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Pd Trimer Catalysis

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C-I Selective Cross-Coupling Enabled by a Cationic Pd Trimer

Claudia J. Diehl, Thomas Scattolin, Ulli Englert and Franziska Schoenebeck*

Abstract: While there is a growing interest in harnessing synergistic effects of more than one metal in catalysis, relatively little is known beyond bimetallic systems. This report describes the straightforward access to an air-stable Pd trimer and presents unambiguous reactivity data of its privileged capability to differentiate C-I over C-Br bonds in C-C bond formations (arylation and alkylation) of polyhalogenated arenes, which typical $Pd^{(0)}$ and $Pd^{(1)}$ - $Pd^{(1)}$ catalysts fail to deliver. Experimental and computational reactivity data, including the first location of a transition state for bond activation by the trimer are presented, supporting direct trimer reactivity to be feasible.

While mononuclear catalysts have dominated the field of homogeneous catalysis in the past decades, there is a growing interest in harnessing the synergistic interplay of multi-metal catalysts to access novel reactivities and selectivities.^[1] However, with more than one metal in a catalyst, there is also an associated inherent challenge of speciation, as a multi-metallic system could in principle act as reservoir to alternative catalytically active species. Nature overcomes this challenge through the use of a protein backbone that covalently controls structure (and hence function) of metal clusters in metalloenzymes.^[2] By contrast, with the exception of specifically tailored systems,^[3] synthetic homogeneous catalysts in solution generally lack these elements of control. As such, the understanding of the fate, dynamic exchange and reactivity behaviour of multi-metal clusters will be imperative to advance this promising field of research. This knowledge, however, is currently in its infancy.

In this report we showcase the ligand-assisted transformation of a dinuclear Pd^(I) catalyst to a cationic palladium trimer. The trimeric system is demonstrated to behave as a privileged catalyst in overcoming the challenge of differentiating C-I from C-Br bonds in the functionalization of polyhalogenated arenes (Figure 1). As such, we provide unambiguous support that the trimeric Pd catalyst triggers reactivity which typical Pd^(I) dimer or Pd⁽⁰⁾ monomer catalysts fail to deliver.

As part of our ongoing program to explore the potential of alternative catalysis modes with dinuclear $Pd^{(I)}$ complexes,^[4] we recently discovered that the air- and moisture stable, commercially available iodide-bridged $Pd^{(I)}$ dimer **1** forms a trimeric Pd complex upon subjection to diphenylphosphine. Addition of 4 equivalents of diphenylphosphine led to formation of trimer **2** in 99% yield as an air- and moisture stable solid (Figure 2, top). The structure of **2** was

[*] M.Sc. Claudia J. Diehl, M.Sc. Thomas Scattolin, Ulli Englert (Xray), Prof. Dr. Franziska Schoenebeck Institute of Organic Chemistry, RWTH Aachen University Landoltweg 1, 52074 Aachen E-mail: <u>franziska.schoenebeck@rwth-aachen.de</u> Homepage: <u>http://www.schoenebeck.oc.rwth-aachen.de/</u> unambiguously confirmed through X-ray crystallography. It is characterized by a symmetric triangular Pd arrangement that is overall cationic.



Figure 1. Challenges in multi-metal catalysis (top), in chemoselective Pd catalyzed cross-coupling reactions (middle) and this work (bottom).

Our computational analysis suggested that trimer 2 is a singlet, closed shell species and of aromatic nature.^[5] Similar trimers were previously isolated and characterized,^[6] however, there are only few reported applications in catalysis^[7] and little is known about their potential to display privileged reactivities over mononuclear catalysts. Encouragingly, Malacria and Maestri recently observed highly promising activities with Pd trimers in cycloadditions and hydrogenations.^[1f,7a-c] As such, we were keen to study the reactivity of trimer 2. We initially subjected the Pd trimer to a series of aryl halides (ArX, with X = I, Br, Cl) in a stoichiometric manner. Interestingly, the subjection of trimer 2 to *para*-iodo acetophenone led to complete conversion of 2 to corresponding iodide-bridged trimer 3 under concomitant formation of ArPPh₂, while no reaction was observed with the corresponding aryl bromide and chloride. As such, a net exchange of the PPh₂ bridging unit in 2 with iodide had taken place (see Figure 2, middle).^[8]

