Reaction Mechanisms

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Formal *anti*-Carbopalladation Reactions of Non-Activated Alkynes: Requirements, Mechanistic Insights, and Applications**

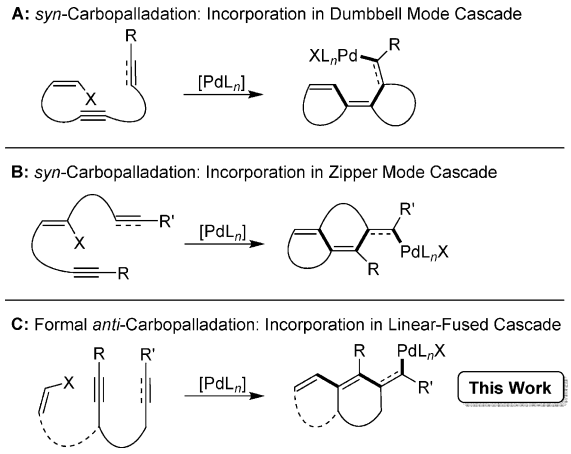
*Martin Pawliczek, Tobias F. Schneider, Christian Maaß, Dietmar Stalke, and Daniel B. Werz**

Dedicated to Professor Reinhard Brückner on the occasion of his 60th birthday

Abstract: *Formal anti-carbopalladation reactions of C–C triple bonds are uncommon, but highly useful transformations. Alkynes can be designed to give anti-carbopalladation products. Prerequisite is the exclusion of other reaction pathways to provoke the cis–trans isomerization of the syn-carbopalladation intermediate. Detailed mechanistic studies of this crucial step by experimental and computational means were performed. Application of an intramolecular version for the synthesis of oligocyclic compounds and substituted dibenzofurans is also described.*

A characteristic feature of carbopalladation reactions is the *syn*-attack of the organopalladium species [Pd]-R on the reacting π system.[1] Such a step results in compounds bearing Pd and R on the same side of the alkene moiety. Embedded into longer domino sequences, complex structures are obtained by a repetition of this *syn*-carbopalladation step. In this way, linear oligoynes can be cyclized to give benzene or higher oligoenes (Scheme 1 A).[2] With two alkyne chains opposing each other, zipper-mode[3] cyclizations can occur (Scheme 1 B).

Inspired by the recent breakthroughs in the *anti*-addition of silanes,[4] hydrogen,[5] boranes,[6] and stannanes[7] across a C–C triple bond we raised the question whether we might trigger a formal *anti*-carbopalladation process of non-activated alkynes. In contrast to hydrosilylations, hydrogenations, hydroborylations, and hydrostannylations the adducts being obtained from carbopalladations are still reactive organometallic intermediates and have to be intercepted in some way.[1] Thus, an incorporation of this step into a domino sequence similar to the examples depicted in Scheme 1 might be a suitable method for this purpose.



Scheme 1. *syn*-Carbopalladations of alkynes in domino sequences (A, B) and our work involving a formal *anti*-carbopalladation (C).

Major prerequisite for a formal *anti*-carbopalladation is the absence of any β-hydrogen atoms after attack of [Pd]-R on the C–C triple bond has taken place. By preventing the common pathway of β-hydride elimination we anticipated that other reaction channels would become energetically accessible. However, possibilities to react should only become available after the Pd atom has changed side. Such scenarios are provided by a simple tethered diyne or enyne as depicted in Scheme 1 C. To distinguish between the two different π systems we chose $R = CMe_2(OH)$ as a directing residue to afford a chemo- and regioselectively well-defined vinylpalladium intermediate (Scheme 2). In addition, this moiety serves as a termination unit later on. To test our design principle we chose diynes of type **1**. Our intention was to allow the possibly emerging *anti*-carbopalladation intermediate **4** to instantaneously undergo a subsequent carbopalladation to form product **5** which should be intercepted by the tertiary hydroxy group.

