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# Pd(dba)$_2$ vs Pd$_2$(dba)$_3$: An in-Depth Comparison of Catalytic Reactivity and Mechanism via Mixed-Ligand Promoted C−N and C−S Coupling Reactions

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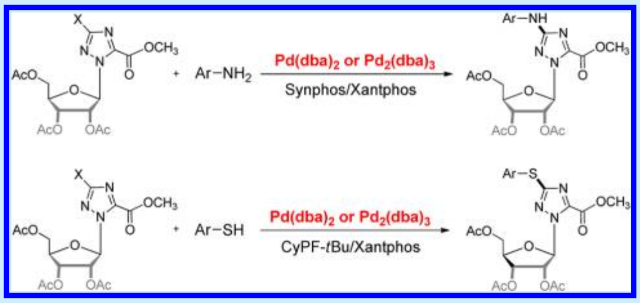
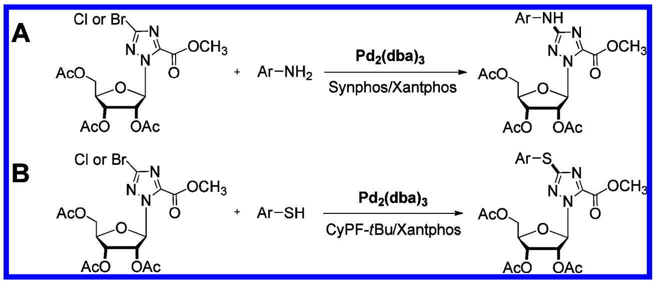
*Supporting Information*

**ABSTRACT:** With the help of mixed ligand catalytic systems, the analogous mechanisms behind the cognate performance by Pd(dba)$_2$ and Pd$_2$(dba)$_3$ in catalyzing C−N and C−S coupling reactions were demonstrated. This information is instrumental in organic synthesis requiring Pd-catalyzed cross-coupling reactions and may also be valuable to other Pd-catalyzed transformations.



Palladium-catalyzed cross-coupling reactions constitute one of the most important transformations in organometallic chemistry and have been increasingly and widely employed in organic synthesis both in academic research and in industrial production.[1−3] In these reactions, Pd(0) or Pd(II) reagents play a crucial role and are often used in combination with ligands (L) such as phosphine, amine, and *N*-heterocyclic carbene, to generate *in situ* the active catalytic "Pd(0)L$_n$" species and consequently promote efficient cross-coupling of poorly reactive and/or sterically hindered substrates.[4] Among myriads of Pd reagents developed to date, Pd$_2$(dba)$_3$ and Pd(dba)$_2$ (dba = *trans,trans*-dibenzylidene acetone) are the most frequently employed Pd(0) sources for cross-coupling reactions by virtue of the ideal balance that they offer between reactivity and stability. The "dba" in these reagents acts as a competent ligand to cooperate with the unstable Pd(0) to provide reactive yet robust Pd(0) precatalysts. Also, the once presumed "innocent" dba ligand presented in Pd(dba)$_2$ or Pd$_2$(dba)$_3$ can actually participate toward catalysis via alkene ligation to the PdL complexes, generating the active Pd(dba)L complexes.[5] In fact, Amatore and Jutand have proposed that the ligand dba plays an important role in the reactivity of Pd(0) complexes by stabilizing Pd(0) species and/or slowing the rate of catalysis.[6] Recently Buchwald et al. also mentioned that dba might interfere with the reaction.[7] Yet, many scientists have noted that despite the different Pd/dba ratios in Pd(dba)$_2$[8] and Pd$_2$(dba)$_3$, these two Pd reagents shared similar catalytic reactivity and could be interchanged in many cross-coupling reactions.[9−12] Nevertheless, the catalytic mechanism behind the observed similar catalytic effect has to our knowledge remained largely unexplored. Understanding this mechanism would likely prove instrumental and eventful for the Pd-catalyzed cross-coupling reactions and other reactions as well.

