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Redox Reactions in Palladium Catalysis: On the Accelerating and/or Inhibiting Effects of Copper and Silver Salt Additives in Cross-Coupling Chemistry Involving Electron-rich Phosphine Ligands**

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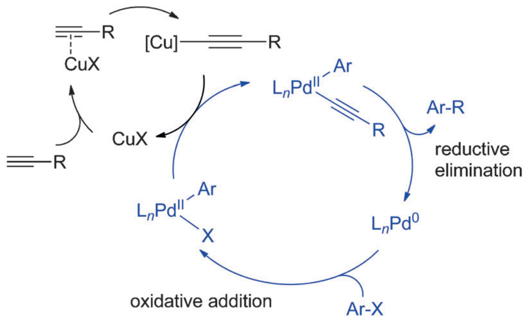
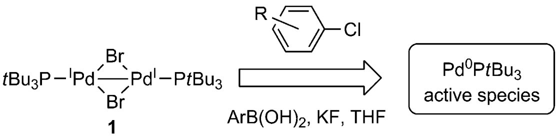
Palladium-catalyzed cross-coupling reactions are widely used to construct carbon–carbon or carbon–heteroatom bonds.[1] These transformations are frequently assisted by more than one metal, and Cu/Pd is probably one of the most frequently applied combinations, for example, in the Sonogashira and Stille reactions.[2] The precise effects of Cu salts in these transformations are not fully understood, but Cu^I is thought to play a catalytic, accelerating role in the transfer of an alkynyl group to Pd in the Sonogashira coupling (through formation of an organocopper species, $[Cu(C{\equiv}CR)]$, which in turn is more readily transferred to Pd^{II}, Scheme 1).[3] Other reports suggest the facilitation of transmetalation by Cu^I salts via organocopper species in the Stille and Suzuki reactions also.[4,5] On the other hand, a ligand-scavenging effect was also ascribed to CuI.[6,7] Another possibility of Cu effect was added by Chen and co-workers recently, who reported a transmetalation of a methyl group at platinum, involving a Pt^{II}-Cu^I bimetallic species.[8] In contrast to these "accelerating" effects of Cu salts, Buchwald and co-workers also reported an inhibitory effect of Cu salts in Sonogashira cross-coupling reactions of aryl chlorides.[9] A number of alternative, Cu-free variants of the Sonogashira transformation, or processes involving Ag salts instead,[10] were subsequently developed in recent years.[11]



Scheme 1. Generally accepted mechanism of Sonogashira coupling.

We herein report our observations of redox transformations of Pd^0 catalysts to dinuclear Pd^I complexes in the presence of Cu and Ag salts, and address the origin of enhancement and/or inhibition of cross-coupling reactivity in the presence of oxidizing salts. Our results suggest the possibility of alternative cross-coupling cycles involving bimetallic Pd^I over the currently accepted co-existing, synergistic cycles involving Pd^0/Pd^{II} and Cu (as shown in Scheme 1).

We recently reported our study on the reactivity and stability of the dinuclear Pd^I complex $[\{(PtBu_3)PdBr\}_2]$ (Scheme 2).[12,13] When this complex was used as precatalyst in Suzuki cross-coupling reactions, high reactivities were observed, leading to quantitative conversion of aryl bromides in as few as 15 minutes.[14,12] Aryl chlorides also reacted rapidly under Pd^I-dimer conditions (ca. 80% conversion in 20 min), but the catalytic activity dropped quickly in these reactions, and full conversion was not achieved as a consequence of a competing precatalyst deactivation process.[12] Our previous investigations showed that the reactivity derived from this complex with aryl chlorides is consistent with highly reactive monoligated Pd^0PtBu_3 as active catalytic species in THF,[12] and the Pd^I dimer liberates the active species more readily than $Pd^0(PtBu_3)_2$, accounting for the faster rates under Pd^I-dimer conditions[12,13c,14] (Scheme 2).[12] Following these studies, we recently began to explore the redox activity of $[Pd^0(PtBu_3)_2]$ against typical oxidizing agents to study the propensity to form the dinuclear Pd^I complex in the inverse process. We found that upon mixing one equivalent of $Cu^{II}Br_2$ with one equivalent of $[Pd(PtBu_3)_2]$, the dinuclear complex $[\{(PtBu_3)Pd^IBr\}_2]$ **1** was formed essentially instantaneously, and according to ^{31}P NMR spectroscopy the reaction was complete after 15 minutes at room temperature (Figure 1).[15] Thus, the Cu^{II} salt triggered a one-electron oxidation of Pd^0 to give the dinuclear Pd^I complex **1**. Cu^{II} was reduced to Cu^I in the same process. This latter event



Scheme 2. $[\{(PtBu_3)Pd^IBr\}_2]$ activation.