Compound **1a** ($R^1 = Me$; $X = CH_2$; $Ar^1 = Ph$) and PhI were chosen to investigate the anticipated process. Several ligand systems, solvents, and temperatures were screened to afford dienol ether **2a**. PPh_3 (4 mol%), $[PdCl_2(PhCN)_2]$ (2 mol%), and NEt_3 as base in a 0.025 M solution of polar dimethylacetamide (DMA) at 100 °C proved to be most effective and **2a** could be obtained in 84% yield (for

[*] Dr. T. F. Schneider, Prof. Dr. D. B. Werz
Institut für Organische Chemie
Technische Universität Braunschweig
Hagenring 30, 38106 Braunschweig (Germany)
E-mail: d.werz@tu-braunschweig.de
Homepage: http://www.werzlab.de
M.Sc. M. Pawliczek
Institut für Organische und Biomolekulare Chemie
Georg-August-Universität Göttingen (Germany)
Dr. C. Maaß, Prof. Dr. D. Stalke
Institut für Anorganische Chemie
Georg-August-Universität Göttingen
Tammannstrasse 4, 37077 Göttingen (Germany)

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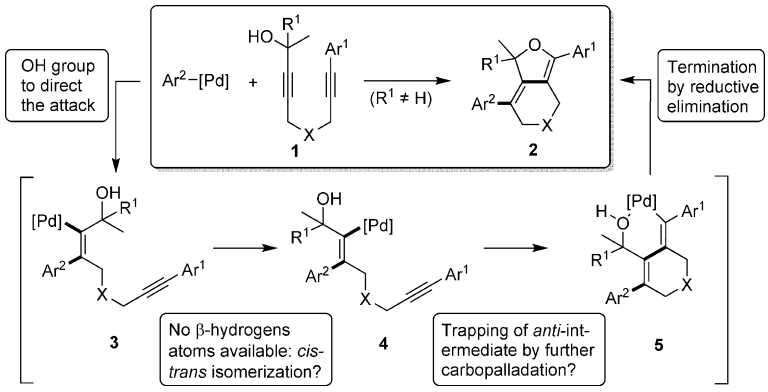
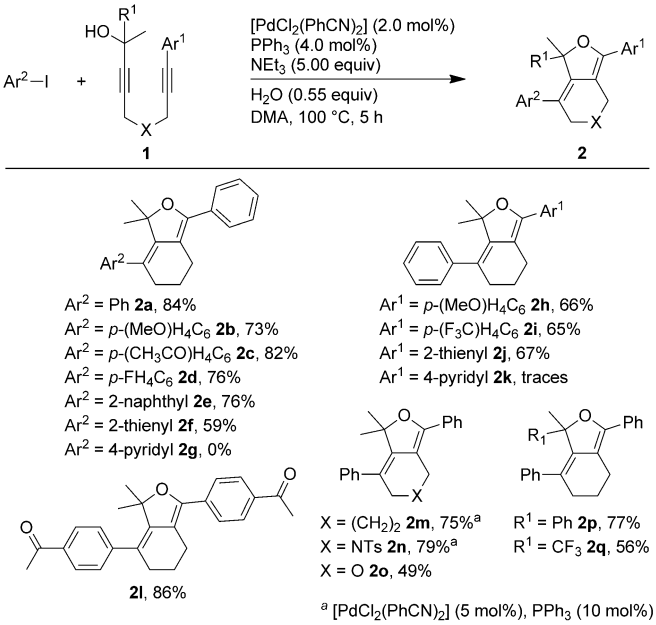


Scheme 2. Design of our system and anticipated sequence to intercept the formal *anti*-carbopalladation intermediate **4**.

optimization see Supporting Information). In toluene or with bidentate ligands, such as 1,2-bis(diphenylphosphino)ethane (dppe), the reaction did not take place. In addition, we observed that small amounts of water had a beneficial effect on the reaction outcome.

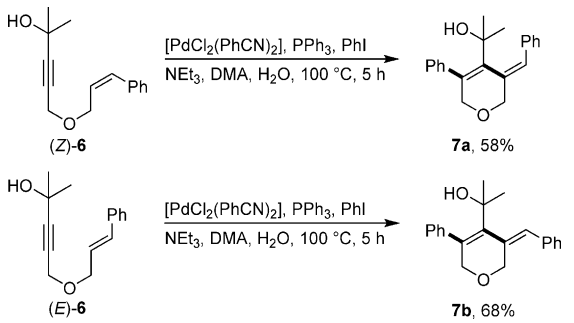
With the optimized reaction conditions in hand, the substrate scope was examined (Scheme 3). We started with the variation of the added aryl iodide. With respect to diyne



Scheme 3. Scope using various aryl residues, different tethers and tertiary alcohols. Ts = tosyl (4-methylphenylsulfonyl).

