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Air- and moisture-stable Xantphos-ligated palladium dialkyl complex as a precatalyst for cross-coupling reactions

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Although Xantphos has been employed in a variety of palladium-catalyzed cross-coupling reactions, there have been few progresses in developing Xantphos-ligated precatalysts. In this report, we describe a Xantphos-ligated palladium dialkyl complex that acts as a powerful precatalyst for C–N, C–S, and C–C cross-coupling reactions. This precatalyst is air- and moisture stable but can be thermally activated in the absence of external reagents. Additionally, potential catalyst inhibitors are not generated during the precatalyst activation. This complex thus represents a convenient alternative to previously reported classes of Xantphos-ligated precatalysts.

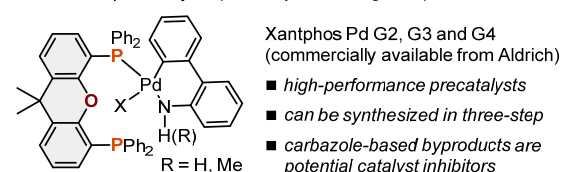
Palladium-catalyzed cross-coupling reactions have become one of the most powerful and versatile methods for the formation of C–C and C–X bonds in academic and industrial settings.¹ The development of specialized phosphine- and *N*-heterocyclic-carbene-(NHC)-based ligands, which promote fundamental steps in the catalytic cycle such as oxidative addition, transmetalation, and reductive elimination, has led to significant advances in this field.¹ Furthermore, recent studies have revealed that the generation of catalytically active and coordinatively unsaturated monoligated Pd(0) species is crucial for the success of cross-coupling reactions.^{1,2} In this context, the development of readily available and bench-stable palladium precatalysts that form monoligated Pd(0) species has attracted considerable interest in the synthetic-chemistry community.¹

Xantphos, a diphosphine ligand with a large bite angle, has been employed in a variety of palladium-catalyzed C–C- and C–heteroatom-bond-forming reactions.³ However, Buchwald and co-workers have reported that the catalytically inactive bis-

ligated palladium species Pd(Xantphos)₂ is readily formed during such reactions, which significantly decreases the reaction rate due to the very high binding constant for the ligand in the bis-ligated species.⁴ Thus, the development of a Xantphos-ligated precatalyst that does not form bis-ligated palladium species should be highly desirable.

Buchwald and co-workers have developed a series of highly active palladacyclic precatalysts that bear a variety of phosphine ligands.⁵ These complexes are commonly referred to as Buchwald precatalysts and have become a valuable tool for cross-coupling reactions. Moreover, such Xantphos-ligated palladacyclic precatalysts are now commercially available as Xantphos Pd G2 (Aldrich, product no. 763047), Xantphos Pd G3 (Aldrich, product no. 763039) and Xantphos Pd G4 (Aldrich, product no. 900329) (Figure 1a). However, these precatalysts form carbazole-based byproducts upon catalyst activation, which could potentially lead to subsequent catalyst inhibition and complicate the purification step.

a. Buchwald palladacyclic precatalysts bearing Xantphos



b. This work: Xantphos-ligated dialkyl complex as precatalyst

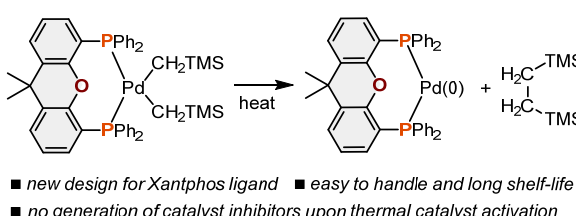


Figure 1. Xantphos-ligated palladium(II) precatalysts for cross-coupling reactions.

In this report, we describe the synthesis of air- and moisture-stable palladium dialkyl complex bearing Xantphos

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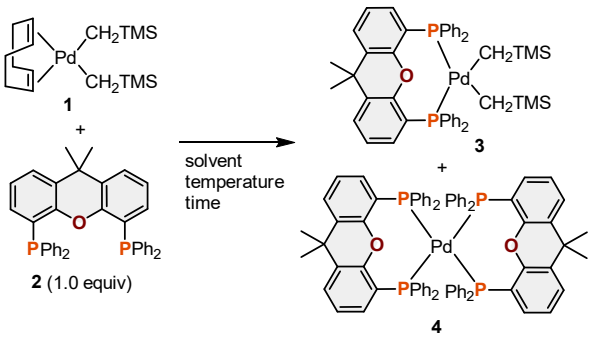
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ligand and its application as a precatalyst for cross-coupling reactions (Figure 1b).^{6,7} This precatalyst can be activated thermally via a reductive elimination under concomitant formation of a catalytically active, coordinatively unsaturated $L_nPd(0)$ species. The sole byproduct of this activation is 1,2-bis(trimethylsilyl)ethane, which does not interfere with the catalyst. Notably, this newly developed precatalyst is easy to handle and exhibit a long shelf-life, i.e., strict exclusion of air and water is not necessary.

