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# Mechanistic study of Pd/NHC-catalyzed Sonogashira reaction: discovery of NHC-ethynyl coupling process

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Supporting information for this article is given via a link at the end of the document.

Abstract: The product of a revealed transformation - NHC-ethynyl coupling - was observed as a catalyst transformation pathway in the Sonogashira cross-coupling, catalyzed by Pd/NHC complexes. The 2-ethynylated azolium salt was isolated in individual form and fully characterized, including the X-ray analysis. A number of possible intermediates of this transformation with common formulae  $(NHC)_xPd(C_2Ph)$  (x = 1,2) were observed and subjected to collisioninduced dissociation (CID) and infrared multiphoton dissociation (IRMPD) experiments to elucidate their structure. Measured bond dissociation energies (BDEs) and IRMPD spectra were in an excellent agreement with quantum calculations for coupling product  $\pi$ -complexes with Pd(0). Molecular dynamics simulations confirmed the observed multiple CID fragmentation pathways. An unconventional methodology to study catalyst evolution suggests the reported transformation to be considered in the development of new catalytic systems for alkyne functionalization reactions.

## Introduction

Functionalized acetylenes play a key role in natural products, are actively utilized as synthetic intermediates, and find their applications in pharmaceuticals and organic materials.<sup>[1-3]</sup> Over the last decades, Sonogashira coupling has become one of the key approaches towards alkyne functionalization in modern organic synthesis.<sup>[4-12]</sup> Amongst numerous palladium catalysts utilized in this transformation Pd/NHC (NHC = N-heterocyclic carbene) complexes have firmly established their utility as highly active catalysts which are much more stable towards air and moisture than popular Pd-phosphine complexes.<sup>[13-15]</sup> This important feature makes it possible to perform the reaction in aqueous media.

The reaction usually requires copper(I) salts as a co-catalyst, which (i) are unstable toward oxygen and may be easily oxidized by some organic compounds and (ii) often catalyze Glaser-type side reactions. These problems may be overcome by application of other co-catalysts, such as AgOTf, or by avoiding any metal co-catalysts. The latter option led to use of Pd/NHC catalysts in Cu-free reaction conditions (Scheme 1).<sup>[16-22]</sup>



Scheme 1. Sonogashira coupling catalyzed by Pd/NHC complexes.

Although a general rationalization of the mechanism has enabled activation of different classes of electrophiles and the development of synthetic protocols, a detailed mechanistic understanding of the complete reaction pathways and especially catalyst stability issues remain a challenge. Ligands of metal complexes may not only facilitate the reactivity and stabilize intermediates, but react with each other.<sup>[23]</sup> On the one hand, these reactions may be crucial for the catalyst performance, if the ligands participate in the catalyst activation step; on the other hand, they may be responsible for the catalyst deactivation, leading to the loss of active species and preventing possible recycling of the catalysts with well-defined structure.<sup>[23]</sup>

Our attempts to understand the role of NHC ligands in the Pdcatalyzed Sonogashira reaction led to discovery of a transformation, which, to the best of our knowledge, was not reported before: NHC-ethynyl coupling (Scheme 1). The transformation was extensively studied by means of massspectrometry, DFT calculations, and molecular dynamics; and the Pd-intermediates structures were confirmed. We found that this transformation occurs from one of the key reaction intermediates and can be responsible for the limited success in the development of advanced synthetic approaches when neglected.

## **Results and Discussion**

In the established mechanism of this reaction, prior to the reductive elimination step leading to the product formation, an intermediate having an NHC-bound palladium with phenyl and acetylide groups is proposed.<sup>[24-27]</sup> According to our previous study, such an intermediate can undergo R-NHC coupling and activate NHC-disconnected type of catalysis.<sup>[23, 28]</sup> In the present study, we have performed the Sonogashira coupling of iodobenzene (PhI) and phenylacetylene (PhC<sub>2</sub>H) using three different Pd/NHC complexes **1a,c,d** (Chart 1). The reactions were conducted under three different conditions: Cu-free, with CuBr, and with CuI.



