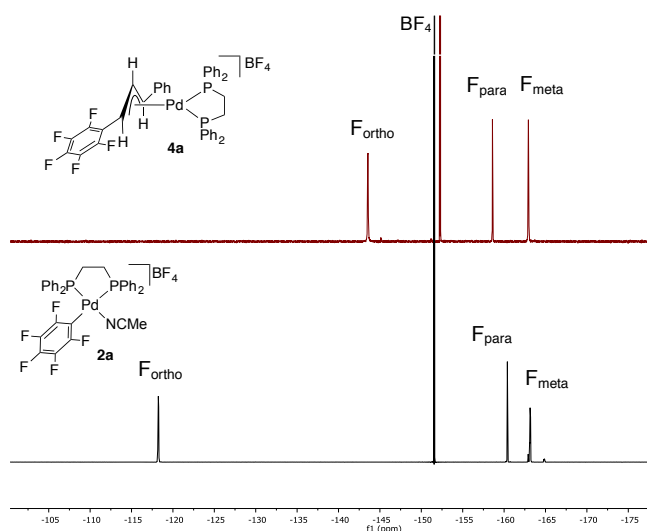
Scheme 2. Reactions of Pd-aryl complexes with diazoalkanes.

Figure 1. ^{19}F NMR (470.17 MHz, $CH_3CN/(CD_3)_2SO$ capillary) at 298 K of complexes **2a** and **4a** showing the dramatic shift of the F_{ortho} signals.

Characteristic signals for the asymmetric η^3-allyl complex **4a** are observed in the ^{1}H, ^{13}C and ^{31}P NMR spectra whereas a symmetric η^3-allyl was found for **4b** (see characterization data in the ESI). The analogous reaction of the diazo compound **5** with **2a** leads to the benzylic palladium complex **6**. Again the migration of the pentafluorophenyl group to the organic fragment is clearly seen by ^{19}F NMR. The spectroscopic features of **6** show the typical behavior of a fluxional benzylic derivative with broad *ortho* phenyl signals in the ^{1}H NMR at room temperature by exchange via a η^3-σ-η^3 fluxional process (see Figures S20 and S25-S27 in the ESI).[15] The formation of complex **6** supports the intermediacy of benzylic palladium derivatives in catalytic coupling reactions of phenyldiazomethane derivatives, as has been suggested before.[13]

The molecular structures of complexes **4a** and **6** were obtained by X-ray crystal diffraction and they are shown in Figure 2. Complex **4b** is an η^3-allyl with both substituents in a syn arrangement. The benzylic derivative **6** also shows a syn-pentafluorophenyl arrangement. In this derivative, the Pd-C3 bond length (2.155(4) Å) is clearly shorter than the Pd-C distances for the coordinated phenyl ring (Pd-C2, 2.275(4) Å and Pd-C1, 2.284(4) Å) reflecting a weaker interaction that involves the loss of aromaticity. This is characteristic of other η^3-benzylic complexes.[16]
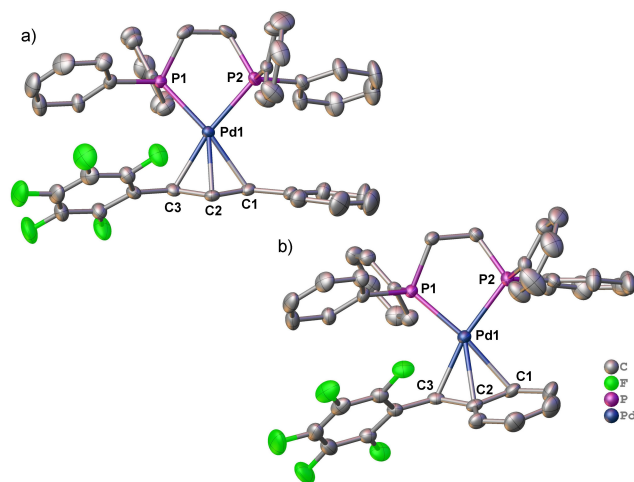

Figure 2. X-ray molecular structures of **4a** (a) and **6** (b) (ORTEP 40% probability ellipsoids). Hydrogen atoms and the counterion BF_4^- are omitted for clarity.