Our initial effort focused on the synthesis of a Xantphos-ligated palladium dialkyl complex through a ligand-exchange reaction between $(COD)Pd(CH_2TMS)_2$ (**1**) (COD = 1,5-cyclooctadiene; TMS = trimethylsilyl) and Xantphos (**2**) (Table 1).⁸ Unfortunately, when the reaction was carried out in tetrahydrofuran (THF) at room temperature, the desired product, $(Xantphos)Pd(CH_2TMS)_2$ (**3**), was not obtained. Instead, an insoluble compound, which was identified as the bis-ligated palladium species, $Pd(Xantphos)_2$ (**4**), was obtained (entry 1).^{4,9} Reactions in simple alkane solvents also failed to generate **3** (entries 2 and 3). Pleasingly, the reaction in acetonitrile (MeCN) provided **3** in moderate yield (entry 4), and **3** was obtained in high yield when the reaction time was shortened to 20 minutes (entry 5). These results indicate that shorter reaction times may suppress the undesired reductive elimination from **3** that decreases the yield of **3**. We also found that lowering the reaction temperature avoided the formation of **4** in favour of **3** in THF or diethyl ether (entries 6 and 7). Complex **3** was obtained as an air- and moisture-stable solid that can be handled at room temperature. For the long-term storage, low temperatures ($-30\text{ }^\circ\text{C}$) are required in order to avoid decomposition (see the ESI for details).

Table 1. Preparation of the Xantphos-ligated palladium dialkyl complex **3a**^a



Entry	Solvent	Temperature (°C)	Time	Yield (%) of 3 ^b
1	THF	rt	16 h	—
2	cyclohexane	rt	16 h	—
3	pentane	rt	16 h	—
4	CH ₃ CN	rt	16 h	52
5	CH ₃ CN	rt	20 min	84
6	THF	0	16 h	43
7	Et ₂ O	0	20 min	89

^aConditions: **1** (0.10 mmol) and **2** (0.10 mmol) in the specified solvent (0.1 M) were stirred under an atmosphere of nitrogen. ^bIsolated yields based on the initial amount of **2**.

The molecular structure of **3** was determined by a single-crystal X-ray diffraction analysis (Supplementary Figure 2), which revealed a square-planar *cis* geometry around the Pd center.

To determine the conditions required for the thermal activation of **3** to generate the catalytically active species, the progress of the reductive elimination reaction was monitored at different reaction temperatures using ¹H NMR spectroscopy (Figure 2). The reductive elimination of **3** proceeded rapidly at 80 °C and 60 °C to form 1,2-bis(trimethylsilyl)ethane (**5**) quantitatively within 60 minutes. In contrast, the reductive elimination was slow at 40 °C. These results indicate that **3** could potentially be used as a precatalyst for a number of cross-coupling reactions, as palladium-catalyzed cross-coupling reactions are typically carried out at 60 °C or higher.

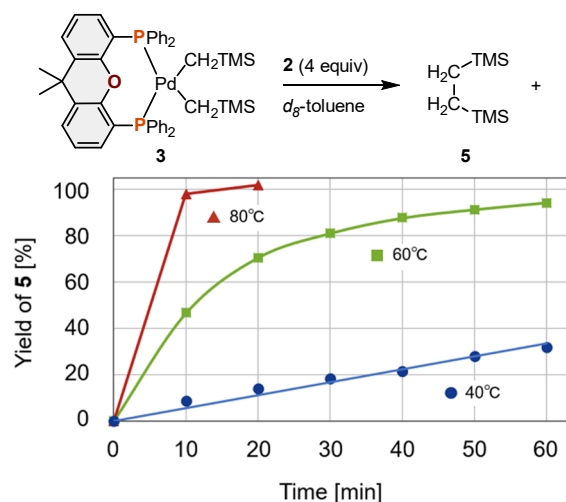


Figure 2. Monitoring the temperature-dependent reductive elimination of 1,2-bis(trimethylsilyl)ethane (**5**) from **3**.