Chart 1. Pd/NHC complexes studied for NHC-ethynyl coupling (Py – pyridine, Mes – 1,3,5-trimethylphenyl, Dipp – 1,3-diisopropylphenyl)

After 1 h product yields were determined by GC-MS (Table 1) and the reaction mixtures were analyzed by ESI-MS. Depending on the precatalyst and on the reaction conditions, tolane yields varied from low to high. Cu-free conditions appeared to be unselective resulting in 17-31% yields (Table 1, Entries 1-3). Moreover, tolane was not the major product for the complexes with **BIMe** (1a) and **IMes** (1c) ligands. As a major reaction product, we have isolated and characterized (*Z*)-but-1-en-3-yne-1,2,4-triyltribenzene (50% isolated yield), which has also been reported previously.<sup>[29-31]</sup> In the presence of 3 mol% copper, the reaction appeared to become significantly more efficient with up to 90% yield, with no significant difference between CuBr and Cul (Table 1, Entries 4-9).



Scheme 2. Transformation of Pd/NHC complex into the NHC-ethynyl coupling product

Analysis of the mass spectra (ESI) of all reaction mixtures consistently along with expected [NHC-Ph]<sup>+</sup> cations<sup>[28, 32]</sup> revealed the formation of an NHC-ethynyl coupling product. Cations [BIMe-C<sub>2</sub>Ph]<sup>+</sup>, [IMes-C<sub>2</sub>Ph]<sup>+</sup>, and [IPr-C<sub>2</sub>Ph]<sup>+</sup> were abundant in the mass spectra and confirmed the presence of reactive intermediates of Pd with the NHC and ethynyl

substituents in the system. This observation encouraged us to further study the nature of these species. Noteworthy, 2-ethynylated azolium cations is a rare and interesting class of organic moieties.<sup>[33-35]</sup>



Pd/NHC cat.        Cs2CO3        DMSO, 1 h, 80 °C				
Entry	Pd source	Cu source	Yield of tolane, %	
1	1a		27 (23) <sup>[b]</sup>	
2	1c	Cu-free	32	
3	1d		38	
4	1a		90	
5	1c	CuBr	85	
6	1d		85	
7	1a		85	
8	1c	Cul	81	
9	1d		85	

[a] Reaction conditions: 1 eq. of PhI and PhC<sub>2</sub>H, 3 eq. of Cs<sub>2</sub>CO<sub>3</sub>, 1 mol% of Pd, 3 mol% of CuX (if stated), in DMSO, 1 h at 80  $^{\circ}$ C. [b] Isolated yield (GC-MS).

In order to characterize the product of the NHC-ethynyl coupling, we performed the reaction between complex 1a and PhC<sub>2</sub>Li solution at -78 °C, but the attempts to directly isolate 2a have failed. It was not possible to isolate individual compounds due to rapid polymerization, especially at elevated temperatures. This problem was overcome by addition of AgOTf to the reaction mixture (Scheme 2). Silver bound the iodide under the reaction conditions, and thus increased the coupling rate relative to the polymerization rate by conversion of the complex to its cationic form. The ESI-MS analysis of the reaction mixture immediately after addition of AgOTf confirmed the presence of [BIMe-C<sub>2</sub>Ph]<sup>+</sup> and OTf and the absence of iodide in the system. The BIMe-C<sub>2</sub>Ph<sup>+</sup>OTf<sup>-</sup> (2a·OTf<sup>-</sup>) salt was isolated with 10% yield (12% NMR yield) and characterized by  $^1\text{H},~^{13}\text{C}\{^1\text{H}\},$  and  $^{19}\text{F}$  NMR, FT-IR, ESI-MS, IRMPD, and X-ray analysis (Figure 1). Even within the optimized conditions, highly reactive nature and susceptibility to polymerization challenges isolation of pure 2a.OTf and affects the yield significantly.



Figure 1. Molecular structure of 2a determined by single crystal X-ray analysis.