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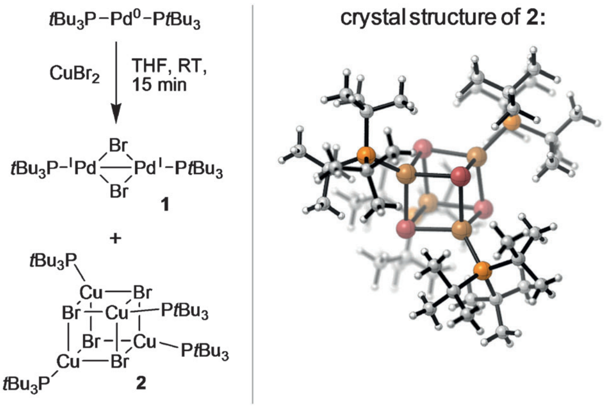


Figure 1. Oxidation of $[Pd(PtBu_3)_2]$ by $CuBr_2$ and X-ray structure of Cu cubane **2**.[16] After 15 minutes, $[Pd(PtBu_3)_2]$ was fully converted to **1**.

became apparent upon crystallization of the product mixture. We identified two different kinds of crystals. One type corresponded to the Pd^I dimer crystals, which are dark-green in color. The other type was white in color and was identified as the Cu cubane complex **2**[16] (see Figure 1 for the crystal structure). The Cu cubane **2**[16] gives a broad peak of low intensity at 55–59 ppm in the ^{31}P NMR spectrum in THF at room temperature, and showed relatively high stability.[17] Our DFT calculations[18] predict a driving force (ΔG) of $-5.4\ kcal\,mol^{-1}$ for monomeric "$CuBrPtBu_3$" to assemble as cubane **2** in THF.

Having observed this very facile oxidation of $[Pd(PtBu_3)_2]$, we turned our attention to Cu^I salts, as those are more frequently employed in cross-coupling reactions. We once again observed the formation of the dinuclear Pd^I complex **1** upon employing one equivalent of CuBr along with $[Pd(PtBu_3)_2]$ (Figure 2). The Pd^I dimer **1** is already detected after a reaction time of 15 minutes. We hypothesize that the oxidation occurs as a consequence of the tendency of Cu^I to disproportionate to Cu^0 and Cu^{II}. The thus generated Cu^{II} then triggers rapid oxidation of Pd^0 to dinuclear complex **1**.

The use of dinuclear complex $[\{(PtBu_3)Pd^IBr\}_2]$ (**1**) leads to much higher rates of cross-coupling reactions with aryl chlorides than $[Pd(PtBu_3)_2]$.[12,14] The formation of **1** might therefore be the origin of some of the frequently observed accelerating effects of Cu additives in catalysis. To address this issue, we performed reactivity studies and used the Suzuki cross-coupling of aryl chloride **3** as our benchmark reaction (Scheme 3). Our reactivity survey of dimer **1** versus $[Pd(PtBu_3)_2]$ in the presence and absence of $CuBr_n$ ($n = 1$ or 2) indeed shows increased reactivity under conditions that would favor formation of Pd^I dimer, that is, higher conversions are observed in the presence of $CuBr_n$ relative to $[Pd(PtBu_3)_2]$ in one hour (Table 1). To establish that the Pd^I dimer **1** is also formed under the applied reaction conditions, we mixed arylboronic acid (1 equiv), KF (3 equiv), $[Pd(PtBu_3)_2]$ (5 mol %) and CuBr (5 mol %) in THF. Examination of the mixture by ^{31}P NMR spectroscopy indeed showed the ^{31}P NMR signal of Pd^I dimer **1** after five minutes mixing time.