**Scheme 1. Mixed Bidentate Ligand Systems Promoting (A) C−N Cross-Coupling and (B) C−S, Respectively**



As part of our longstanding interest in and contributions toward the synthesis of biologically active nucleoside analogues,[13−15] we recently emphasized the key role of mixed-ligand[16,17] Pd catalysts in C−N and C−S cross-coupling reactions for the preparation of *N*-arylamino- and *S*-arylthiotriazole nucleosides that are otherwise very difficult to obtain (Scheme 1).[18,19] In those mixed ligand catalytic systems Pd$_2$(dba)$_3$ turned out to be the precatalyst of choice.[20] We were curious as to whether Pd(dba)$_2$ as the Pd(0) source could be also effective in these mixed ligand catalytic systems in a similar way as Pd$_2$(dba)$_3$.[21] We therefore studied and compared the catalytic efficiency and the corresponding mechanism of both Pd$_2$(dba)$_3$ and Pd(dba)$_2$ as the Pd(0) source in the C−N and C−S coupling reactions with the aim of uncovering general trends of such mixed-ligand catalytic systems and gaining more insight into their underlying mechanism. In this work, we will

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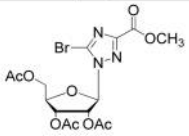
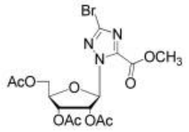
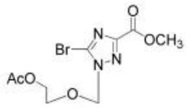
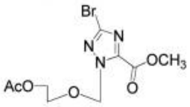
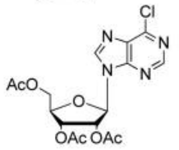
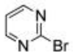
present and discuss our findings and their relevance in Pd-catalyzed reactions.

We first conducted a comprehensible comparison between $Pd(dba)_2$ and $Pd_2(dba)_3$ in regard to their catalytic activities in C−N cross-coupling reactions with various challenging substrates including heterocyclic aryl halides (Tables 1) and sterically hindered or electron-deficient arylamines (Table 2). Interestingly, all examined reactions led to the desired products in similarly excellent yields, highlighting a possible cognate catalytic efficiency for $Pd(dba)_2$ and $Pd_2(dba)_3$ in such mixed ligand systems regardless of substrate. Likewise, similar results were attained for C−S coupling reactions (Table S1), supporting again that $Pd(dba)_2$ and $Pd_2(dba)_3$ might effectively exhibit a common catalytic pathway. These data are in line with those previously reported in literature based on simple single ligand or ligand-free Pd systems.[9−12]

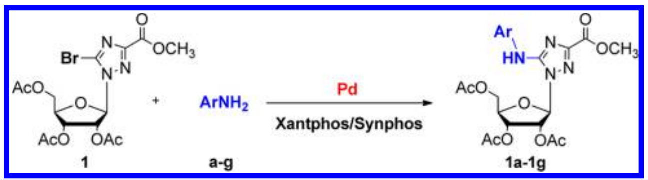
### Table 1. $Pd(dba)_2$ and $Pd_2(dba)_3$ Assisted Mixed Ligand Systems of Pd/Xantphos/Synphos for C−N Coupling with Various Heterocyclic Substrates

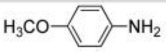
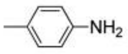
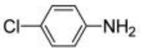
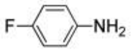
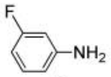
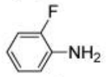
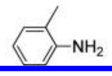
| entry | halide substrate (1-6) | product | yields (%) with $Pd(dba)_2$[a] | $Pd_2(dba)_3$[b] |
|---|---|---|---|---|
| 1 |  | 1a | 87 | 92 |
| 2 |  | 2a | 87 | 91 |
| 3 |  | 3a | 87 | 88 |
| 4 |  | 4a | 86 | 89 |
| 5[c] |  | 5a | 86 | 90 |
| 6 |  | 6a | 91 | 92 |

[a] Reaction conditions: halide (0.10 mmol), arylamine (0.20 mmol), $Pd(dba)_2$ (0.010 mmol), [Pd]/[ligand] = 1/1.2, [Xantphos]/[Synphos] = 1/2, $K_2CO_3$ (0.20 mmol), toluene (2.0 mL), 110 °C, 2−6 h, isolated yield. [b] The reaction conditions were the same as (a) except $Pd(dba)_2$ (0.010 mmol) was replaced by $Pd_2(dba)_3$ (0.0050 mmol). [c] 20 mol % Pd; reaction time was 14 h.