Indeed, unusual structure and side-reactions, easily occurring in a typical reaction mixture, complicate mechanistic studies and probably result in these compounds not being reported earlier. Due to ionic nature of proposed intermediates and catalyst evolution product, mass spectrometry offers the best capabilities to solve mechanistic problems as electrospray ionization is a soft ionization technique. In such a case, utilization of ESI-MS,<sup>[24, <sup>36]</sup> CID<sup>[37-38]</sup>, and IRMPD<sup>[39-41]</sup> is the best choice to get an insight into the system.</sup>

To trap Pd-containing intermediates in the reaction mixtures, we mixed solutions of **1a-d** in dry THF with a solution of PhC<sub>2</sub>Li in THF at -78 °C (PhC<sub>2</sub>Li was obtained by an NMR controlled procedure to avoid PhC<sub>2</sub>H or *n*-BuLi contamination as described in the Supporting Information). ESI-MS analysis of these reaction mixtures revealed abundant signals of the NHC-ethynyl coupling products. Moreover, for the reaction mixtures of **BMIM** (**1b**), **IMes (1c**), and **IPr (1d)** complexes we were able to detect [(NHC)<sub>n</sub>(C<sub>2</sub>Ph)Pd]<sup>+</sup> cations, which could be the reactive intermediates of the NHC-ethynyl coupling. With **BIMe** as the NHC, the same ion was only detected at sufficient abundance after addition of AgOTf to the reaction mixture, binding excessive amounts of iodine and likely substituting the ligand by non-coordinating TfO<sup>-</sup> (see SI).

**Collision induced dissociation experiments.** We have studied the fragmentation of the  $[(NHC)_n(C_2Ph)Pd]^+$  (n = 1 or 2) cations. These complexes can either represent the palladium(II) intermediates or the palladium(0) coordinated products. In both alternatives, we expect that the fragmentation should lead to the elimination of palladium(0) either by the reductive elimination mechanism or by a simple ligand detachment. Hence, we decided to measure energy-resolved collision induced dissociations (*CIDs*) that permit extraction of bond dissociation energies<sup>[42-48]</sup> for the fragmentation channels.<sup>[47]</sup>

The isolated palladium complexes in the ion trap readily reacted with background gases (with N2 and H2O) indicating that palladium in the complexes is highly coordinatively unsaturated. This interaction with background gases led to artifact signals during the mass-isolation of the complexes and therefore might have resulted in a larger experimental error in the determination of bond dissociation energies (BDEs) from the CID spectra. The fragmentation of all  $[(NHC)_n(C_2Ph)Pd]^+$  complexes (n = 1 or 2) led to the product cations  $[NHC-C_2Ph]^+$  concomitant with the eliminated palladium(0) (either naked for n = 1 or bearing one NHC ligand for n = 2). This major fragmentation pathway was accompanied by a minor or, in the case of [(IPr)(C<sub>2</sub>Ph)Pd]<sup>+</sup>, a substantial fragmentation of the NHC ligand. The energyresolved CIDs illustrating the dissociation pathways are given in the Supporting information (Figures S34-S37). The derived experimental bond-dissociation energies for the elimination of palladium(0) are summarized in Table 2. Taking into account possible limitations in the accuracy of theoretical calculations, a reasonable correlation between the experimental and calculated values should be mentioned.

The fragmentation experiments in the ion trap correspond to a slow heating of the ions in multiple collisions with helium. Hence, next to the kinetically favored elimination of bare palladium, fragmentations leading via constrained transition structures could be also observed. This fact is the most evident in the fragmentation of  $[(IPr)(C_2Ph)Pd]^+$ . The initial fragmentation of  $[(IPr)(C_2Ph)Pd]^+$  leads to elimination of one of the [Dipp - H] molecules leading to the fragment in which the NHC part bears

the Dipp ligand only at one nitrogen atom, whereas the second nitrogen atom bears a hydrogen atom or the hydrogen atom could be transferred to palladium (see Figure 2). This is supposedly the energetically favored fragmentation pathway, but disfavored entropically at larger collision energies, where the simple elimination of bare palladium prevails.