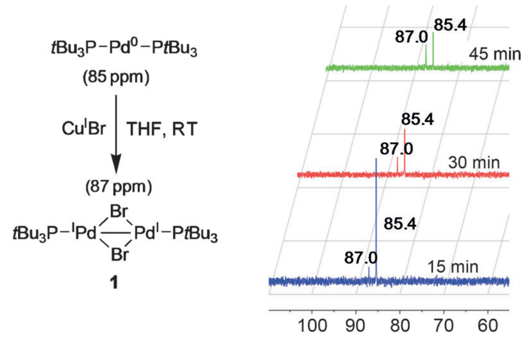
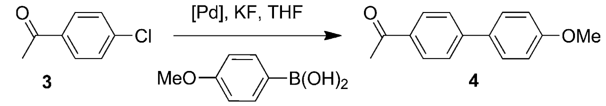


Figure 2. ^{31}P NMR analysis of the formation of **1** in the presence of one equivalent of CuBr (relative to $[Pd(PtBu_3)_2]$) versus internal standard (Me_3PO_4) in THF.



Scheme 3. Reactivity comparison of Pd/Cu system (see Table 1).

Table 1: Comparison of the effects of the [Pd]/Cu system on the reactions in Scheme 3.

Entry	[Pd]/Cu system[a]	Yield **4** [%]	Recov. **3** [%]
1	$[\{(PtBu_3)PdBr\}_2]$ **1** (2.5 %)	87	10
2	$[Pd(PtBu_3)_2]$ (5 %)/$CuBr_2$ (5 %)	52	36
3	$[Pd(PtBu_3)_2]$ (5 %)/CuBr (5 %)	48	49
4	$[Pd(PtBu_3)_2]$ (5 %)	11	84
5	$[Pd_2dba_3]$ (2.5 %)/$PtBu_3$ (5 %)	23	75
6	cubane **2** (2.5 %)	0	99
7	Pd^I **1** (2.5 %)/cubane **2** (1.25 %)	36	62

[a] Reaction conditions: KF (3.0 equiv), THF, RT, reaction time: 1 h.

Previous observations of reactivity enhancing effects of Cu^I salts in Suzuki reactions with ArBr or ArI were presumed to be a result of the formation of an organocopper species that would facilitate the transmetalation step.[5] However, for the coupling of aryl chlorides with $[Pd^0L_2]$ (in which L is a bulky ligand, such as $PtBu_3$), the initial ligand dissociation step ($[PdL_2] \rightarrow [PdL] + L$) to form the monoligated, highly active Pd species ([PdL]) is considered to be the reactivity limiting step.[19] Thus, facilitation of the transmetalation step (via an organocopper species) should be mostly irrelevant for the overall reaction rate, as it would not constitute the slowest step in the catalytic cycle. However, our finding that a change of the precatalyst from $[Pd(PtBu_3)_2]$ to the more active precatalyst $[\{(PtBu_3)Pd^IBr\}_2]$ takes place (which in turn liberates [PdL] more readily), is fully consistent with the observed reactivity enhancement.

Considering the rapid formation of Pd^I dimer in the presence of Cu salts, we wondered why we did not observe as high conversions as under Pd^I dimer catalysis itself (compare entries 1–3 in Table 1: ≈50 % vs. 87 % conversion). For efficient catalysis, the presence of Pd^I dimer at ppm levels should be sufficient, and given that the dimer can be very rapidly observed macroscopically by ^{31}P NMR spectroscopy (Figures 1 and 2), we questioned whether Cu cubane **2**, which is formed upon oxidation of $[Pd(PtBu_3)_2]$ and co-exists in solution, might influence the overall reactivity. We first established that cubane **2** does not trigger the Suzuki coupling reaction (Table 1, entry 6: no conversion was observed). When we added cubane **2** to Pd^I dimer **1** and then studied the transformation shown in Scheme 3, we observed lower conversion than under Pd^I dimer catalysis in the absence of cubane (compare entries 7 and 1). Through kinetic studies (Figure 3), we established further that the reactivity of the Pd^I dimer **1** in the presence of Cu cubane **2** (red) is particularly inhibited in the first 15 minutes, that is, the time window when the Pd^I dimer usually shows greatest activity (blue). Separate ^{31}P NMR investigations showed that the Pd^I dimer is stable in the presence of Cu^I cubane for the time that we monitored the mixture (4 h). We speculate that the transformation of the Pd^I dimer to the active catalytic species is inhibited by the Cu cubane, therefore leading to a lower reaction rate.