1 the yields were neither affected by electron-donating nor by electron-withdrawing groups (**2a–2d**). Also naphthalene and thiophene residues could be incorporated in good yields (**2e**, **2f**). While changing the aryl moiety at the diyne, the yields of **2h–2j** decreased slightly independent of the substitution pattern whereas the fluorescent acetophenone derivative **2l** was obtained in 86% demonstrating the facile access to a variety of compounds. To our surprise, when the pyridine derivatives, generally not troublesome in carbopalladation chemistry,[8] were exposed to our reaction conditions no conversion to **2g** or only traces of **2k** were observed (cf. mechanistic investigations). In addition, the influence of the tether between the alkyne moieties and the nature of the tertiary propargylic alcohol were evaluated. The reaction proceeded smoothly with substrates of both increased tether length (**2m**) and with heteroatoms in the tether (**2n**, and **2o**). Also other tertiary alcohol moieties were tolerated (**2p**, and **2q**).

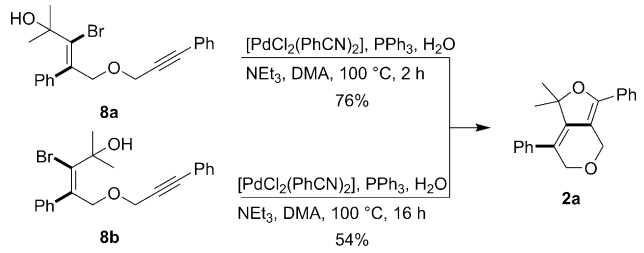
The successful realization of the unusual *anti*-connection provoked us to investigate the mechanism of this key step. To exclude a nucleopalladation[9–11] by the second triple bond one alkyne moiety was replaced with an alkene resulting in enynes (*Z*)-**6** and (*E*)-**6** exhibiting different double bond geometries (Scheme 4). Exposing these substrates to our reaction conditions, enyne (*Z*)-**6** delivered **7a** and (*E*)-**6** delivered diene **7b**, exclusively. These results were in accordance with a Mizoroki–Heck reaction mechanism as the terminating step and exclude carbocationic intermediates as these would lead to (*E*/*Z*)-mixtures.[12]



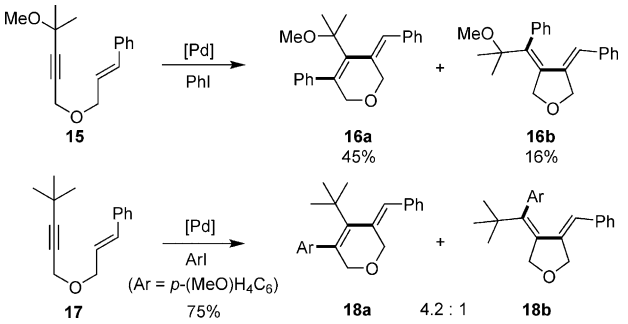
Scheme 4. Formal *anti*-carbopalladation terminated by a Mizoroki–Heck reaction to exclude the mechanistic possibility of nucleopalladation.

To further corroborate the mechanistic idea of *cis–trans* isomerization in the coordination sphere of the Pd, vinylic bromides **8a** and **8b** were prepared to mimic possible intermediates obtained after the carbopalladation (Scheme 5). As expected, compound **8a** reacted smoothly to the anticipated product **2a** in 76% yield. In addition, compound **8b** was also converted into **2a** in 54% yield after 16 h. Although there are reports on random *cis–trans* isomerization processes (e.g. with extended π-systems[13] or α,β-unsaturated systems[14]) being explained by zwitterionic species, in styrene moieties this is not a common process.

Literature precedence revealed exposing tertiary propargylic alcohols[15a] or amines[15b] to palladium in the presence of aryl iodides leads to the construction of tetrasubstituted allenes. These allenes were formed by carbopalladation and subsequent β-hydroxy elimination. Such a β-heteroatom elimination is not a favored process[16] compared with the β-



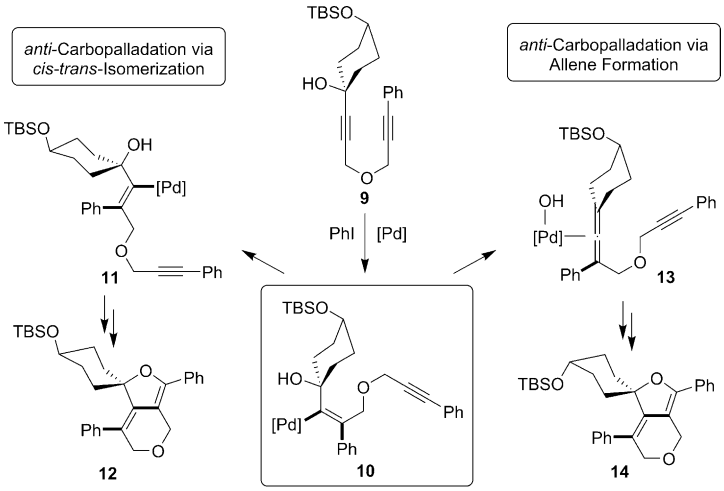
Scheme 5. Mimicking *syn*- and *anti*-carbopalladation intermediates by using vinylbromides.