Given that we saw only exchange with ArI, we wondered whether we could exploit this activation mode in catalysis to address a pertinent challenge in the cross-coupling arena. Arguably, carboncarbon bond formations, both in sp² and sp³ fashion, are of tremendous importance. In particular, the selective bond formation of polyhalogenated arenes is of interest, as it would enable access to densely functionalized arenes and rich libraries of compounds. While Pd⁽⁰⁾ based protocols generally suffer from substrate-specificity and lack of predictability, we recently solved the challenge to selectively and *a priori* predictably functionalize C-Br, C-OTf and C-Cl sites in poly(pseudo)halogenated arenes, utilizing Pd⁽¹⁾ dimer 1.^[4g, 4h, 4j, 4k] A remaining challenge in the Pd-catalyzed cross-coupling arena is to differentiate the much more reactive C-I from C-Br sites.^[9]





Figure 2. Synthesis of the Pd trimer (top), its stoichiometric reactivity with aryl halides (middle) and comparison of the site-selectivity in arylations using different Pd (pre)catalysts (bottom; yields determined by quantitative GC-MS analysis using mesitylene as internal standard).^{[11] a}: 1.5 eq **5a** were used.

To get more insight, we initially challenged the C-I versus C-Br selectivity in the cross-coupling of 1-bromo-4-iodobenzene (4a) with PhMgCl and Pd^(I) dimer 1 and several other widely used Pd⁽⁰⁾ (pre)catalysts, e.g. Pd(PPh₃)₄, Pd₂dba₃/JohnPhos, ligand-free Pd₂dba₃ or Pd(OAc)₂ and more (see Figure 2 and Supporting Information). In accord with common assumptions and literature precedence, none of the tested catalysts were selective. Sluggish reactivity and bisfunctionalization (from the beginning of the reaction) was observed, indicating that C-I and C-Br bonds are similarly reactive under Pd⁽⁰⁾ and Pd^(I) enabled catalysis.^[10] In stark contrast, subjection of trimer 2 gave the selectively functionalized product 4-bromobiphenyl (6aa) in 88% yield in 2 hours at room temperature, without any formation of bis-functionalized product. Moreover, we found that trimer 2 can also be formed in situ. Simple pre-stirring of 1.5 mol% of the air- and moisture stable Pd^(I) dimer 1 and 6 mol% of PHPh₂ for 10 min at room temperature, before adding the cross-coupling partners, led to equally efficient and selective conversion.

Overall, the trimer appears to trigger distinct reactivity over its dimeric or mononuclear counterparts. We were hence keen to explore the generality of this reactivity mode and tested a range of differently substituted brominated aryl iodides as well as polyhalogenated heterocycles and a diverse set of aryl Grignard reagents under trimer 2 catalysis (Scheme 1). To our delight, coupling of 4a with different aryl Grignard reagents resulted exclusively in the C-I coupled products in good yields without any bis-functionalization (6ab to 6ad) using just 1 mol% of trimer 2. The use of easily accessible and non-specialized Grignard reagents (despite their usual tendency to undergo metal/halogen exchange reactions with aryl iodides^[12]) allowed for good yields and excellent selectivities at room temperature.



Scheme 1. Scope of the C-C cross-coupling with cationic trimer **2** as catalyst. Reaction conditions: Arl **4** (0.3 mmol, 1 eq), Grignard reagent **5** (1.5 eq), trimer **2** (1 mol%), toluene (4.5 mL). Isolated yields are shown (¹H NMR yield in parentheses as determined by quantitative ¹H NMR spectroscopic analysis using mesitylene as internal standard). ^a: 1.2 eq Grignard reagent used; ^b: 5 d reaction time; ^c: conversion determined by quantitative ¹⁹F NMR spectroscopic analysis; ^d: 1.1 eq Grignard reagent used; ^e: yield determined by quantitative ¹⁹F NMR spectroscopic analysis; ^d: 1.1 eq Grignard reagent used; ^e: yield determined by quantitative ¹⁹F NMR spectroscopic analysis using 1,4-difluorobenzene as internal standard.



Even cross-coupling reactions with sterically hindered *ortho-ortho* dialkylated Grignard reagents like 2-mesitylmagnesium bromide or 2,4,6-triisopropyl phenylmagnesium chloride proceeded efficiently and selectively (**6ad**, **6cd**, **6ag**, **6cg** and **6dg**). Moreover, bulky substituents *ortho* to the iodide of the substrate are tolerated as well (**6da**, **6df** and **6ef**). The medicinally and agrochemically important polyhalogenated *N*-containing heterocycles as substrates (**6if** and **6jf**) were also successfully coupled selectively at C-I, while tolerating bromide and chloride sites regardless of their relative positioning (*para*, *meta* and *ortho* to the iodide, *e.g.* **6ad**, **6cd**, **6be**, **6bf** and **6gc**). However, functionalization *ortho* to electron-withdrawing groups appears to be restricted to electron-poor Grignard reagents (**6fc** to **6hc**).^[13]