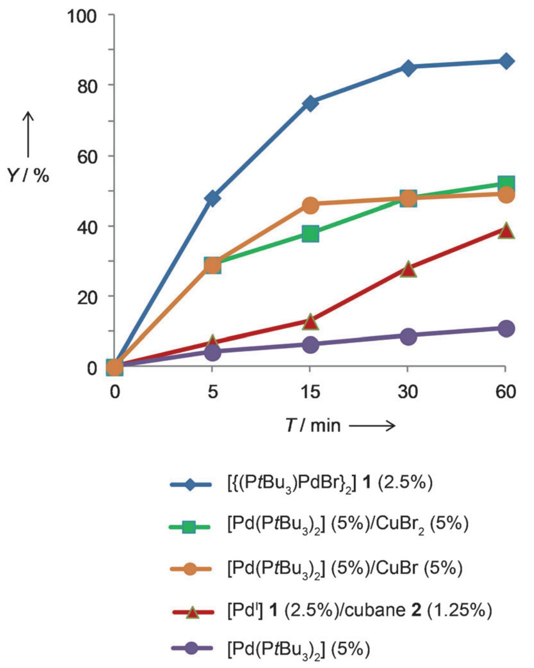


Figure 3. Kinetic study of reaction in Scheme 3. The conversion (Y) of **3** in the presence of different catalysts is plotted.

Since CuI is much more frequently used in cross-coupling reactions than CuBr, we next explored the effect of CuI. Upon mixing of one equivalent of CuI and one equivalent of $[Pd(PtBu_3)_2]$, we observed the analogous results, that is, the dinuclear Pd^I–I complex $[\{(PtBu_3)PdI\}_2]$ **5**[13b] was formed (see the Supporting Information, page S9). Through in situ ^{31}P NMR analysis, we were also able to show that Pd^I–I dimer forms rapidly also under Suzuki cross-coupling conditions (see pages S16–S17 in the Supporting Information).

The Pd^I–I dimer **5** was previously studied by Mingos, Vilar, and co-workers, and was found to be less reactive toward small molecules, such as H_2, than Pd^I–Br dimer **1**;[13b] however, information on the reactivity of **5** in cross-coupling reactions is sparse.[20] We set out to explore the reactivity of Pd^I–I dimer **5** in the identical Suzuki coupling of 4-chloroaryl ketone **3** (Scheme 3 and Table 2). Essentially, Pd^I–I dimer **5** showed similar reactivity as $[Pd(PtBu_3)_2]$, but much lower reactivity than Pd^I–Br dimer **1**. While the Pd^I–Br dimer results in nearly full conversion after one hour at room temperature (87 %, Table 1), the iodo analogue **5** leads to no conversion at all in the same time. Even after 24 hours reaction time, only moderate conversion was achieved (45 %, Table 2), similar to the reactivity with $[Pd(PtBu_3)_2]$. We presume that the reason for the lower reactivity of the Pd^I–I dimer **5** compared to its Br analogue **1** is the lower propensity of the latter to form the active catalytic species (i.e., $[PdPtBu_3]$) as a consequence of its higher stability. We are currently exploring the precise pathway for precatalyst activation. Our preliminary calculations of the driving force for 1) the dissociation of the homolytic dimer to $[Pd^IPtBu_3I]$ radicals, and 2) disproportionation of the complex to $[Pd^0PtBu_3]$ and $[Pd^{II}I_2PtBu_3]$ emphasize the stability of the Pd^I dimer **5** (26.8 $kcal\,mol^{-1}$ were calculated for the former and 40.2 $kcal\,mol^{-1}$ for the latter process).[18,21] These results suggest that $CuBr_x$ has a reactivity-enhancing effect in reactions with aryl chlorides in Suzuki coupling because of the formation of Pd^I–Br dimer **1**, whereas CuI has an inhibitory effect because of the formation of Pd^I–I dimer **5**, which in turn shows low reactivity in cross-coupling reactions.

Table 2: Comparison of the effects of the [Pd]/Cu system on the reaction in Scheme 3.

Entry	[Pd]/Cu system[a]	*t* [h]	Yield **4** [%]	Recov. **3** [%]
1	$[\{(PtBu_3)PdI\}_2]$ **5** (2.5 %)	24	45	53
2	$[Pd(PtBu_3)_2]$ (5 %)/CuI (5 %)	24	29	58
3	$[Pd(PtBu_3)_2]$ (5 %)	24	38	59
4	$[\{(PtBu_3)PdI\}_2]$ **5** (2.5 %)	1	0	99
5	$[Pd(PtBu_3)_2]$ (5 %)/CuI (5 %)	1	5	93
6	$[Pd(PtBu_3)_2]$ (5 %)	1	11	84

[a] Reaction conditions: KF (3.0 equiv), THF, RT.