The similar catalytic efficiencies of $Pd(dba)_2$ and $Pd_2(dba)_3$ in the above mixed ligand systems might be related to the genesis of similar active Pd species during the course of the reaction. Our previous experiments carried out respectively on the tripartite mixed-ligand catalytic systems $Pd_2(dba)_3$/Xantphos/Synphos and $Pd_2(dba)_3$/Xantphos/CyPF-*t*Bu suggest that the ligand Xantphos promotes the formation of the active Pd catalyst via facile and favorable ligand exchange with either Synphos (for C−N coupling) or CyPF-*t*Bu (for C−S coupling) (Scheme 2).[18−20] Based on these considerations, we were curious as to whether the mechanism involving $Pd_2(dba)_3$ in the catalytic system could also operate with $Pd(dba)_2$. We therefore undertook a straightforward investigation on the mechanisms behind both mixed ligand systems, involving either $Pd(dba)_2$ or $Pd_2(dba)_3$.

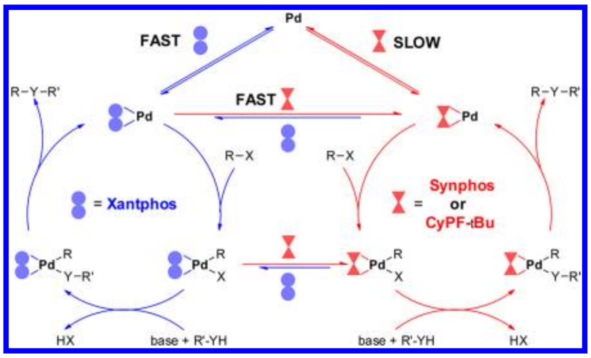
### Table 2. $Pd(dba)_2$ and $Pd_2(dba)_3$ Assisted Mixed Ligand Systems of Pd/Xantphos/Synphos for C−N Coupling with Various Arylamines



| entry | $ArNH_2$ (a-g) | product | yields (%) with $Pd(dba)_2$[a] | $Pd_2(dba)_3$[b] |
|---|---|---|---|---|
| 1 |  | 1b | 82 | 86 |
| 2 |  | 1c | 83 | 82 |
| 3 |  | 1d | 73 | 73 |
| 4 |  | 1e | 83 | 86 |
| 5 |  | 1f | 82 | 90 |
| 6 |  | 1g | 83 | 90 |
| 7 |  | 1h | 80 | 81 |

[a] Reaction conditions: 1 (0.10 mmol), arylamine (0.20 mmol), $Pd(dba)_2$ (0.010 mmol), [Pd]/[ligand] = 1/1.2, [Xantphos]/[Synphos] = 1/2, $K_2CO_3$ (0.20 mmol), toluene (2.0 mL), 110 °C, 2−6 h, isolated yield. [b] The reaction conditions were the same as (a) except $Pd(dba)_2$ (0.010 mmol) was replaced by $Pd_2(dba)_3$ (0.0050 mmol).

### Scheme 2. Proposed General Mechanism for Mixed Bidentate Ligand Participating Pd-Catalyzed C−N and C−S Cross-Coupling Reactions



To obtain intrinsic information on the catalytic mechanism, $^{31}P$ NMR experiments were carried out to inspect the characteristic $^{31}$P signals associated with the phosphorus ligands of Xantphos and Synphos for C−N coupling (Figure 1).