Table 2. Appearance energies of NHC-ethynyl cations obtained from CIDMS/MS experiments with helium collision gas and corresponding DFT-<br/>calculated bond dissociation energy, BDE (PBE1PBE/Def2TZVP GD3BJ<br/>theory level)

Entry	Parent ion	BDE <sub>exp</sub> kcal/mol[a]	BDE <sub>calc</sub> , kcal/mol
1	[(IMes-C <sub>2</sub> Ph)Pd]+	61 ± 5	54.5
2	[(IPr-C <sub>2</sub> Ph)Pd]+	63 ± 5	56.0
3	[(BIMe)(BIMe-C <sub>2</sub> Ph)Pd]+	60 ± 5	51.6
4	[(BMIM)(BMIM-C <sub>2</sub> Ph)Pd]+	63 ± 5	56.3

[a] The experimental errors are generous based on possible systematic shift due to the reactivity of the complexes with background gases.

These experimental results suggest that the dominant, kinetically preferred palladium elimination most likely happens from simple bond cleavage implying that the isolated complexes correspond to the product  $\pi$ -complexes. The reductive elimination might represent a kinetically preferred pathway compared to hydrogen-rearrangement reactions involving ligands. The energy demands for  $\pi$ -complex dissociations and reduction eliminations are similar, albeit the latter processes usually are slightly higher in energy.



Figure 2. Possible kinetically favored fragmentation pathway of  $[(IPr-C_2Ph)Pd]^{\star}.$ 



Figure 3. Infrared multiple photon dissociation and computed IR spectra. (a) DFT calculated spectra for *cis*- or *trans*-σ- and π-complexes and experimental spectrum of **8b**; (b) DFT calculated spectra for *cis*- or *trans*-σ- and π-complexes and experimental spectrum of **5b**.

As discussed above, three isomers of studied mono-NHC intermediate are possible: *trans*- or [*cis*-NHC-Pd-C<sub>2</sub>Ph]<sup>+</sup> (**3** and **4** correspondingly) or a  $\pi$ -complex [(NHC-C<sub>2</sub>Ph)Pd]<sup>+</sup> (**5**). Also, for the bis-NHC intermediates, three isomers are conceivable: *trans*- or [*cis*-(NHC)<sub>2</sub>-Pd-C<sub>2</sub>Ph]<sup>+</sup> (**6** and **7** correspondingly) or  $\pi$ -complex [(NHC)(NHC-C<sub>2</sub>Ph)Pd]<sup>+</sup> (**8**). NHC-ethynyl coupling cation **2** can be formed after reductive elimination from complexes **4** and either **6** or **7**, followed by dissociation of the solution gradient complexes, we have measured their infrared multiphoton dissociation (IRMPD) spectra.<sup>[39]</sup>

Infrared ion spectroscopy. To confirm the CID fragmentation hypothesis and in particular the structure of the reactant and product ions, IR spectra were recorded for species 5 and 8 after m/z-isolation in the mass spectrometer. Infrared ion spectroscopy was performed using a modified quadrupole ion trap mass spectrometer and the FELIX free-electron laser, which enabled us to cover the entire frequency range from 600 to 2100 cm<sup>-1.[49-50]</sup> These results are illustrated in Figure 3 which contains comparisons of experimental versus computationally predicted IR spectra for structures 5b and 8b. These spectral comparisons allow us to unambiguously conclude that  $\pi$ complexes containing Pd-triple bonds are present in both systems. This fact is especially evident from the position of the carbon-carbon triple bond vibration that is redshifted as a result of Pd binding to approximately 1900 cm<sup>-1</sup> in both experimental IR spectra, matching well only to the predicted IR spectrum of the  $\pi$ -complex of the (BMIM-C<sub>2</sub>Ph)-Pd(L) structure. Both potential σ-complexes (trans- or cis-(BMIM)<sub>2</sub>-Pd-C<sub>2</sub>Ph<sup>+</sup>) have a much lower red shift of the triple bond vibration in their spectra, and, thus, do not match the experimental data. Analogous results were found for all other studied ions: complexes 5a,c,d and 8a (see the Supporting Information for more details). The πbound Pd-alkyne complexes are clearly identified in all cases, also primarily based on the redshifted positions of the C-C triple bond vibrations.