Complexes **4** and **6** are the result of the migratory insertion reaction of the aryl into a putative palladium carbene complex, as shown in Scheme 3, and they model intermediate **C** in Scheme 1. The palladium alkyl complex formed right after the migratory insertion can be trapped and stabilized by coordination of the double bond (**4**) or the phenyl ring (**6**) present in the substituents of the diazoalkanes used.
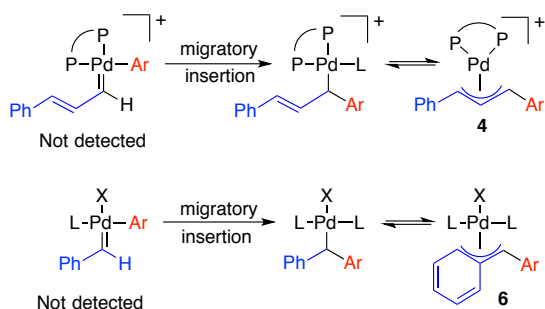
Scheme 3. Generation of complexes **4** and **6** by migratory insertion in a putative palladium carbene and stabilization of the generated palladium alkyl.

With the aim of detecting some of the intermediates involved before the migratory insertion, we carried out the reaction of **2a** with diazoalkanes **3** and **5** in CD_2Cl_2 at -90 °C and monitored it by ^{19}F NMR. Upon addition of the diazoderivative, complexes **4a** and **6** were the only new species formed and they coexist with the starting solvento complex (Figure 3 and Figures S2 and S3 in the ESI). Neither the coordination of the diazo compounds nor the formation of the palladium carbene was detected. This failure at observing any intermediate preceding the formation of the aryl-carbene insertion product indicates that the steps involved in the overall reaction are fast and they cannot be experimentally studied separately. Therefore, to obtain more information, we modeled the reaction using Density Functional Theory (DFT) calculations using the M06 functional and including solvation (MeCN) through the SMD implicit solvent method (see computational details in the ESI). The calculated profile for the reaction with the diazoalkane **3** is shown in Figure 4.[‡] The coordination of the diazoalkane either in a κ^1-N (**I1-N**) or in a κ^1-C (**I1-C**) coordination mode leads to intermediates that are less stable than the starting solvento complex (**2a**) by about 3 kcal mol^{-1}. **I1-C** can undergo extrusion of nitrogen to give a palladium carbene (**I2**) via a transition state with an accessible energy barrier (14.1 kcal mol^{-1}, **TS-I1C-I2**).
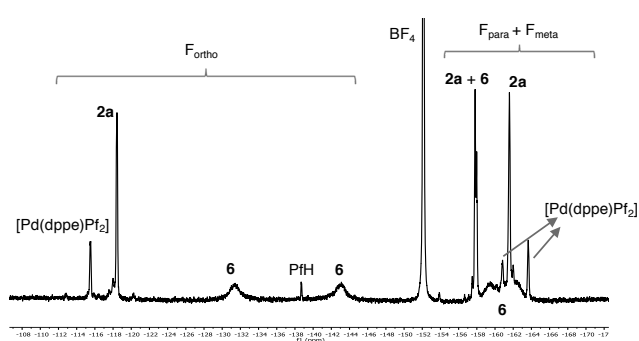

Figure 3. ^{19}F NMR (470.17 MHz, CD_2Cl_2) of a mixture of complex **2a** and the diazo compound **5** at -90 ºC (Pf = C_6F_5). Only complex **6** and a small amount of aryl reorganization [Pd(dppe)(Pf)$_2$] were formed. Slow rotation of the C_6F_5 group in complex **6** is observed at this temperature (broad inequivalent *ortho* and *meta* fluorines).