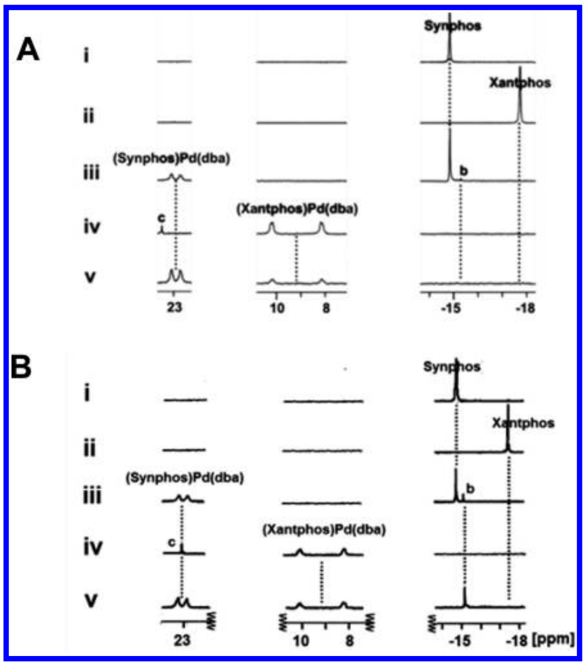


**Figure 1.** $^{31}$P NMR study on single ligand and mixed ligand systems with Pd(dba)$_2$ (A) and Pd$_2$(dba)$_3$ (B) as Pd sources, respectively.[a] (A) $^{31}$P NMR spectra of (i) free Synphos, (ii) free Xantphos, (iii) Pd(dba)$_2$/Synphos, (iv) Pd(dba)$_2$/Xantphos, and (v) Pd(dba)$_2$/Synphos/Xantphos. (B) $^{31}$P NMR spectra of (i) free Synphos, (ii) free Xantphos, (iii) Pd$_2$(dba)$_3$/Synphos, (iv) Pd$_2$(dba)$_3$/Xantphos, and (v) Pd$_2$(dba)$_3$/Synphos/Xantphos. [a] The spectra were obtained in toluene-$d_8$. All the reaction mixtures were first refluxed at 110 °C for 1 h under protection of argon and then cooled to rt. The solutions were subsequently transferred to NMR tubes in a glovebox directly. In mixed-ligand samples, Synphos/Xantphos = 2/1. [b] Pd complex in which Synphos works as monodentate ligand.[22] [c] Pd complex in which Xantphos works as a monodentate ligand.[22]

Indeed, $^{31}$P NMR serves as the method of choice to monitor *in situ*, on the NMR time scale, the formation and exchange of active species. As displayed in Figure 1, the (Xantphos)Pd(dba) complex was formed almost quantitatively in the binary catalytic Pd(dba)$_2$/Xantphos system (Figure 1A, iv), similar to that already observed for the Pd$_2$(dba)$_3$/Xantphos system (Figure 1B, iv), as no free Xantphos could be detected in both cases. When the binary Pd(dba)$_2$/Synphos system was examined under the same conditions, although a complex of (Synphos)Pd(dba) was formed (Figure 1A, iii), its formation was largely unfavored as shown by the predominant $^{31}$P signals of the free Synphos remaining in the $^{31}$P NMR spectrum. The formation of the (Synphos)Pd(dba) complex was found to be less efficient than that of the (Xantphos)Pd(dba) whatever the reagent, Pd(dba)$_2$ or Pd$_2$(dba)$_3$. Nevertheless, Synphos in both mixed ternary ligand systems Pd(dba)$_2$/Synphos/Xantphos and Pd$_2$(dba)$_3$/Synphos/Xantphos underwent complete conversion into the (Synphos)Pd(dba) species, as demonstrated by the complete disappearance of the $^{31}$P NMR signals ascribed to the free Synphos. Altogether, these results point out that the formation of the (Synphos)Pd(dba) complex was favorably and successfully promoted by the presence of Xantphos via a beneficial ligand exchange process. The similarities in both cases suggest that an analogous catalytic mechanism might take place implicating the same intermediates and/or active species, regardless of the ratio of Pd/dba in Pd(dba)$_2$ or Pd$_2$(dba)$_3$.

