Article

Understanding the Unusual Reduction Mechanism of Pd(II) to Pd(I): Uncovery of Hidden Species and Implications in Catalytic Cross-Coupling Reactions

Carin C. C. Johansson Seechurn, Theresa Sperger, Thomas G. Scrase, Franziska Schoenebeck, and Thomas J. Colacot

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.7b01110 • Publication Date (Web): 16 Mar 2017

Understanding the Unusual Reduction Mechanism of Pd(II) to Pd(I): Uncovery of Hidden Species and Implications in Catalytic Cross-Coupling Reactions

Carin C. C. Johansson Seechurn,[†] Theresa Sperger,[‡] Thomas G. Scrase,[†] Franziska Schoenebeck,*[,‡] Thomas J. Colacot*[,§]

[†] Johnson Matthey Catalysis and Chiral Technologies, Fine Chemicals Division, Orchard Road, Royston, SG8 5HE, U.K.

[‡] RWTH Aachen, Institute of Organic Chemistry, Landoltweg 1, 52074 Aachen, Germany

franziska.schoenebeck@rwth-aachen.de

[§] Johnson Matthey Catalysis and Chiral Technologies, Fine Chemicals Division, 2001 Nolte Drive, West Deptford, NJ 08066, U.S.A.

thomas.colacot@jmusa.com

ABSTRACT: The reduction of Pd(II) intermediates to Pd(0) is a key elementary step in a vast number of Pd-catalyzed processes, ranging from cross-coupling, C-H activation to Wacker chemistry. For one of the most powerful new generation phosphine ligands, P*t*Bu$_3$, oxidation state Pd(I), and not Pd(0), is generated upon reduction from Pd(II). The mechanism of the reduction of Pd(II) to Pd(I) has been investigated by means of experimental and computational studies for the formation of the highly active precatalyst [{Pd(μ-Br)(P*t*Bu$_3$)}$_2$]. The formation of dinuclear Pd(I) as opposed to the Pd(0) complex, [Pd(P*t*Bu$_3$)$_2$] was shown to depend on the stoichiometry of Pd to phosphine ligand, the order of addition of the reagents and, most importantly, the nature of the palladium precursor and the choice of the phosphine ligand utilized. In addition, through experiments on gram scale in palladium, mechanistically important additional Pd- and phosphine-containing species were detected. An ionic Pd(II)Br$_3$ dimer side product was isolated, characterized and identified as the crucial driving force in the mechanism of formation of the Pd(I) bromo dimer. The potential impact of the presence of these side species for *in situ* formed Pd complexes in catalysis was investigated in Buchwald-Hartwig, α-arylation and Suzuki-Miyaura reactions. The use of preformed and isolated Pd(I) bromo dimer as precatalyst provided superior results, in terms of catalytic activity, to catalysts generated *in situ*.

INTRODUCTION

The quote in a recent issue of *Chemical and Engineering News*, "palladium is the king of transition metal catalysts"[1] echoes with Trost's 2015 statement, "palladium has moved from being an esoteric metal of no known use to one being among the most versatile type of transition metal homogeneous catalyst of any metal today".[2] The above statement is very appropriate today as the status of palladium among its relatives has been elevated to the metal of the 21st century. One of the reasons behind the rapid ascendance of Pd is its tendency to undergo a clean "two electron"-based reduction of Pd(II) complexes to Pd(0). This reduction is the key step in the activation of many versatile precatalysts, but also a fundamental part of the mechanism of cross-coupling or C-H activation processes. Despite its importance and ubiquity, there is surprisingly little understanding of the mechanism. To date, the reduction of Pd(II) precursors to form catalytically active Pd(0) species has been proposed to be mediated by either base (e.g. base in conjunction with an alcohol[3] or alkoxides[4]) or organometallic cross-coupling partners such as organomagnesium, organozinc and -boronates.[5] The studies of its efficiency, rate and mechanism have led to novel insights and facilitated the improvement of precatalysts.[6] In addition, recent research has uncovered that for some of the most successful and widely used trialkylphosphine ligands, particularly with P*t*Bu$_3$, Pd(II) precursors may not necessarily be reduced to Pd(0) in the presence of excess ligand or additional base, but instead to the odd oxidation state complex Pd(I)-Pd(I) (Figure 1).[7] The Pd-P*t*Bu$_3$ system was identified relatively early on to per-

form exceptionally well for challenging cross-coupling reactions.[8]

As part of the newer trends in cross-coupling, in recent years much attention has been devoted to the development of novel Pd-phosphine precatalysts for the *in situ* formation of highly active twelve-electron based monophosphine Pd(0)L as the catalytically active species (Figure 1).[9] In this context, the dinuclear Pd(I) complex, [{Pd(μ-Br)(P*t*Bu$_3$)}$_2$] identified as the first example of the L$_1$Pd(0) type precatalyst has been shown to give exceptionally high catalytic activity in a number of cross-coupling reactions.[9a,10]

With regard to synthetic procedures for the formation of Pd(I) bromo dimer [{Pd(μ-Br)(P*t*Bu$_3$)}$_2$],[7b,11,12] the Colacot group identified a method by treating [Pd(cod)(Br)$_2$] (cod = 1,5-cyclooctadiene) with one equivalent of P*t*Bu$_3$ followed by the addition of NaOH in MeOH. This atom economical method yielded the Pd(I) dimer [{Pd(μ-Br)(P*t*Bu$_3$)}$_2$] (**1**) in nearly quantitative yield, notably with no sacrificial phosphine ligand.