To evaluate the performance of **3** as a precatalyst, we examined its efficacy in promoting C–N cross-coupling reactions between aryl halides and amides (Figure 3).¹⁰ 1-Bromo-2-methylbenzene (**6a**) reacted with benzamide **7a** in the presence of **3** to afford the desired product (**8a**) in high yield. For comparison, we also tested the Buchwald palladacycle precatalyst G3 (Xantphos Pd G3) instead of **3** for this coupling reaction, which provided the almost same product yield. These results show that the catalytic activity of **3** is comparable to that of the Buchwald precatalyst G3.^{1c} Moreover, **3** showed significantly higher catalytic activity than traditional catalyst precursors such as $Pd(OAc)_2/Xantphos$ or $Pd(dba)_2/Xantphos$ in these C–N coupling reactions.

Next, we investigated the catalytic performance of **3** in C–N coupling reactions using various amine nucleophiles (Table 2a and 2b).^{10,11} A variety of aryl halides reacted efficiently with benzamide to give the desired products (**8a–8c**) in good to excellent yield (Table 2a). The reaction using 2-pyrrolidone also proceeded efficiently to form **8d** in good yield (Table 2a). 4-

Methoxy-substituted aniline (**9**) reacted with aryl halides that bear electron-donating and -withdrawing groups to afford the desired products (**10a–10c**) in good to high yield (Table 2b).

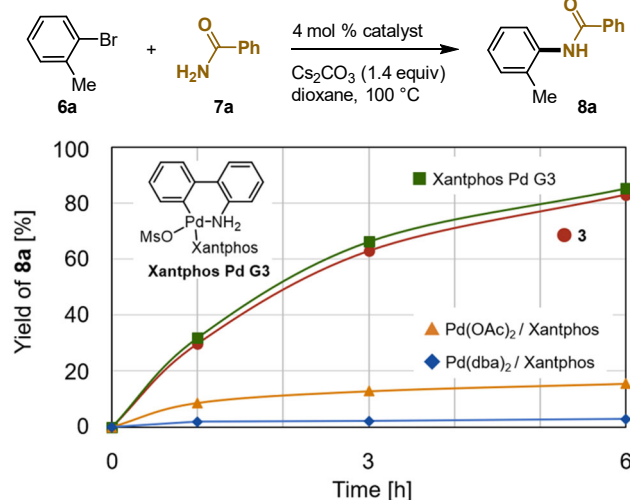


Figure 3. Comparison of the catalytic performance of **3** with those of other catalyst precursors.

The performance of **3** was further evaluated in C–S coupling reactions with thiol nucleophiles (Table 2c).¹² The reaction of 4-methoxybenzyl thiol proceeded to afford the desired products (**12a–12c**) in high yield, and the reaction with thiophenol provided the corresponding diaryl sulfide (**12d**) in high yield.

We also confirmed that the developed precatalyst **3** was applicable to Suzuki–Miyaura cross-coupling reactions with a variety of arylboronic acids (**13**) (Table 2d). Notably, the use of 0.1 mol% of the catalyst provided excellent yield of **14a**. The reaction of base-sensitive 2-furylboronic acid (**13j**) proceeded smoothly to give the desired coupling product (**14j**) in good yield.

We speculated that **3** might also be a suitable precatalyst for base-free Suzuki–Miyaura cross-coupling reactions, as **3** can be activated thermally. To this end, we investigated the coupling reactions between aryl halide (**6k**) and triol borate (**15**) in the presence of **3** as a precatalyst (Scheme 1).¹³ The targeted coupling product (**16**) was obtained in high yield.

Recently, mechanochemical organic synthesis using ball milling has attracted considerable interests due to the attractive advantages, which include the avoidance of potentially harmful organic solvents and simple operational handling.¹⁴ In this context, we applied mechanochemical ball milling to the solvent-free gram-scale synthesis of **3**. The reaction between **1** (3.0 mmol) and **2** was carried out in a stainless-steel ball-milling jar (25 mL) with two stainless-steel balls (diameter: 10 mm), which furnished **3** in 97% yield (2.5 g) (Scheme 2). This result demonstrates the synthetic utility of mechanochemical ball milling for the preparation of **3**, which does not require organic solvents and temperature control.