We next considered the effect of AgBr. Ag salts have recently been identified as proficient alternatives to Cu in Sonogashira and Suzuki cross-coupling reactions.[10] With AgBr as additive, we also found an acceleration of the Suzuki coupling compared with additive-free $[Pd(PtBu_3)_2]$ catalysis, giving 53 % conversion after one hour for the transformation shown in Scheme 3. With ^{31}P NMR investigations of a 1:1 mixture of AgBr and $[Pd(PtBu_3)_2]$ in THF, we observed also formation of Pd^I–Br dimer **1** within one hour at room temperature (see the Supporting Information for the ^{31}P NMR spectra, pages S12–S15). In this process, an analogous Ag cubane **6** is formed, which we identified by X-ray crystal structure analysis (Figure 4).[22] The latter is the first crystallographic evidence that such a structure, involving the bulky ligand $PtBu_3$, is stable.

To this point, we only discussed the effect of additives on Suzuki cross-coupling reactions. What are the effects of

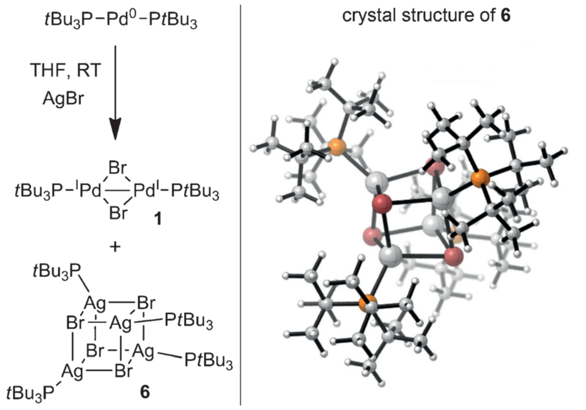
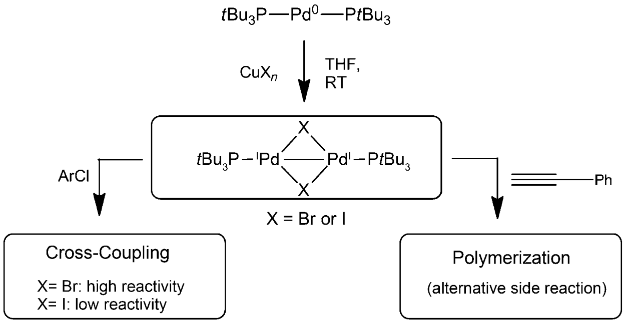


Figure 4. Reaction of [Pd(PtBu$_3$)$_2$] with AgBr (1:1) and X-ray structure of Ag cubane **6**.[22]

precatalyst transformation for the Sonogashira reaction? Buchwald and co-workers reported, for example, that CuI would inhibit the Sonogashira coupling of aryl chlorides, as the alkyne cross-coupling partner was consumed in a side reaction.[9] The oxidation of [PdL$_2$] by CuX to the Pd$^{\mathrm{I}}$ complex would be completely consistent with these observations. Pd$^{\mathrm{I}}$–I dimer **5** and Pd$^{\mathrm{I}}$–Br dimer **1** react with alkynes to give polymerization side products.[13b] When we exposed phenylacetylene to Pd$^{\mathrm{I}}$ dimers **1** and **5** along with diisopropylamine as base (at 50 °C in dioxane), we found that the alkyne was nearly fully consumed within one hour with dimer **1** (3 % alkyne left; with dimer **5**: 30 % left).[23] Thus, oxidation of the [PdL$_2$] to Pd$^{\mathrm{I}}$ dimer opens an alternative reaction pathway for alkyne polymerization, which competes with the "standard" cross-coupling pathway, and for more challenging substrates (such as ArCl, for which the oxidative addition is slower than for, e.g., ArBr) the side reaction wins over the cross-coupling process (Scheme 4).



Scheme 4. Polymerization side reaction in Sonogashira coupling as a consequence of Pd$^{\mathrm{I}}$ dimer formation.