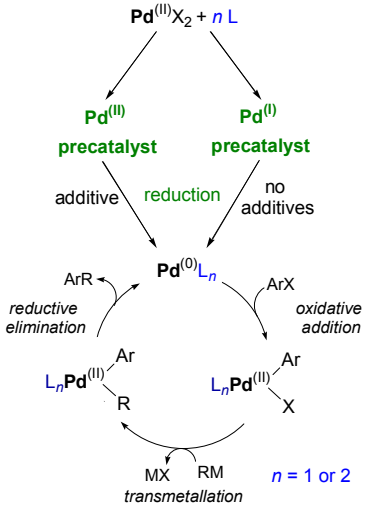


Figure 1. Generation of monophosphine LPd(0) *via* the activation of Pd(II) precatalysts, [7a-b] or *via* the halide-bridged Pd(I) dimer.[7a,13]

Concurrently in-depth computational and experimental studies on the activation requirements and the nature of the catalytically active species formed from **1** have been carried out by Schoenebeck and co-workers and are in line with the reactivity of a monophosphine Pd(0) species.[7a,13] For related more robust Pd(I) dimers, recent work by Schoenebeck and co-workers supported that direct reactivity at Pd(I) may also be feasible.[13,14]

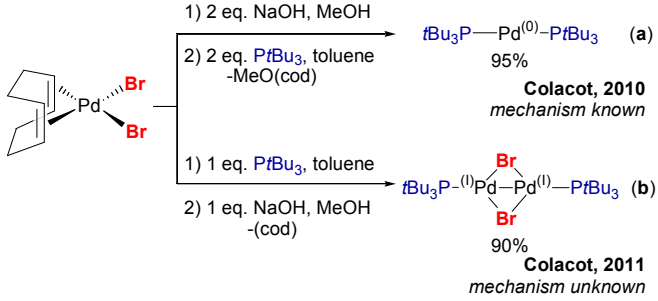
This article seeks to unravel the origins of the unusual formation of the observed Pd(I) complex and provide an understanding of the underlying factors and mechanism of reduction of Pd(II) precursor complexes. For the purpose of this study, P*t*Bu$_3$ was chosen as a representative electron-rich trialkylphosphine ligand. This ligand, along with few others, such as P*i*Pr*t*Bu$_2$,[15] have been found to be crucial for the formation of the Pd(I)dimer. A link to synthetically useful catalytic transformations is ultimately also presented.

RESULTS AND DISCUSSION

In the following sections conclusive evidence is being presented on how Pd(II) is selectively reduced to Pd(I), by systematically performing experiments in conjunction with theoretical calculations. The implication of this reduction pathway in cross-coupling reactions where the Pd(I) precatalyst is generated *in situ*, is illustrated by studying model amination, Suzuki-Miyaura and α-arylation reactions.

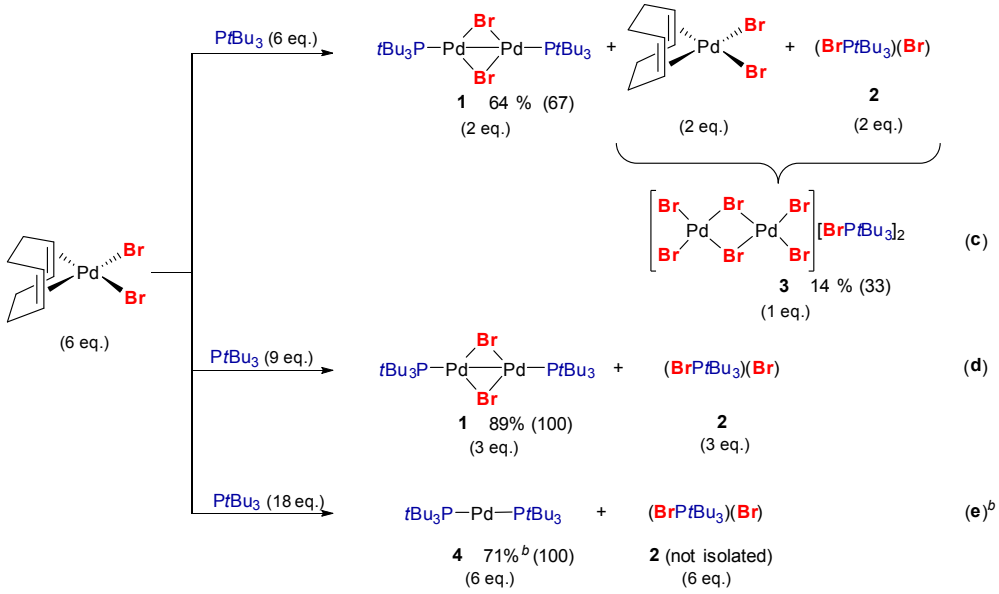
Experimental Investigation of Reaction Pathway for Formation of [{Pd(μ-Br)(P*t*Bu$_3$)}$_2$], (1). A few years ago, the Colacot group reported that upon treating [Pd(cod)(Br)$_2$] with a NaOH (2 eq.) solution in MeOH, followed by the addition of two equivalents of P*t*Bu$_3$ exclusively assisted the formation of bisligated Pd(0)L$_2$ complexes (Scheme 1, a).[16]

Scheme 1. Selective Reduction of Pd(II) to Pd(0) or Pd(I).



Although no sacrificial ligand was used for reducing Pd(II) to Pd(0), the cod ligand in combination with NaOH/MeOH was shown to be crucial in the reduction process of Pd(II) to Pd(0), where MeO-cod was identified as a byproduct.[16] However, as mentioned in the introduction, reversing the order of addition, i.e., base is added (1 eq.) at the last step of the reaction and by employing only one equivalent of P*t*Bu$_3$, quantitative formation of the Pd(I) dimer, [{Pd(μ-Br)(P*t*Bu$_3$)}$_2$] (Scheme 1, b) was observed.[12b] While the mechanism

Scheme 2. Experimental Identification of Side Products in the Formation of Pd(I) Bromo Dimer.[a]



[a]Yields based on Pd, theoretical yields in parentheses. [b]isolated as a 93 : 7 wt% mixture of 4 : 1, as determined by ^{31}P NMR.