To reinforce the mechanistic insight deduced from the $^{31}$P NMR experiments, we performed cyclic voltammetry investigations with the aim of acquiring a more precise and sensitive overview of the catalytic features via the detection of transient species.[23] Similar to previously reported results,[19] cyclic voltammograms (CV) of the free Xantphos (Figure 2A, I and 2B, I) exhibited a one-electron irreversible redox system (**O$_1$**) ascribed to the radical cation of Xantphos. Likewise, Synphos (Figure 2A, II and 2B, II) also revealed one irreversible wave (**O$_2$**). In the CVs of both Pd(dba)$_2$/Xantphos (Figure 2A, III) and Pd$_2$(dba)$_3$/Xantphos systems (Figure 2B, III), a new oxidation potential (**O$_3$**), assigned to the (Xantphos)Pd(dba) complex, emerged rapidly within 5 min upon addition of either

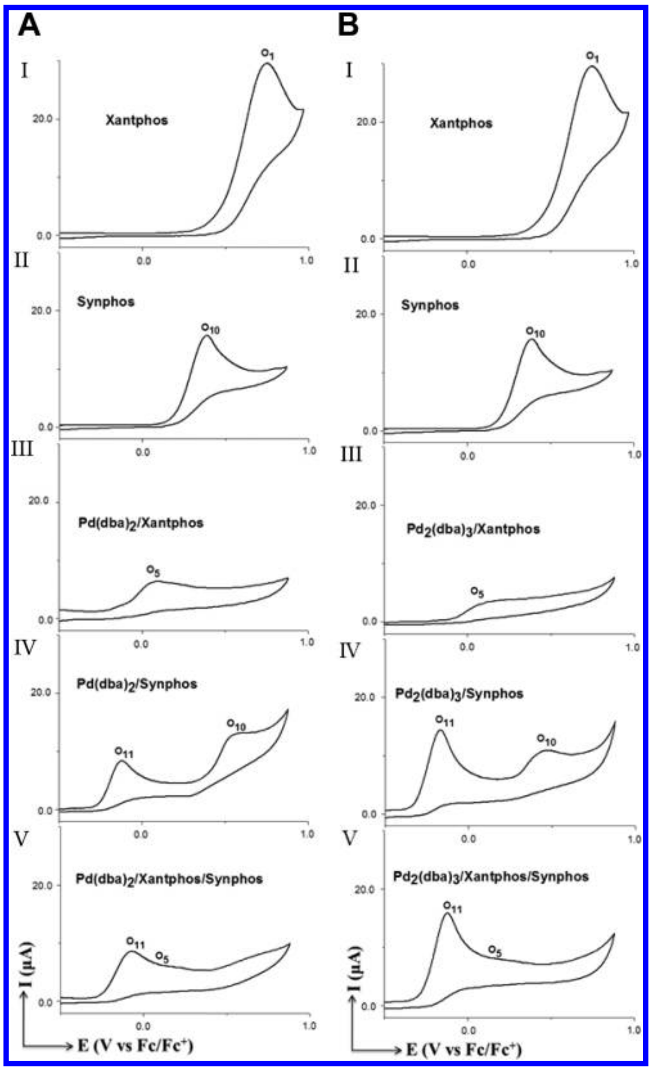


**Figure 2.** Cyclic voltammetry study on single ligand and mixed ligand systems with Pd(dba)$_2$ (A) and Pd$_2$(dba)$_3$ (B) as Pd sources, respectively. (A) Cyclic voltammograms of (I) Xantphos, (II) Synphos, (III) Pd(dba)$_2$/Xantphos, (IV) Pd(dba)$_2$/Synphos, and (V) Pd(dba)$_2$/Xantphos/Synphos. (B) Cyclic voltammograms of (I) Xantphos, (II) Synphos, (III) Pd$_2$(dba)$_3$/Xantphos, (IV) Pd$_2$(dba)$_3$/Synphos, and (V) Pd$_2$(dba)$_3$/Xantphos/Synphos. Cyclic voltammetry was performed in THF solutions using $n$-Bu$_4$NBF$_4$ (0.30 M) as the electrolyte at a stationary gold disk electrode (0.50 mm diameter) at 293 K with scan rate = 100 mV/s.