Lastly, we also performed analogous investigations with alternative ligands, such as PCy$_3$ and (2-dicyclohexylphosphino)-biphenyl phosphine ligands. Our ^{31}P NMR analyses showed rapid formation of new species in the ^{31}P NMR spectrum upon mixing the corresponding [PdL$_2$] with CuI or CuBr$_x$ (see pages S18–S25 in the Supporting Information). Our future research is directed toward the structural elucidation of these species. The preliminary investigations indicate however that the discussed oxidation might be general in Pd catalysis across a range of electron-rich ligands. Our results might therefore also be of relevance for other types of coupling reactions, such as direct arylation reactions (C–H functionalization)[24] or Wacker processes.[25] For these processes, the formation of Pd$^{\mathrm{II}}$ species after oxidation of Pd^0 by Cu/Ag salts, but not the formation of dinuclear Pd$^{\mathrm{I}}$ complexes, is mechanistically assumed.

In conclusion, we have shown that oxidation of Pd^0 catalysts to dinuclear Pd$^{\mathrm{I}}$ complexes takes place in the presence of Cu and Ag salts. In the same process, Cu$^{\mathrm{I}}$ or Ag$^{\mathrm{I}}$ cubanes are formed, which in turn effect the activity of the dinuclear Pd$^{\mathrm{I}}$ complexes. The Pd$^{\mathrm{I}}$ complexes react readily with alkynes and initiate polymerization reactions, thus accounting for the inhibitory effects of Cu salts in Sonogashira reactions with ArCl. For Suzuki cross-coupling reactions with ArCl, the effect of oxidants depends on the anion. If $X = I$ (i.e., CuI), the dinuclear Pd$^{\mathrm{I}}$–I complex **5** is formed, which causes moderate transformations in cross-coupling as a consequence of its high stability and low propensity to form the active species [Pd^{0}PtBu$_3$]. If $X = \mathrm{Br}$, a more active precatalyst (**1**) results, which liberates [Pd^{0}PtBu$_3$] more readily and hence leads to much higher reaction rates than [PdL$_2$]. Our results suggest the possibility of alternative cycles involving bimetallic Pd$^{\mathrm{I}}$ [26] over the currently accepted co-existing, synergistic catalytic cycles involving Pd^0/Pd$^{\mathrm{II}}$ and Cu. In our future studies, we will focus on the latter and also expand our investigations to alternative ligands and additives (e.g., with noncoordinating counterions or anions that are less common as bridging halides).

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[18] a) CPCM (THF) M06L/6-31+G(d)//B3LYP/6-31+G(d) with SDD (for Cu or Pd) or QM/QM′ method was applied. The standard state was converted to 1 M in solution. See also the Supporting Information for details on calculation; b) M. J. Frisch et al. Gaussian09, Revision A.01—full reference in the Supporting Information.

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[21] We calculated only 3 $kcal\,mol^{-1}$ lower dissociation energies for the Pd^I–Br dimer **1** (for both pathways), thus suggesting that an alternative activation mechanism is likely. Compare reference [12].

[22] Selected X-ray data for **6**: $C_{55}H_{116}Ag_4Br_4P_4$, $M = 1652.48$, clear pale bronze prism; space group $R\bar{3}$; $a = 13.9482(4)$, $b = 13.9482(4)$, $c = 60.5717(13)$ Å; $V = 10205.6(5)$ Å^3; $Z = 6$; $\rho_{calcd} = 1.613\ Mg\,cm^{-3}$; $T = 100(2)$ K; reflections collected: 120779, independent reflections: 5243 [$R(int) = 0.0432$], $R1 = 0.0267$, $wR2 = 0.0556$, Flack parameter = 0.0(0). CCDC 874110 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[23] We also reacted phenylacetylene with $[Pd(PCy_3)_2]$ in the presence of 1) CuI or 2) $CuBr_2$ (with base in dioxane at 50 °C). Consumption of alkyne was also seen; 1 % of alkyne was recovered in (1) and 2 % in (2) after one hour.

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[26] Recent reports claim a direct involvement of Pd^I dimers and suggest a catalytic cycle in which the Pd–Pd bond stays intact, see: a) R. K. Das, B. Saha, S. M. W. Rahaman, J. K. Bera, *Chem. Eur. J.* **2010**, *16*, 14459; b) T. Murahashi, K. Takase, M. Oka, S. Ogoshi, *J. Am. Chem. Soc.* **2011**, *133*, 14908.