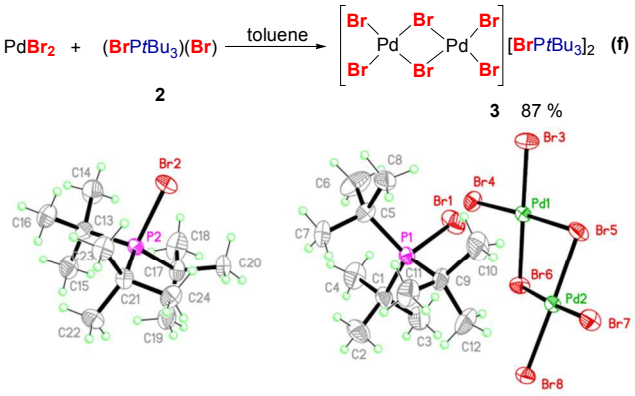
for the reduction of Pd(II) to Pd(0) in (a) is well established,[16] the mechanism by which the Pd(II) starting material is reduced to Pd(I) (b) is completely unknown.

In contrast to the process by which Pd(II) is reduced to Pd(0), the reduction of Pd(II) to Pd(I) proceeded also in the absence of cod.[17] The use of $PdBr_2$ as starting material, (see supporting information) also produced the Pd(I) compound (**1**), thus excluding any participation of cod in the reduction mechanism.[18] Notably, the final isolated yield of **1** prepared from $PdBr_2$ was only half of that obtained from $[Pd(cod)(Br)_2]$ (50% and 89%, respectively). This can be explained by the fact that $[Pd(cod)(Br)_2]$ is more soluble than $PdBr_2$.

In order to systematically elucidate the reduction process of Pd(II) to the unusual Pd(I) dimer species, we carried out reactions by varying the number of equivalents of P*t*Bu$_3$ ligand with respect to the Pd(II) precursor, $[Pd(cod)(Br)_2]$ (Scheme 2), as phosphines are known to reduce Pd(II). Employing one equivalent of phosphine ligand, Pd(I) dimer **1** was isolated in 64% yield (67% theoretical yield based on Pd) along with an unusual Pd-containing side product (**3**), which was unambiguously identified by elemental analysis, NMR and a single crystal X-ray diffraction study to be $[Pd_2Br_6][PtBu_3(Br)]_2$, containing a hexabromo-Pd(II) dianion $[Pd_2Br_6]^{2-}$ and two tri(tert-butyl)phosphonium bromide cations (Scheme 2, c). The formation of **3** is proposed to be the result of the reaction between $[Pd(cod)(Br)_2]$ with two equivalents of the phosphonium byproduct **2** (Scheme 2, c). Importantly reaction (c) had to be carried out on a larger scale (5 g scale), to facilitate the isolation of the side product **3,** as a key intermediate in elucidating the mechanism.

Side product **3** was also independently synthesized by reacting purified $PdBr_2$ with $(BrPtBu_3)(Br)$ (**2**) synthesized for this study. This resulting $Pd_2(II)Br_6$ salt **3** (Scheme 3), was identical to the one isolated from reaction c in Scheme 2. This experiment clearly suggests that one third of the phosphine is converted to phosphonium salt (**2**) with one third of the $[Pd(cod)(Br)_2]$ remaining unreacted, hence explaining the 67% theoretical yield of **1** in Scheme 2, c.

Scheme 3. Independent synthesis of side product 3 and crystal structure.[a]



[a]Selected Bond Lengths (Å) and Angles (deg): Pd1-Br5 2.450(5); Pd1-Br6 2.446(1); Pd1-Br3 2.410(1); Pd1-Br5-Pd2 90.0(0); Br5-Pd1-Br6 86.3(2); Br3-Pd1-Br5 91.8(2).

Subsequently, by increasing the mole ratio of P*t*Bu$_3$ to $[Pd(cod)(Br)_2]$ to 1.5:1, a bromide salt $(BrPtBu_3)(Br)$ (**2**) was obtained as a side product along with an isolated yield of 89% of the Pd(I) dimer (**1**) (Scheme 2, d). The yield of the Pd(I) dimer formed in reaction (d) is comparable to the yield of the previously reported process (Scheme 1, b). Further scale up of the process (Scheme 2, d) to 125 g gave a near-quantitative yield of **1**.