Scheme 7. Formal *anti*-Carbopalladations without a free hydroxy group.

hydride elimination. If such an intermediate occurs, the Pd might easily change the side by interaction with the two orthogonal p orbitals of the central sp-hybridized carbon. Re-addition of Pd and OH on the other side in a *syn*-fashion would result in the required formal *anti*-carbopalladation intermediate.

To investigate such a possibility, we made use of diyne **9** (Scheme 6). In the case *cis–trans* isomerization of the double bond in **10** takes place, the reporter group *tert*-butyldimethylsilylether (OTBS) on the cyclohexane ring stays *cis* to the reactive hydroxy group (in **11**), in the event of allene formation to **13** and subsequent hydroxypalladation a 1,4-*trans*-arrangement of the two oxygen atoms would result. By X-ray structural analyses of starting material **9** and the corresponding product, allenic intermediates could be ruled out. The only product detected was compound **12**, but not **14**.



Scheme 6. Use of a reporter group (OTBS) to see whether the formal *anti*-carbopalladation proceeds by *cis–trans* isomerization of or by allene formation.

Taking into account that the hydroxy group seems only to be necessary as a directing group, enynes **15** and **17** were synthesized containing a methoxy and a methyl instead of the hydroxy group, respectively (Scheme 7). The conversion of methoxy derivative **15** proceeded smoothly, yielding the desired compound **16a** in 45% accompanied with side-product **16b** in 16% yield. The origin of the side-product can be ascribed to a "wrong" and hence inverted regiochemistry in the first carbopalladation step. When *tert*-butyl derivative **17** was employed, an inseparable mixture of desired isomerization product **18a** and side-product **18b** was obtained in 75% overall yield and a ratio of 4.2:1.

To further elucidate the fate of the double bond after the initial *syn*-carbopalladation we made use of DFT calculations[17–19] employing a simplified system. The chain with the second alkyne was replaced by a methyl group and PMe_3 was used instead of PPh_3.[20] We started our investigations with tetrasubstituted 16 valence electron (VE) Pd complex containing two phosphine ligands, iodine, and the vinyl residue obtained after carbopalladation. In contrast to recent suggestions[21] we were not able to find a metallocarbene species as local minimum, neither with nor without the help of an external nucleophile. Attempts to localize and isomerize such a complex led to huge energy barriers. However, after removing one PMe_3 from the metal complex generating the 14 VE Pd species *syn*-**19**, a transition state for the *cis–trans* isomerization 21.5 kcal mol^{-1} higher in energy than the starting complex could easily be localized (Figure 1). However, its structure did not resemble a common carbene complex.[22] Further computations including solvation demonstrate the beneficial effects of polar solvents.[19] In dimethylacetamide (DMA), the transition state is 3.7 kcal mol^{-1} lower than in vacuum.