Additionally, IR spectra are presented for the cationic reaction products **2a-d** (Figures S30-S33) and compared to computationally predicted spectra to demonstrate that we indeed observed the NHC-ethynyl coupling product when generated by

CID of the relevant Pd containing species. Moreover, the IRMPD spectrum of **2a** matches with its spectrum in the condensed phase, showing that the condensed phase structure is conserved when isolated in the mass spectrometer.

**Computational modelling**. Reductive elimination of the NHC and ethynyl Igands has a low activation barrier of 14.5 kcal/mol. This energy barrier is close to the NHC-Ph coupling (13.9 kcal/mol), however higher than the actual reductive elimination leading to the reaction product (7.7 kcal/mol; see Supporting Information for the computational details).

In this section, we analyze the electronic structure of the detected palladium complexes. The calculated enthalpy values  $(\Delta H)$  for the dissociation reactions **5**  $\rightarrow$  **2** + Pd (for systems with one NHC) and  $8 \rightarrow 2 + Pd-NHC$  (for systems with two NHCs) vary from 44.3 to 56.3 kcal/mol (Figure 4). Compounds 5a and **5b** have significantly lower  $\Delta H$  compared with **8a** and **8b**. This is an unusual result since in most cases the ligands in the transposition lower the binding energy to the Pd atom, as if they tend to push each other out of the coordination sphere of the metal. In this case, the  $[NHC-C_2Ph]^+$  ligand is a cation; therefore, the ligand-metal electrostatic interaction is of relevance. The Mulliken charges on the palladium atom in Pd-NHC are negative, since NHC is a donor ligand. In the Pd-BMIM and Pd-BIMe compounds, they are almost equal at -0.35. Accordingly, the electrostatic interaction between Pd-NHC and [NHC-C<sub>2</sub>Ph]<sup>+</sup> in 8 is stronger than between the bare Pd atom and the same cation in 2. We emphasize that these arguments are valid only for processes occurring in the gas phase, since the solvation energy should be accounted for in solution.

On the other hand, the enthalpy of dissociation of compounds **5** depends on the substituents of the NHC ligand. Systems with bulky aromatic substituents **5c** and **5d** have a larger  $\Delta H$  than structures **5a** and **5b** with small alkyl substituents. This is due to the additional  $\pi$ -coordination of aryl substituents with the palladium atom, which stabilizes the complex (Figure 5). Note that the palladium-acetylene binding energy in the Pd(0) coordination complex is 38.6 kcal/mol.<sup>[51]</sup>



Figure 4. Calculated energy profile ( $\Delta H$  in kcal/mol) for NHC-ethynyl coupling at the PBE1PBE/def2TZVP D3BJ level for (a) mono-NHC palladium complexes and (b) bis-NHC palladium complexes (NHC = BIMe, BMIM, IMes, IPr). The plots include only thermodynamic energies, no activation barriers were presented.



Figure 5. Calculated structures of 5c and 5d. Interatomic distances shown in angstrom; hydrogen atoms are omitted for clarity.

High calculated dissociation energies probably have the same origin: electrostatic interaction of  $[NHC-C_2Ph]^+$  and Pd-NHC in compounds **8a** – 51.6 kcal/mol and **8b** – 56.3 kcal/mol; additional  $\pi$ -coordination in compounds **5c** – 54.5 kcal/mol and **5d** – 56.0 kcal/mol (Table 2). Based on the calculated data, the dissociation enthalpy decreases in the order: **8b** ~ **5d** > **5c** > **8a**, which is consistent with the experimental BDE data. The values of appearance energies, as well as the calculated enthalpies of dissociation, differ from each other in a consistent fashion (Table 2), although the calculated  $\Delta H$  values are systematically below compared the experimental data by 10 – 12%. Thus, calculations support the hypothesis that the observed ions represent [(NHC-C\_2Ph)Pd]<sup>+</sup>  $\pi$ -complexes.