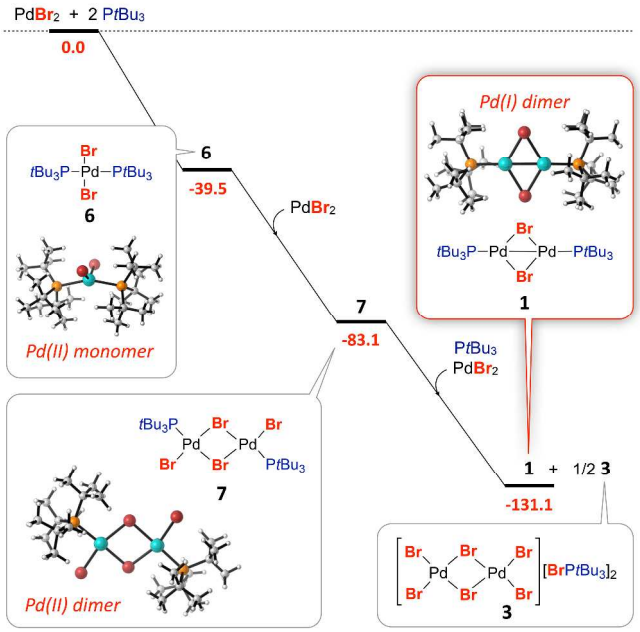
Further increasing the ratio of phosphine to Pd(II) to 3:1 resulted in the isolation of $Pd(PtBu_3)_2$ (**4**) in 95% purity, by ^{31}P NMR spectroscopy (Scheme 2, e). The remaining 5% of the reaction mixture was identified as the palladium(I) bromide dimer, **1**. Although this shows that no base is necessary for the reduction of Pd(II) to Pd(0), the $L_2Pd(0)$ catalyst is obtained in a purer form using the base-assisted process with $[Pd(cod)(Br)_2]$ starting material (Scheme 1, b).[16] A control experiment showed that by reacting Pd(I) bromo dimer **1** with 3 additional equivalents of $PtBu_3$ provided mostly $Pd(PtBu_3)_2$ **4**.

Precise monitoring of these reactions by NMR spectroscopy was not possible due to the difference in solubilities of the products (**1**, **2**, **3** and **4**). Pd(I) dimer **1** and $L_2Pd(0)$ **4** are soluble in toluene and benzene while insoluble in methanol. The side products (**2** and **3**) are soluble in methanol, but insoluble in toluene and benzene.

DFT Calculations on the Potential Mechanism of Reduction. With the above results in hand, we set out to computationally evaluate potential mechanistic pathways for the phosphine mediated formation of the Pd(I) bromo dimer **1**. The calculations at the CPCM (toluene) M06L/def2-TZVP//B3LYP/6-31G(d)(LANL2DZ) level of theory indicated that a direct reductive elimination of Br_2 from either $[Pd(PtBu_3)(Br)_2]$ (**5**) or $[Pd(PtBu_3)_2(Br)_2]$ (**6**) is energetically not feasible since both reactions are highly endothermic with ΔG of 54.2 and 28.7 kcal/mol, respectively. This is in line with experiments, since all efforts to detect Br_2 in the reaction mixtures were unsuccessful. In addition, a reductive elimination of $[BrPtBu_3]^+$ from $(PtBu_3)_2PdBr_2$ **6** and concomitant salt formation was found to be thermodynamically unfavorable (ΔG = 38.7 kcal/mol).

Therefore, we investigated an alternative ligand-assisted formal reductive elimination of Br_2 from **6** or **7** (Scheme 4). This would form the observed side product **2** (Scheme 2, (c)). Under reaction conditions explored in Scheme 2, (c), i.e. using an equimolar ratio of Pd(II) to phosphine the Pd(I) dimer **1** would be expected to form. Notably, the concomitant formation of $[Pd_2Br_6][PtBu_3(Br)]_2$ (**3**), by the reaction of bromide salt **2** with $PdBr_2$ (Scheme 3) constitutes an energetic sink and acting as the driving force for the reaction, thus rendering Pd(I) bromo dimer **1** as the thermodynamically most favorable species. All competing processes such as the formation of bis- or monophosphine Pd(II) (**6** and **5**, respectively) and dimerization of the latter to form Pd(II) dimer **7** are thermodynamically less favored.

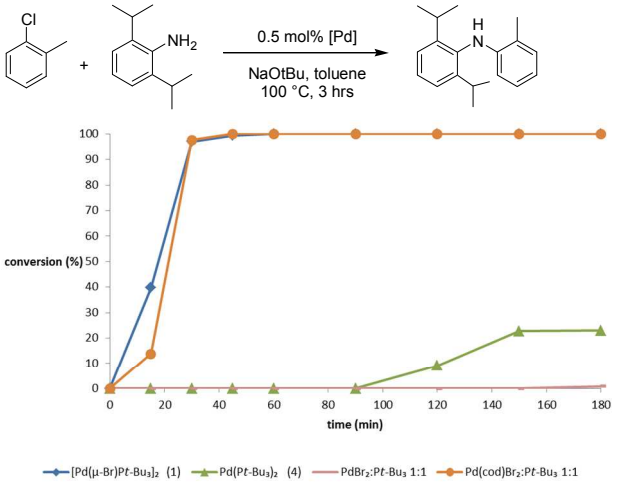
Scheme 4. Energetically available species relevant to the proposed mechanism.[a]



[a] Energies (in kcal/mol) were calculated at the CPCM (toluene) M06L/def2-TZVP//B3LYP/6-31G(d)(LANL2DZ) level of theory.

Implication in Catalysis. Having identified $(BrPtBu_3)(Br)$ (**2**), the $[Pd_2(II)Br_6]^{2-}$ salt (**3**), and in some cases also $[Pd(PtBu_3)_2]$ (**4**), as side products in the formation of Pd(I) bromo dimer **1**, we set out to investigate whether these previously unidentified species would have any impact in catalysis when precursors such as $PdBr_2$ or $[Pd(cod)(Br)_2]$ used under *in situ* conditions.

Scheme 5. Catalyst evaluation study in the coupling of 2-chlorotoluene with 2,6-diisopropylaniline.[a]



[a]Conversions determined using GC/MS.