$Pd(dba)_2$ or $Pd_2(dba)_3$ respectively, with the concomitant disappearance of the $\mathbf{O_1}$ oxidation potential. These results perfectly matched those obtained with $^{31}P$ NMR, confirming a rapid and efficient formation of the (Xantphos)Pd(dba) complex. When Synphos was added to $Pd(dba)_2$, a new oxidation peak $\mathbf{O_4}$ appeared referring to the (Synphos)Pd(dba) complex. However, only partial conversion was attained as highlighted by the remaining $\mathbf{O_2}$ potentials on the CV (Figure 2A, IV). This finding demonstrates that the formation of (Synphos)Pd(dba) is not efficient in the binary system of $Pd(dba)_2$/Synphos. Analogous results were obtained with $Pd_2(dba)_3$, evidencing once again that the formation of (Synphos)Pd(dba) is not favored in the binary system (Figure 2B, IV), which is in perfect agreement with the $^{31}P$ NMR results. Additionally, the CV obtained from the ternary system with $Pd(dba)_2$/Synphos/Xantphos (Figure 2A, V) closely resembled that with $Pd_2(dba)_3$/Synphos/Xantphos (Figure 2B, V). Most importantly, all oxidation peaks, namely $\mathbf{O_3}$, $\mathbf{O_4}$, persisted in the mixed ligand system, and no new oxidation peaks were detected (as confirmed by deconvoluted CV). This acknowledges the absence of differences in the catalytic species formed in the mixed ligand systems containing $Pd(dba)_2$ and $Pd_2(dba)_3$, in line with the results acquired using $^{31}P$ NMR. Likewise, equal results were obtained between $Pd(dba)_2$- and $Pd_2(dba)_3$-catalyzed C−S coupling reactions (Figures S2 and S3), further supporting the notion of analogous catalytic mechanisms in $Pd(dba)_2$- and $Pd_2(dba)_3$-catalyzed coupling reactions.

To summarize, both $Pd(dba)_2$ and $Pd_2(dba)_3$ offer equivalent catalytic efficiency in the reported Pd-catalyzed C−N and C−S cross-coupling reactions involving the ternary mixed ligand catalytic systems. Further combined $^{31}P$ NMR spectroscopy and cyclic voltammetry experiments yielded convergent results and enabled an insightful investigation and precise description of the underlying mechanism. Indeed, $Pd(dba)_2$ and $Pd_2(dba)_3$ offer equivalent catalytic efficiencies and display similar catalytic mechanisms in these mixed ligand Pd-catalyzed cross-coupling reactions. This information will be certainly useful and valuable in performing organic synthesis requiring Pd-catalyzed cross-coupling reactions and may also be extended to other Pd-catalyzed reactions due to the importance of these two Pd reagents.[24]

## ■ ASSOCIATED CONTENT

### Supporting Information

Chemical synthesis, analytical data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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(8) $Pd(dba)_2$ is formulated more correctly as $Pd_2(dba)_3{\cdot}dba$, in which the binuclear complex consists of two Pd atoms bridged by three dba molecules via the C═C olefin portions and the last dba does not coordinate to the Pd center (*J. Chem. Soc., Chem. Commun.* **1970**, 1065; *J. Organomet. Chem.* **1974**, *65*, 253). The main difference between $Pd_2(dba)_3$ and $Pd(dba)_2$ is the Pd/dba stoichiometry.

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(20) Fan, Y.; Cong, M.; Peng, L. *Chem.—Eur. J.* **2014**, *20*, 2698.

(21) Although it has been reported that $Pd_2(dba)_3$ exhibited a higher catalytic activity than $Pd(dba)_2$ since an excess loading of "dba" may sometimes be poisonous to the catalytic process.[6,7] Nevertheless some controversies have also been brought into debate due to a more convoluted and substrate-dependent mechanism involved.

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(24) $Pd_2(dba)_3$ is more frequently used in synthesis thanks to its better stability, whereas $Pd(dba)_2$ is better for mechanism investigation by virtue of its simple and precise Pd/dba ratio.