**Molecular dynamics (MD) simulations.** To make additional insight into the fragmentation pathways we have performed ab initio molecular dynamics (AIMD) simulation of CID process for [(BMIM)(BMIM-C<sub>2</sub>Ph)Pd]<sup>+</sup> **8b**. We were looking for fragmentation pathways that matches ones observed experimentally after a single collision. AIMD provides only short-time limit trajectories and only qualitative result was expected, and no attempt to address observed ion intensities was made.<sup>[52-53]</sup> In our model, complex **8b** moving at a velocity of 8.8 km/s collided with a fixed

argon atom. Due to the high cost of AIMD calculations and the inability to obtain long trajectories, the velocity of the complex was chosen so that approximately half of the collisions led to fragmentation in two picoseconds. This approach allows one to obtain a distribution of the fragmentation products close to the experiment (whether a single collision can lead to an observed fragmentation pattern). The energy balance of the process can be expressed by equation given in Figure S4b. It reflects the redistribution of energy within the considered molecular system. Calculated collision paths lead to 6 different product cations (Figure 6a, Table S5). In 18 trajectories fragmentation did not occur, although the internal energy increased by 142.3 -306.6 kcal/mol and the complex heated up to a temperature of 729.8 – 1198.5 K. In 17 MD simulations the Pd-BMIM bond was broken with formation of compound 5b. Another 5 collisions resulted in the cleavage of the  $\pi$ -coordination of Pd and the formation of 2b, while the Pd-BMIM  $\sigma$ -bond could both be preserved and broken. The remaining 5 trajectories were associated with the fragmentation of the butyl substituent of the heterocycle. The collision-induced internal energy increase E<sub>col</sub> for different calculated trajectories ranged from 142.3 to 351.6 kcal/mol.

According to the data obtained, the minimum value  $E_{cnl}^{min}$ , which have to be transferred to the system in order for fragmentation to occur, is 223.6 kcal/mol. This value is much higher than the calculated dissociation enthalpy of the system (56.3 kcal/mol), since upon impact the translational energy is transferred not to one degree of freedom, but is distributed over several degrees of freedom at the collision zone.

The more  $E_{col}$  the system receives, the higher the probability of fragmentation. This is evidenced by the average values of collision-induced internal energy increase for various events in MD simulations (Table S5). Collision and fragmentation events are clearly visible in the plot of potential energy versus time (Figure 6b). The figure shows graphs for simulations in which the Pd-NHC bond is broken.



**Figure 6.** AIMD simulation of CID process for [(BMIM)(BMIM-C<sub>2</sub>Ph)Pd]<sup>+</sup> **8b.** (a) A generalized representation of the collision trajectories with speed  $v_1 = 8.8$  km/s and distribution of the events in MD simulations. (b) Evaluation of potential energy with simulation steps for simulations resulting in Pd-NHC bond cleavage. Trajectories with the minimum (violet curves) and maximum (marine curves) values of  $E_{col}$  are shown.

The collision appears in the graphs in the form of peaks of potential energy. The top of peak corresponds to the closest distance between **8b** and the argon atom (Figure 6, events A and D). The argon atom then moves away from **8b** which leads to a decrease in potential energy. Gradual increases in potential energy in the graphs indicate structural changes in the system, such as isomerization or fragmentation (Figure 6, events B, C, E).

**Quantitative observation in the Sonogashira reaction.** We were able to quantify NHC-ethynyl product concentrations in the reaction mixture using the isolated coupling product as an added internal standard. The reaction was performed in Cu-free conditions, to avoid the possibility of copper catalyzing these transformations.<sup>[34]</sup> For further analysis, we used the Sonogashira reaction with triethylamine as a base due to it giving decent yields (up to 70%) at ambient conditions (r.t., air). Analysis of the reaction mixture resulted in an abundant signal of the NHC-ethynyl coupling product, but with only 1.4% percent yield, calculated by NMR. With the low activation energy barrier

for the NHC-ethynyl coupling in mind, we questioned if the amount of product observed is much lower than the amount actually formed (i.e. due to decomposition of **2a** or side-reactions). Moreover, in mass spectra we observed multiple compounds, which, we believe, are the products of further reactions of **2a**. To verify this hypothesis, we performed MS-monitoring of the Sonogashira reaction.