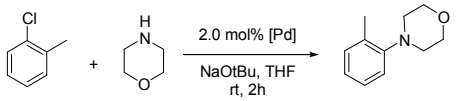
We decided to study two sets of Buchwald-Hartwig model amination reactions. In one of these, sterically hindered 2,6-diisopropylaniline was coupled with 2-chlorotoluene in toluene at 100 °C, using NaO*t*Bu as the base. Catalytically active species formed from the

1:1 reaction of $Pd(dba)_2$ with $PtBu_3$ were previously reported to efficiently catalyze amination reactions.[19]

As summarized in the graph in Scheme 5, using 0.5 mol% Pd loading, pre-formed Pd(I) catalyst [{Pd(μ-Br)($PtBu_3$)}$_2$] **1** gave 100% conversion of the secondary amine to the coupled product within 45 minutes. Under identical conditions, the pre-formed $L_2Pd(0)$ catalyst [$Pd(PtBu_3)_2$] **4** provided only 22% conversion to the product, although the reaction time was extended to 3 hours. This reflects the requirement in this reaction for the need for a $L_1Pd(0)$ based catalytically active pre-formed 12-electron species, *vs.* the 14-electron pre-formed, $L_2Pd(0)$. The *in situ* catalytic system from $PdBr_2$ with added $PtBu_3$ afforded the coupled product in very low conversion (0.8%), presumably due to the poor solubility of $PdBr_2$ in toluene. The catalyst formed *in situ* from [Pd(cod)(Br)$_2$] and added $PtBu_3$ gave comparable results at this scale of operation in comparison to the pre-formed [{Pd(μ-Br)($PtBu_3$)}$_2$] (**1**), which gave full conversion within *ca.* 45 minutes.

In order to further investigate the effect of the nature of the precatalyst under less challenging conditions, a room-temperature coupling reaction of 2-chlorotoluene with morpholine was evaluated, using tetrahydrofuran as the reaction solvent. In this case, Pd(I) dimer **1** was the only precatalyst yieldedany product formation. Using 2 mol% Pd loading, 98% conversion was observed within 120 minutes (Scheme 6, entry 1), while neither [$Pd(PtBu_3)_2$] **4** nor the *in situ* [Pd(cod)(Br)$_2$]/$PtBu_3$ system provided any of the desired coupling product (entries 2-3). This suggests that under these reaction conditions, only preformed Pd(I) dimer **1** is able to efficiently generate a catalytically active Pd(0) species, explaining the superiority of the precatalyst system under the specified reaction conditions.

Scheme 6. Room-temperature coupling of 2-chlorotoluene and morpholine.[a]



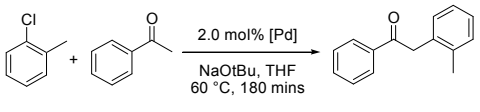
entry	catalyst	[Pd]:$PtBu_3$	conversion (%)
1	[Pd(μ-Br)$PtBu_3$]$_2$ **1**	1:1	98
2	$Pd(PtBu_3)_2$ **4**	1:2	0
3	Pd(cod)Br_2/$PtBu_3$	1:1	0

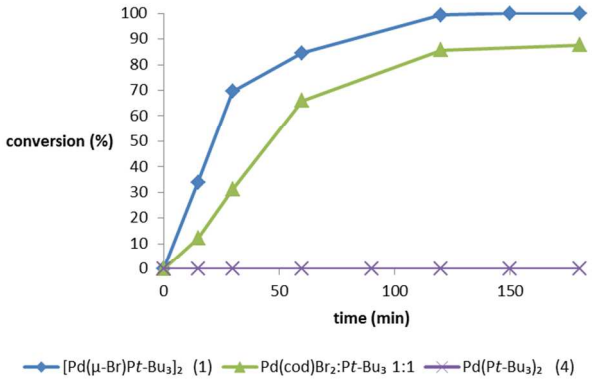
[a]Conversions determined using GC/MS.

Next, the impact of the precatalyst or Pd precursor was investigated in mono-arylation of acetophenone with 2-chlorotoluene.

Again, there is a striking difference between the use of Pd(I) bromo dimer **1** and Pd(0) precatalyst **4**. The use of **1** resulted in 100% conversion in ca. 120 minutes, whereas **4** did not provide any of the desired product (Scheme 7). In contrast to the room temperature amination reaction, in this case, [Pd(cod)(Br)$_2$] with added $PtBu_3$ in a 1:1 ratio generates a catalytically active species, although the reaction rate is slower than that of the pre-formed **1**. This result shows a similar trend to the amination reactions (Scheme 5) and can be explained by the fact that **1** is generated from [Pd(cod)(Br)$_2$] and $PtBu_3$. The slightly lower activity of the 1:1 [Pd(cod)(Br)$_2$]/$PtBu_3$ system relative to the pre-formed **1** is presumably due to the conversion of *ca.* 33% [Pd(cod)(Br)$_2$] to **3** (Scheme 2, (c)).

Scheme 7. Catalyst evaluation study in the mono-arylation of acetophenone with 2-chlorotoluene.[a]

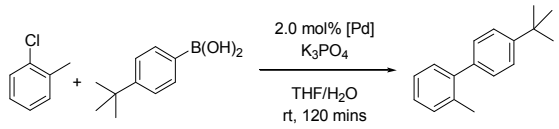




[a]Conversions determined using GC/MS.