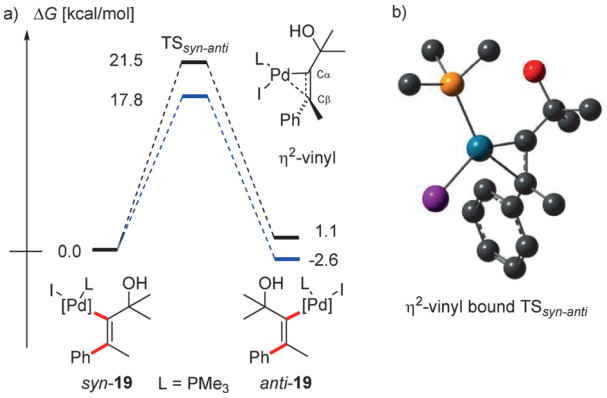
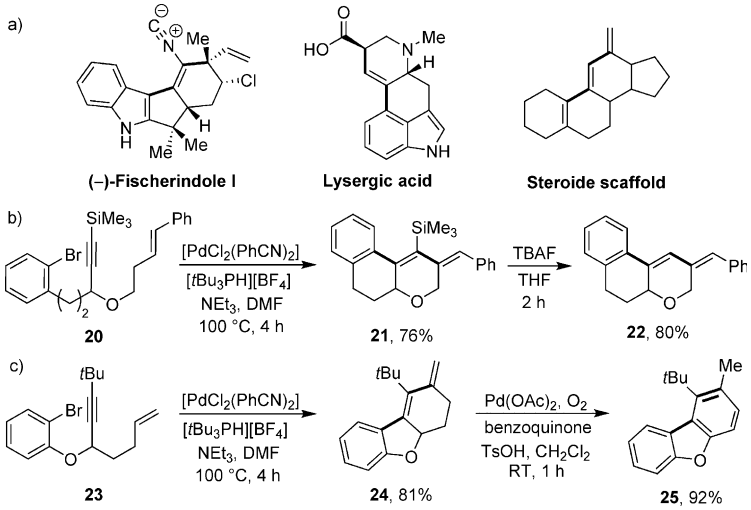


Figure 1. a) Calculated relative Gibbs energies for the *cis–trans* isomerization of [R-Pd(L)I]. Gas phase (black), DMA (blue). b) Computed structure of $TS_{syn\text{-}anti}$. Hydrogen atoms have been omitted for the sake of clarity; C gray, Pd blue, P orange, I purple, O red.

The fact that we could not localize an isomerization pathway with 16 VE Pd species nicely correlates with our experimental observation when we used bidentate ligand systems. The necessity for the 14 VE species might explain the inability to convert pyridines and secondary propargylic amides. Presumably, the binding affinity of these functional groups to Pd^{II}[23] entirely inhibits the formation of the η^2-vinyl transition state and hence the isomerization process.

The results prompted us to investigate intramolecular processes, paving the way for the preparation of natural product frameworks (Scheme 8a). In preliminary results, the formal *anti*-carbopalladation cascade using bromoarene **20** proceeded smoothly to afford diene **21**. The trimethylsilyl (TMS)-substituent could be easily removed, as was shown for



Scheme 8. a) *anti*-Carbopalladation motif in natural products. Intramolecular formal *anti*-carbopalladation b) using TMS at the alkyne, c) to dibenzofuran. TBAF = tetrabutylammoniumfluoride, TsOH = 4-methylbenzenesulfonic acid.

model compound **22** (Scheme 8b). Employing enyne **23** we designed a novel method to access substituted dibenzofurans. Formal *anti*-carbopalladation and a subsequent Heck reaction afforded tricycle **24** in 81% yield. Aromatization under Bäckvall-type oxidation conditions provided dibenzofuran **25** (Scheme 8c).

In summary, we have designed alkyne systems that are able to undergo a distinct, formal *anti*-carbopalladation. Our mechanistic rational of this process involves a common *syn*-carbopalladation in the first step. Since any β-hydrogen atoms in our constructs are absent, a *cis–trans* isomerization across the double bond generated is enabled. Embedded in a domino sequence the formal *anti*-carbopalladation intermediate is intercepted by a subsequent carbopalladation step. A variety of mechanistic experiments as well as DFT calculations of the crucial intermediate elucidated the nature of the formal *anti*-carbopalladation process. Substantiated by our mechanistic investigations we propose a 14 VE Pd species that is able to isomerize through a η^2-vinyl palladium transition state. Further studies with the defined integration of formal *anti*-carbopalladation processes into more complex domino cascades allowing *trans*-oligoenes to be prepared by short and efficient synthetic routes are ongoing.

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Keywords: *anti*-carbopalladation · domino reaction · palladium · reaction mechanisms

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Communications

Reaction Mechanisms

M. Pawliczek, T. F. Schneider, C. Maaß, D. Stalke, D. B. Werz* ——— ■■■–■■■

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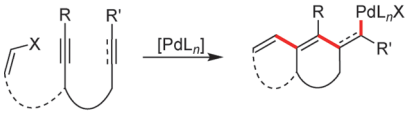

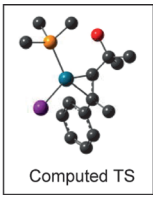

Reduced options: Diyne and enyne systems are designed that lead exclusively to formal *anti*-carbopalladation reactions. A prerequisite is the absence of β-hydrogen atoms that could offer other reaction channels. The mechanism is demonstrated by means of experiments as well as DFT calculations.