Under studied conditions, Sonogashira reaction was catalyzed by 5 mol % of deuterium labeled complex **1a**-*d*<sub>3</sub>. The reaction mixture also contained small amount of **2a**-**TfO**<sup>-</sup>, which was used to detect a concentration decrease of forming **2a**-*d*<sub>3</sub>. Due to matrix effects, the ionization efficiency may vary during the course of the reaction. Therefore, we used the **2a**-*d*<sub>6</sub>-**TfO**<sup>-</sup> standard to get accurate **2a** and **2a**-*d*<sub>3</sub> concentrations (to account potential consumption of **2a**-*d*<sub>3</sub> internal standard during the reaction course). We assumed its reactivity to be low in highly-diluted samples, because spectra were measured as quickly as possible after sampling (<1 min for the first point).

#### (A) Scheme of the experiment







Scheme 3. Formation and transformations of NHC-ethynyl coupling product in the course of the reaction. The reaction was performed in the following conditions: iodobenzene (0.17 mmol), phenylacetylene (1 eq), triethylamine (1 eq), 5 mol % of the catalyst in 3 mL of DMSO at 18 °C.

A change of  $2a-d_3$  concentration represents the difference between the rate of formation and the rate of further reactions of  $2a-d_3$ , while a change of 2a concentration is only related to the rate of further reactions of  $2a-d_3$  (both compounds were assumed to have the same reactivity, and be represented in the rate equation by their total concentration). The difference between relative changes (see SI for complete equation) helps to calculate cumulative amount of formed  $2a-d_3$  in the course of the reactions, and the yield of the NHC-ethynyl coupling product (Figure S1).

Results indicate that a large fraction of the product indeed reacts with different substances in the solution (formation of possible Pd-containing intermediate is represented by A in Scheme 3). The experimental data shows that the concentration of 2a-d<sub>3</sub> decreases with time with maximum observed amount correspond to the yield of 9%. But in assumption of equal reactivity of 2a and 2a-d<sub>3</sub> the concentration should reach a plateau without any further change when the formation stops. This observation might be due to formed from the catalyst **2a-d**<sub>3</sub>. having a much higher reactivity than the product 2a.TfO<sup>-</sup> added to the reaction mixture. This can be the case if at least one further reaction is occurring on a palladium atom (see Scheme 3), and  $k_1$  is comparable with one of the slowest steps in the pathway and much smaller than  $k_2$ . Thus, we can conclude that the real yield of the NHC-ethynyl coupling product may be underestimated and is greater than 9%.

One may also use another approach for the interpretation of the data. For the secondary reaction with Pd have to have a coordination vacancy. The reaction product  $2a-d_3$  is formed in the reductive elimination process within the Pd coordination sphere, while the added  $2a \cdot OTF$  has to go through a ligand exchange on the Pd-atom at least two times. This latter process is much slower, so that the overall pathway for the added product 2a is also much slower. This fact may also support the hypothesis that the NHC-ethynyl coupling product is formed on a palladium atom.

In order to ensure that this process generally occurs in the Sonogashira reaction, we have examined several substrates (under the same conditions but without internal isotope-labeled standards). Both processes of NHC-Ph and NHC-ethynyl coupling were observed for electron withdrawing and electron donating phenyl acetylenes (4-fluoro- and 4-ethoxy-) and iodobenzenes (4-nitro- and 4-methoxy). Substituents were chosen in order to avoid possible cross contamination; both [NHC-C<sub>2</sub>Ar]<sup>+</sup> and [NHC-Ar]<sup>+</sup> ions were clearly observed in all cases. Noteworthy, NHC-ethynyl products were similarly decreasing in their abundances due to further reactivity, while NHC-Ph products were accumulating (see Supporting Information for details).