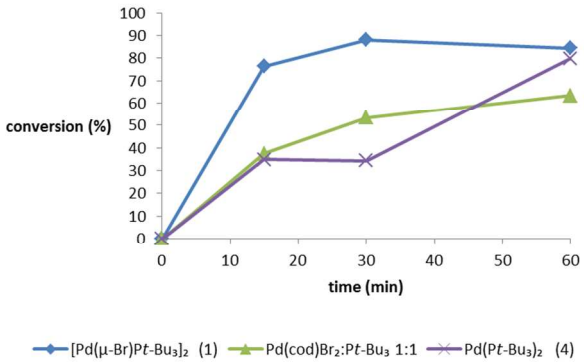
Finally, the impact of the choice of Pd precatalyst was investigated in a room temperature Suzuki-Miyaura reaction. Interestingly, despite our efforts in evaluating different reaction conditions and by varying Pd loadings, it was not possible to achieve full conversion to the desired product using **1** as the precatalyst. However, 90% conversion in ca. 120 minutes was observed by GC-MS (Scheme 8).The same reaction conditions were used to evaluate preformed $Pd(0)L_2$ catalyst **4** and the catalyst generated *in situ* from 1:1 ratio of [Pd(cod)(Br)$_2$] to$PtBu_3$. In contrast to the amination and α-arylation reactions, preformed $L_2Pd(0)$ catalyst, **4** eventually gave the same conversion as that of **1**. The 14 electron based $L_2Pd(0)$ catalysts are known to be relatively more stable than the $L_1Pd(0)$ system from a thermodynamic point of view. However, the initial reaction rate was slower than that of the Pd(I) bromo dimer **1**. The maximum conversion achieved for this model system was only 79%. The 1:1 [Pd(cod)(Br)$_2$]/$PtBu_3$ *in situ* system gave a lower final conversion to the desired product. This trend is similar to the α-arylation reactions, where less amount of Pd(I) precatalyst is formed when a 1:1 ratio of Pd to $PtBu_3$ is used (see Scheme 2, (c)).

Scheme 8. Catalyst evaluation study in the coupling of 2-chlorotoluene with (4-tert-butylphenyl)boronic acid.[a]



[a]Conversions determined using GC/MS.

In conclusion, in the model reactions the preformed Pd(I) catalyst [{Pd(μ-Br)(P*t*Bu$_3$)}$_2$] (**1**) gave higher final

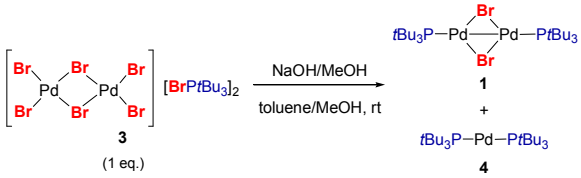


conversions and faster reaction rates than that of the catalysts formed *in situ* from either [Pd(cod)(Br)$_2$] or PdBr$_2$ with P*t*Bu$_3$. The well known preformed 14-electron based Pd(P*t*Bu$_3$)$_2$] (**4**) catalyst also gave inferior results in most cases, with the exception of Suzuki coupling. Based the mechanism elucidated in this study, it is understandable that with a 1:1 Pd:P*t*Bu$_3$ ratio for generating the *in situ* catalyst, ca. 33 % less of the active Pd(I) dimer is formed . In addition, under the conditions studied, if excess phosphine is present the formation of **4** is possible, which has been shown to be a less effective precatalyst in the model studies that we studied. Although it is possible to carefully engineer an efficient process using an *in situ* formed catalyst, it may be very challenging to achieve a robust and reproducible scale-up procedure due to the intrinsic subtleties associated with the mechanism of formation of the catalyst under the reactions employed for the specific cross coupling reactions. Therefore, further studies are needed in order to fully understand why, in the above cases, the in situ processes are less efficient in comparison to the preformed **1**. Several factors such as solubility of Pd source, order of addition of reagents, mole ratio of ligands to Pd, time of pre-mixing of Pd precursor with the ligand, type of base, etc., need to be thoroughly investigated.

The Role of Base or Additional P*t*Bu$_3$ in Equimolar Reaction. Furthermore, we sought to identify the role of the base in the equimolar reaction of [Pd(cod)(Br)$_2$] with P*t*Bu$_3$ (Scheme 1, (b)). As already stated, by omitting the base in this reaction, [Pd$_2$Br$_6$][P*t*Bu$_3$(Br)]$_2$ (**3**) is obtained alongside [Pd(μ-Br)P*t*Bu$_3$]$_2$ (**1**) (Scheme 2, (c)).

It was therefore hypothesized that the role of the subsequently added base was necessary to convert **3** to **1**. Indeed, when **3** was treated with six molar equivalents of methanolic NaOH at room temperature, **1** was isolated in 89% yield (Scheme 9, entry 2), which corresponds to one equivalent of base in the overall reaction starting from [Pd(cod)(Br)$_2$] (Scheme 2, c). Reducing the amount of base to four equivalents resulted in an incomplete reaction, where **1** was isolated in 62% yield (entry 1). The use of a slight excess of base - eight equivalents or 1:1.33 equiv. in the overall reaction from [Pd(cod)(Br)$_2$] – provided a mixture of **1** and **4** in a 9:1 ratio with a combined yield of 86% (entry 3).

Scheme 9. The Role of Base in the Formation of Pd(I) Bromo Dimer 1



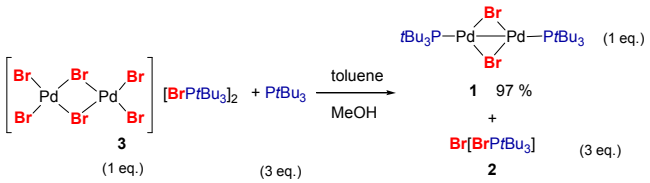
entry	eq. NaOH	% yield **1**	% yield **4**
1	4	62[a]	0
2	6	96	0
3	8	79[b]	7[b]

[a]Unreacted **3** observed. [b]Calculated from NMR ratio (Combined yield of 86%).

Based on this study, the overall equation can be balanced as 6 eq. of [Pd(cod)(Br)$_2$] reacting with 6 eq. of P*t*Bu$_3$ in the presence of 6 eq. of NaOH/MeOH to give 3 eq. of **1** and 6 eq. of NaBr. This corresponds to the 1:1 molar ratio of [Pd(cod)(Br)$_2$] to NaOH base in Scheme 1, reaction (b).