Although formation of palladium carbene **I2** is quite exergonic, the complex is unstable toward a low-barrier (6.1 kcal/mol) migratory insertion to afford the observed product **4a**. This reaction profile is consistent with our experimental results. The energetic span for this reaction has a low value (14.1 kcal mol^{-1}), so the reaction occurs at low temperatures, and the rate determining state is the nitrogen extrusion to give the palladium carbene. Only the complex before this step, the starting solvento derivative **2a**, can be observed considering that the coordinated κ^1-C diazo derivative is 3.1 kcal/mol less stable and therefore the plausible equilibrium **2a**-**I1-C** is shifted toward **2a** (K ≈ 5 x 10^{-3}).[§] Once the palladium carbene is formed the migratory insertion is very fast and just the final product is observed. This is in agreement with previous calculations carried out by other authors on related systems, where they find that the migratory insertion reaction usually has a very low energy barrier.[3e,17] This is expected for the very electrophilic, non-stabilized carbenes used here (CHR) in contrast with the heteroatom-stabilized fragments CR(XR'$_n$), more electron rich, which in some cases can be isolated before a more reluctant migratory insertion follows.[8] The very few examples of the formation of Pd(II) carbene complexes from diazoalkanes occur on palladium precursors with no Pd-R bonds, i.e. no migratory insertion can take place.[18]
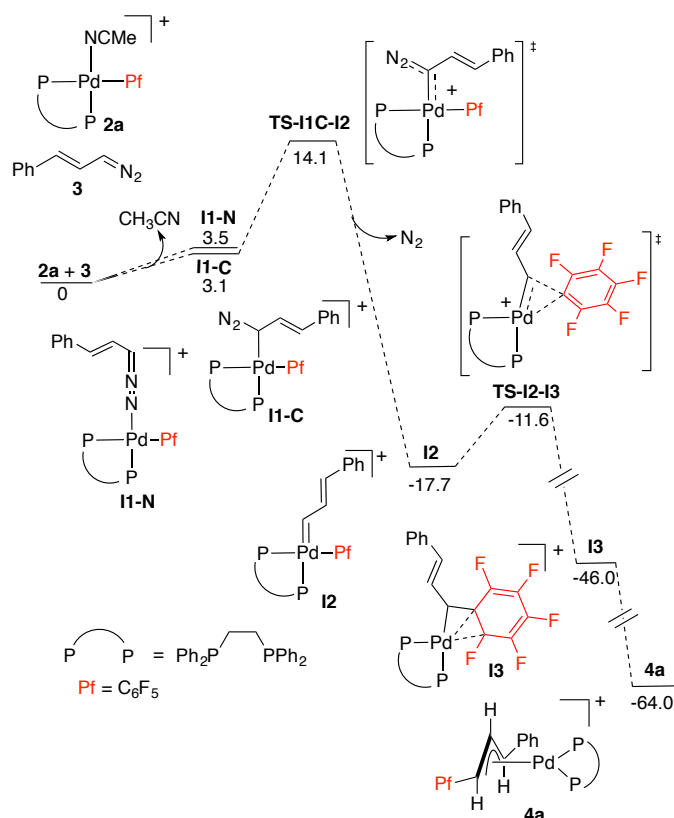

Figure 4. Free-energy profile for the reaction of complex **2a** and the diazo compound **3** to give the migratory insertion complex **4a**. Energies in kcal mol^{-1}.

In conclusion, the formation of a palladium carbene (**B**, Scheme 1) from the diazoalkane N_2CHR occurs by a low barrier N_2 extrusion. We could not detect this intermediate since the very electrophilic palladium carbene undergoes a fast migratory insertion that leads to a new palladium alkyl. We could isolate the palladium derivatives right after migratory insertion of these non-stabilized carbenes (**C**, Scheme 1) by selecting appropriate substituents in the carbene moiety CHR that could stabilize the new organometallic complex via formation of an η^3-allyl complex (R = CH=CHPh, **4**) or a benzylic one (R = Ph, **6**). These complexes unequivocally demonstrate the migratory insertion step for non-stabilized carbenes, the key C-C forming step in Pd-catalyzed coupling reactions of diazoalkanes.

Author Contributions

F.V. conducted the investigation under A. C. A. supervision. A. C. A. wrote the manuscript and F.V. prepared the ESI. All authors contributed to the conceptualization of the project and the review and editing of the manuscript.

Conflicts of interest

There are no conflicts to declare

Notes and references

‡ The energy profile for the reaction of diazoalkane **5** with complex **2a** was also calculated and it is analogous to that in Figure 4 (see details and Figure S6 in the ESI).

§ Other palladium complexes, that can be formed by coordination of the diazoalkane **3** in a different bonding mode, such as the κ^1-N diazo derivative shown in Figure 4 (**I1-N**, 3.5 kcal mol^{-1}) or the η^2-alkene derivative (-1.3 kcal mol^{-1}) have also energies close to the starting mixture (**2a** + **3**) and could not be detected. The η^2-alkene coordination is not possible for the diazocompound **5**.

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