Further extending the generality of this chemoselective crosscoupling to the formation of desirable Csp²-Csp³ bonds, alkyl Grignard reagents were also employed as effective coupling partners in trimer **2** catalysis. Pleasingly, both primary and secondary alkyl magnesium halides were efficiently coupled to the C-I site of polyhalogenated arenes (entries **6ai**, **6kj** and **6lk**), thereby exclusively forming the mono-alkylated products. No competing beta hydride elimination nor metal/halogen exchange was observed, underlining the wider applicability of our method.

To understand the distinct reactivity of trimer **2** we next undertook mechanistic studies. Firstly, our EPR study of the stoichiometric C-I/C-P exchange (Figure 2) and catalytic C-C bond forming reactivity of trimer **2** were EPR silent, suggesting that no (sufficiently long-lived) radicals are involved in the process.

Given the distinct reactivity of trimer **2** (in catalysis and stoichiometric reactions) relative to $Pd^{(0)}$ and $Pd^{(1)}$ - $Pd^{(1)}$, it appears unlikely that the trimer simply serves as precursor to such species. Moreover, we also did tests with pre-formed palladium nanoparticles^[14] which gave rise to unselective cross-coupling of **4a**, suggesting that palladium nanoparticles are also not likely the catalytically active species.

We next turned to density functional theory (DFT) investigations to study mechanistic possibilities for the direct reactivity of the Pd trimer **2** with an aryl halide. Although we have an intuitive picture of the oxidative addition at Pd⁽⁰⁾, and detailed studies by our group shed light on the activation of aryl halides by Pd⁽¹⁾-Pd⁽¹⁾,^[4a, 4b, 4d, 4e] there are currently no data or knowledge on the potential direct reactivity with the aromatic trimer. Consequently, we undertook DFT investigations^[15] and attempted to locate transition states for oxidative addition of an aryl halide to the Pd trimer.

We were able to locate transition states for oxidative addition of PhX (with X = I, Br, Cl) to the cationic Pd trimer, which are characterized by concerted C-halogen bond cleavage and Pd-C bond formation. The activation free energy barriers for oxidative addition of PhX to Pd trimer 2 were found to rise in accord with BDE of the employed aryl halides, from overall $\Delta G^{\ddagger} = 30.7$ kcal mol⁻¹ (for X = I) to 38.8 (X = Br) to 45.3 (X = Cl) kcal mol⁻¹. These differences in oxidative addition barriers are in line with the results of stoichiometric reactions using aryl halides and Pd trimer 2 (vide infra) and potentially account for the observed selectivity for C-I functionalization of trimer 2 (see Figure 3). While the barrier of $\Delta G^{\ddagger} = 30.7$ kcal mol⁻¹ for the oxidative addition to C-I on first sight appears to be rather high for room temperature reactivity, the accurate reproduction of quantitative reactivity data still presents a challenge to computations, particularly if dispersion is of importance and ion pairs are involved. ^[16,17] The significantly greater barriers for addition at C-Br and C-Cl by trimer **2** are likely the origin of lack of reactivity at these sites and hence selectivity.



Figure 3. Comparison of the barriers of oxidative addition of iodo-, bromo- and chlorobenzene to the cationic trimer **2** and transition state geometry of the oxidative addition of PhI. Computed at CPCM (toluene) M06L/6-311++G(d,p) (SDD)// ω B97XD/6-31G(d)(LANL2DZ) level of theory. Free energy values are reported in kcal mol⁻¹.

In summary, the synthesis and distinct reactivity of an air-stable Pd trimer in chemoselective cross-coupling reactions of aryl iodides over bromides and chlorides with non-specialized Grignard reagents at room temperature was showcased. The protocol is operationally simple, employing either pre-formed or *in situ* formed trimer **2**, allowing arylations as well as alkylations of aryl iodides and the coupling of sterically crowded reaction partners. Combined experimental and computational studies suggest direct reactivity of the cationic trimer to be feasible.

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Conflict of interest

The authors declare no conflict of interest.

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Layout 2:

Pd Trimer Catalysis

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C-I Selective Cross-Coupling Enabled by a Cationic Pd Trimer



lodo-selective arylations and alkylations of polyhalogenated arenes were achieved using an air-stable cationic palladium trimer.