Table 2. Evaluation of the catalytic activity of **3**^{a–d}

a C–N Coupling with amides

Reaction: Aryl bromide (**6**) + Amide (**7**) $\xrightarrow[4 \text{ mol \% } \mathbf{3}]{\text{Cs}_2\text{CO}_3 (1.4 \text{ equiv}), \text{dioxane}, 100^\circ\text{C}}$ Product (**8**)

Product	Yield
8a	86% yield
8b	95% yield
8c	65% yield
8d	63% yield

b C–N Coupling with aryl amines

Reaction: Aryl bromide (**6**) + Aryl amine (**9**) $\xrightarrow[0.5 \text{ mol \% } \mathbf{3}]{\text{Na(O-}t\text{-Bu)} (1.4 \text{ equiv}), \text{toluene}, 80^\circ\text{C}}$ Product (**10**)

Product	Yield
10a	89% yield
10b	64% yield
10c	86% yield

c C–S Coupling with thiols

Reaction: Aryl bromide (**6**) + Thiol (**11**) $\xrightarrow[5 \text{ mol \% } \mathbf{3}]{\text{DIPEA (2 equiv)}, \text{dioxane}, 100^\circ\text{C}}$ Product (**12**)

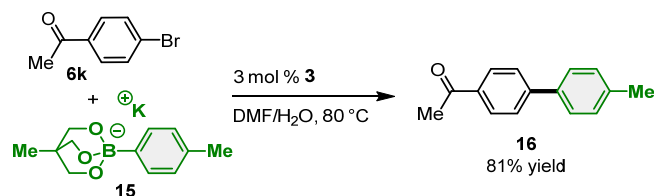
Product	Yield
12a	95% yield
12b	97% yield
12c	92% yield
12d	81% yield

d C–C Coupling with arylboronic acids

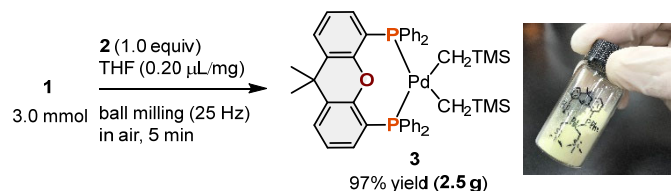
Reaction: Aryl bromide (**6**) + Arylboronic acid (**13**) $\xrightarrow[0.25 \text{ mol \% } \mathbf{3}]{\text{K}_3\text{PO}_4 (2.0 \text{ equiv}), \text{THF/H}_2\text{O (3:1)}, 80^\circ\text{C}}$ Product (**14**)

Product	Yield
14a (R = H)	96% (0.1 mol % 3)
14b (R = NMe ₂)	86% (1 mol % 3)
14c (R = Me)	72%
14d (R = COMe)	92%
14e (R = H)	92%
14f (R = F)	85%
14g	84%
14h	94%
14i	98%
14j	79% (3 mol % 3 , 40 °C)

^aConditions for the C–N coupling with amides: **3** (4.0 mol%), aryl bromides (**6**; 0.5 mmol), amides (**7**; 0.6 mmol), and Cs₂CO₃ (0.7 mmol) in dioxane (0.5 M). ^bConditions for the C–N coupling with aryl amines: **3** (0.5 mol%), aryl bromides (**6**; 1.0 mmol), amine (**9**; 1.2 mmol) and Na(O-*t*-Bu) (1.4 mmol) in toluene (0.5 M). ^cConditions for the C–S coupling with thiols: **3** (5.0 mol %), aryl bromides (**6**; 0.5 mmol), thiols (**11**; 0.5 mmol), and DIPEA (1.0 mmol) in dioxane (0.5 M). ^dConditions for the C–C coupling with boronic acids: **3** (0.25 mol %), aryl bromides (**6**; 0.5 mmol), arylboronic acids (**13**; 0.6 mmol), and K₃PO₄ (1.0 mmol) in THF/H₂O (3:1, 0.38 M).



Scheme 1. Base-free Suzuki-Miyaura cross-coupling reaction catalyzed by **3**.



Scheme 2. Gram-scale synthesis of **3** using mechanochemistry.

In conclusion, we have demonstrated that a Xantphos-ligated palladium dialkyl complex can serve as a high-performance precatalyst for various cross-coupling reactions, thus providing a convenient alternative to previously reported classes of precatalysts. Notably, this complex can be easily prepared, stored for several months and easily activated under thermal conditions without the generation of any potential catalyst inhibitors. We expect that the design of this precatalyst will find wide-spread applications in cross-coupling chemistry.

Acknowledgements

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Conflicts of interest

There are no conflicts to declare.

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