Since the formation of **3** is proposed to be the crucial thermodynamic driving force for the formation of Pd(I) bromo dimer (**1**), this side product, **3**, was also thought to play an essential role in the ligand- assisted reduction of Pd(II) to Pd(I) (Scheme 2, (d)). Pd(II)Br$_3$ dimer salt **3** was therefore treated with three equivalents of P*t*Bu$_3$. From this reaction, **1** was isolated in 97% yield (Scheme 10).

Scheme 10. The Role of Additional P*t*Bu$_3$ Ligand to Equimolar Reaction.



Based on this, the overall equation can be balanced as 6 eq. [Pd(cod)(Br)$_2$] reacting with 9 eq. P*t*Bu$_3$ to give 3 eq. of **1** and 3 eq. (BrP*t*Bu$_3$)(Br) **2** (Scheme 2, (d)). Two equivalents of **1** is formed initially, alongside one

equivalent of **3**, as outlined in Scheme 2, equation (c). A further equivalent of **1** is then formed from the reaction between one equivalent of **3** with 3 equivalents of P*t*Bu$_3$. This corresponds to the here-in established 1:1.5 ratio of [Pd(cod)(Br)$_2$] to P*t*Bu$_3$ required to make **1** without the added methanolic NaOH.

Based on these studies of the base-assisted and the ligand-assisted reduction of Pd(II) to Pd(I), the proposed common intermediate for both reactions is the side product **3**.

The above experiments clearly demonstrate that the mole ratio of base and ligand have a significant effect on the active catalytic species generated while conducting *in situ* reactions.

SUMMARY AND CONCLUSION

This study clearly elucidates the mechanistic features behind the reduction of a Pd(II) precursor in the presence of a phosphine ligand to form an unusual Pd(I) dimer species.

The preference for the formation of Pd(I) dimers *vs* more traditional $L_2Pd(II)X_2$ complexes is influenced by the formation of the ionic Pd(II)Br$_3$ dimer **3** side product, resulting from the stoichiometric reaction of (BrP*t*Bu$_3$)(Br) (**2**) with unreacted Pd(II)Br$_2$. This ionic Pd(II)Br$_3$ dimer **3** is a crucial byproduct as it acts as a "thermodynamic sink",. The experimental isolation and characterization of **3** was only made possible by carrying out experiments on gram-scale in palladium. Treatment of this unusual ionic, dimeric, Pd(II)Br$_3$ side product, **3** with either an alkoxide base or additional free P*t*Bu$_3$ ligand results in the formation of Pd(I) dimer **1**, hence explaining the atom economical synthesis of this Pd(I) complex.

In order to gain insights on the role of the identified side products, model reactions of some of the most applied synthetic transformations in the pharmaceutical industry, namely Buchwald-Hartwig amination, α-arylation and Suzuki-Miyaura cross-coupling reactions were conducted using **1** as a control *vs in situ* systems. The in situ system can be very complex, where many species can dynamically interconvert or interact depending on the amount of ligand, amount and type of base and the reaction conditions. This implies that absolute process precision is required in catalysis to get the optimal results and highlights the improved results using preformed Pd(I) *vs in situ* generated catalysts by mixing Pd(II) salts with a ligand. Further detailed studies to understand the exact fate of the Pd species in the *in situ* generated catalyst systems are on the way. This will hopefully reveal the reasons behind the consistently better performance of the preformed Pd(I) precatalyst.

ASSOCIATED CONTENT

Supporting Information. Experimental and computational procedures, spectral data and copies of spectra for all new compounds. This material is available free of charge *via* the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors

* franziska.schoenebeck@rwth-aachen.de (calculations)
* thomas.colacot@jmusa.com (experimental)

Notes

The authors of Johnson Matthey declare the following competing financial interest(s): [Pd(μ-Br)P*t*Bu$_3$]$_2$ is commercially available through JMCCT (www.jmcct.com).

ACKNOWLEDGMENTS

We thank Dr. Andrew Bond at Cambridge University for X-ray structure determination.