Interesting to note, that NHC-ethynyl coupling still occurs in the absence of PhI. This confirms a general nature of the NHC-ethynyl coupling, which may take place as soon as both ligands are located on the metal center.

#### Detection of nanoparticles in the Sonogashira reaction.

Formation of metal nanoparticles from molecular Pd/NHC complexes is an experimental indication of R-NHC coupling (Figure 7). As both NHC-Ph and NHC-ethynyl products can be observed directly in the reaction mixture, we have conducted a transmission electron microscopy (TEM) nanofishing<sup>[54]</sup> to confirm the formation of bare palladium in the reaction mixture.<sup>[55]</sup> Under regular reaction conditions, ligandless

palladium species should agglomerate and form nanoparticles.<sup>[40, 56-57]</sup> Thereby, we have studied both reaction conditions: (i) with  $Cs_2CO_3$  as base at 80 °C and (ii) with  $Et_3N$  as base at r.t.

In both cases we have clearly observed palladium nanoparticles (Figure 7 and Supporting Information). Individual nanoparticles were clearly detected as well as some aggregates, which are usually expected for a dynamic system in solution. When the mixture was heated up in the presence of carbonate the mean diameter of palladium nanoparticles was 3.2±0.8 nm, while under mild conditions smaller 0.9±0.3 nm nanoparticles were observed. Under studied conditions, NHC-ethynyl and NHC-Ph couplings may contribute to Pd nanoparticles formation. Although it is difficult to determine which process contributes more, the observed formation of nanoparticles is in good agreement with the conclusions made about the nature of the studied catalytic system.



**Figure 7.** Formation of NHC-disconnected Pd due to R-NHC coupling, trapping nanoparticles by nanofishing procedure and experimental TEM images (scale bar – 20 nm in both cases; see Supporting Information for larger images).

# Conclusions

To summarize, we reported here experimental evidence for a novel transformation NHC-ethynyl coupling. This reaction occurs in acetylide Pd/NHC complexes at a high rate and represents a pathway in the dynamic catalytic system of the Sonogashira coupling reactions. The product of NHC-ethynyl coupling was observed under both Cu-assisted and Cu-free conditions with NHC ligands of different nature. Moreover, it can be synthesized by a direct reaction between Pd/NHC and acetylide under mild conditions.

Detailed MS and IRMPD studies provided a valuable understanding of the mechanism of this process. Reductive elimination of NHC with an ethynyl substituent occurs easily due to a low activation barrier, but the dissociation of the NHCethynyl product with Pd center is an endothermic process.

Kinetic studies of the Sonogashira coupling revealed that NHCethynyl coupling occurs from the very beginning of the reaction, but mostly it is excluded from the reaction by further transformations such as oligomerization, which was one of the general limitations to reveal this transformation. We anticipate more detailed mechanistic studies of the nature of NHC-ethynyl

coupling in the near future to expedite the development of a new class of recoverable Pd/NHC catalysts for alkyne C-H functionalization.

Exceptional importance of R-NHC coupling has been recently noted.<sup>[23]</sup> In the presence of R-NHC coupling, cocktail-type NHCdisconnected catalytic cycle is initiated, which operates on another concept<sup>[57]</sup> as compared to regular NHC-connected molecular catalysis. Different principles should be applied for catalyst optimization, especially to address recyclability and sustainability topics, in the cases of molecular NHC-connected or cocktail-type NHC-disconnected catalysis. In the present study, we demonstrate that NHC-disconnection can easily took place during the studied Sonogashira reaction by involvement of NHC-ethynyl coupling. Such a possibility of accessing NHCdisconnected catalysis pathway recalls for critical re-thinking of catalyst design principles.

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Keywords: Sonogashira reaction • CID • IRMPD • ESI-MS • NHC-ethynyl coupling

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# **Entry for the Table of Contents**



Mass spectrometry insight into the M/NHC-catalyzed Sonogashira cross-coupling reaction resulted in the discovery of NHC-ethynyl coupling process. Intermediates of this transformations and 2-ethynylated azolium cations were studied with NMR, ESI-MS, CID, IRMPD, DFT and MD techniques.

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