REFERENCES

(1) Ritter, S. K. *C&EN*, **2016**, *94*, 20.
(2) Trost, B. Foreword. In *New Trends in Cross-Coupling: Theory and Applications;* Colacot, T. J., Ed.; RSC: Cambridge, 2015; pp vii-x.
(3) Melvin, P. R.; Balcells, D.; Hazari, N.; Nova, A. *ACS Catal.* **2015**, *5*, 5596.
(4) (a) Zheng, Q.; Liu, Y.; Chen, Q.; Hu, M.; Helmy, R.; Sherer, E. C.; Welch, C. J.; Chen, H. *J. Am. Chem. Soc.* **2015**, *137*, 14035. (b) Hruszkewycz, D. P.; Balcells, D.; Guard, L. M.; Hazari, N.; Tilset, M. *J. Am. Chem. Soc.* **2014**, *136*, 7300. (c) Farmer, J. L.; Pompeo, M.; Lough, A. J.; Organ, M. G. *Chem. Eur. J.* **2014**, *20*, 15790. (d) Sayah, M.; Lough, A. J.; Organ, M. G. *Chem. Eur. J.* **2013**, *19*, 2749. (e) Chen, M.-T.; Vicic, D. A.; Chain, W. J.; Turner, M. L.; Navarro, O. *Organometallics* **2011**, *30*, 6770.
(5) (a) Serrano, J. L.; García, L.; Pérez, J.; Pérez, E.; García, J.; Sánchez, G.; Sehnal, P.; De Ornellas, S.; Williams, T. J.; Fairlamb, I. J. S. *Organometallics* **2011**, *30*, 5095. (b) Nasielski, J.; Hadei, N.; Achonduh, G.; Kantchev, E. A. B.; O'Brien, C. J.; Lough, A.; Organ, M. G. *Chem. Eur. J.* **2010**, *16*, 10844.
(6) (a) Wei C. S.; Davies G. H. M.; Soltani O.; Albrecht J.; Gao Q.; Pathirana C.; Hsiao Y.; Tummala S.; Eastgate M. D. *Angew. Chem. Int. Ed.* **2013**, 52, 5822. (b) Organ, M. G.; Chass, G. A.; Fang, D.-C.; Hopkinson, A. C.; Valente, C. *Synthesis* **2008**, 2776. (c) Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073. (d) Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 3314. (e) Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 1440.
(7) (a) Proutiere, F.; Aufiero, M.; Schoenebeck, F. J. Am. Chem. Soc. **2012**, 134, 606. (b) Aufiero, M.; Proutiere, F.; Schoenebeck, F. Angew. Chem. Int. Ed. **2012**, 51, 7226.
(8) (a) Nicholas, P. P. J. Org. Chem. **1987**, 52, 5266. (b) Littke, A. F.; Fu, G. C. Angew. Chem. Int. Ed. **1998**, 37, 3387. (c) Nishiyama, M; Yamamoto, T.; Koie, Y. Tetrahedron Lett. **1998**, 39, 617. (d) For a review of Pd-catalyzed coupling of aryl chlorides, see: Littke, A. F.; Fu, G. C. Angew. Chem. Int. Ed. **2002**, 41, 4176.
(9) (a) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. Angew. Chem. Int. Ed. **2002**, 41, 4746. (b) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. J. Am. Chem. Soc. **2003**, 125, 11176. (c) Christmann, U.; Vilar, R. Angew. Chem. Int. Ed. **2005**, 44, 366. (d) Li, H.; Johansson Seechurn, C. C. C.; Colacot, T. J. ACS Catal. **2012**, 2, 1147. (e) Johansson Seechurn, C. C. C.; Li, H.; Colacot, T. J. Pd-

Phosphine Precatalysts for Modern Cross-Coupling Reactions. In New Trends in Cross-Coupling Theory and Applications, Colacot, T. J., Ed.; RSC: Cambridge, UK, **2014**; pp 91-138. (f) Gildner, P. G.; Colacot, T. J. Organometallics **2015**, 34, 5497.
(10) (a) Durà-Vilà, V.; Mingos, D. M. P.; Vilar, R.; White, A. J. P.; Williams, D. J. *J. Organometallic Chem.* **2000**, *600*, 198. (b) Prashad, M.; Mak, X. Y.; Liu, Y.; Repič, O. *J. Org. Chem.* **2003**, *68*, 1163. (c) Colacot, T. *J. Platinum Metals Rev.* **2009**, *53*, 183. (d) Buscemi, G.; Miller, P. W.; Kealey, S.; Gee, A. D.; Long, N. J.; Passchier, J.; Vilar, R. *Org. Biomol. Chem.* **2011**, *9*, 3499. (e) Huang, D. S.; DeLuca, R. J.; Hartwig, J. F. *Org. Synth.* **2011**, *88*, 4. (f) Paton, R. S.; Brown, J. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 10448.
(11) Vilar, R.; Mingos, D. M. P.; Cardin, C. J. *J. Chem. Soc., Dalton Trans.* **1996**, 4313.
(12) (a) Goossen, L.; Arndt, M.; Mamone, P.; Gruenberg, M. WO2013000874, **2013**. (b) Colacot, T. J.; Hooper, M. W.; Grasa, G. A. WO2011012889, **2011**.
(13) Aufiero, M.; Scattolin, T.; Proutière, F.; Schoenebeck, F. *Organometallics* **2015**, *34*, 5191.
(14) (a) Bonney, K. J.; Proutiere, F.; Schoenebeck, F. *Chem. Sci.* **2013**, *4*, 4434. (b) Yin, G.; Kalvet, I.; Schoenebeck, F. *Angew. Chem. Int. Ed.* **2015**, *54*, 6809. (c) Aufiero, M.; Sperger, T.; Tsang, A. S.-K.; Schoenebeck, F. *Angew. Chem. Int. Ed.* **2015**, *54*, 10322.
(15) Proutiere, F.; Lyngvi, E.; Aufiero, M.; Sanhueza, I. A.; Schoenebeck, F. *Organometallics* 2014, *33*, 6879.
(16) Li, H.; Grasa, G. A.; Colacot, T. J. *Org. Lett.* **2010**, *12*, 3332.
(17) All reactions were performed in the absence of oxygen, i.e. in a glove-box or using Schlenk techniques. Under certain conditions, O_2 can act as oxidant of Pd(0) to Pd(I), see: (a) Kalvet, I.; Magnin, G.; Schoenebeck, F. *Angew. Chem. Int. Ed.* **2017,** *56*,1581. (b) Heijnen, D.; Tosi, F.; Vila, C.; Stuart, M. C. A.; Elsinga, P. H.; Szymanski, W.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2017,** doi:10.1002/anie.201700417.
(18) Control experiments of ($BrPtBu_3$)(Br) (**2**) with cod both in the presence and absence of $PdBr_2$ were carried out. No reaction of cod was observed (see supporting information). For halogenation of olefins in the presence of Pd(II), see: Green, M.; Hughes, R. P. *J. Chem. Soc., Dalton Trans.* **1976**, 1880.
(19) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861.

For Table of Contents only: