Buchwald-Hartwig Amination Using Pd(I) Dimer Precatalysts Supported by Biaryl Phosphine Ligands

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We report the synthesis of air-stable Pd(I) dimer complexes featuring biaryl phosphine ligands. Catalytic experiments suggest that these complexes are comptent precatalysts that can mediate cross-coupling amination reactions between aryl halide electrophiles with both aliphatic and aromatic amine nucleophiles. This work represents an expansion of the air-stable precatalyst toolbox for Pd-catalyzed cross-coupling transformations.

Palladium-catalyzed cross-coupling reactions are ubiquitous synthetic tools, providing practitioners with versatile methods to forge carbon–carbon[1] and carbon–heteroatom[2] bonds. The development of air- and moisture-stable Pd(II) precatalysts that can quickly generate the catalytically active Pd(0) species *in situ* has dramatically improved the scope of transformations and increased the efficiency of these reactions when compared to systems that incorporate traditional palladium sources.[3] Typically, Pd(II) precatalysts are activated by an external base followed by a reductive elimination to form the catalytically active Pd(0) species and an organic-based auxiliary (e.g., carbazole,[3a-c] pyridine,[3d-f] allylic ethers,[3g,h] and benzylamines[3i]) as a side product. A Pd-based precatalyst that does not require external base or form side products would result in fewer by-products formed en route to the catalytically active Pd(0) species and overall greater operational simplicity.

A lesser-studied class of air-stable, dinuclear Pd(I) complexes have previously shown promise as precatalysts for cross-coupling reactions (Fig 1).[4-8] In contrast to base-activated Pd(II) precatalysts, Pd(I) dimer precatalysts are thought to either disproportionate to yield both Pd(0) and Pd(II) species upon thermal activation, or form Pd(0) after reduction from nucleophile or base that are also present in the reaction

mixture.[4a] Following the initial report of halide-bridged Pd(I) dimers $Pd_2(\mu\text{-}X)_2(P^tBu_3)_2$ (X = Br, I) in 1996 (Fig. 1),[5] Hartwig and coworkers showed that these complexes were effective precatalysts for both C–C and C–N cross-coupling reactions.[6] More recently, Schoenebeck and colleagues have developed conditions for this precatalyst system that are capable of chemoselective transformations with a wider breadth of substrates.[7]

Selected examples of Pd(I)-Pd(I) dimers as precatalysts:

$Pd_2(\mu\text{-}X)_2(P^tBu_3)_2$
X = Br, I
Hartwig, Schoenebeck
Ref. 5-7

$[Pd_2MeCN_6][SbF_6]_2$
L = MeCN
Weng and Hor
Ref. 8b

$Pd_2X(\mu\text{-}X)(\mu\text{-}P^tBu_2bph)$
X = Cl, Br; Christmann
Ref. 9

This work:

R_{Aryl} groups are omitted for clarity

L1: R = ^tBu; R' = H
L2: R = Cy; R' = NMe_2
L3: R = ^tBu
**L4**: R = Cy
L5: R = OMe
L6: R = O^iPr
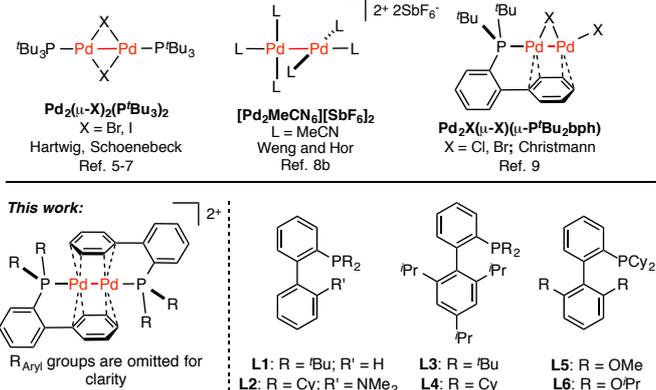
Fig. 1 Top: selected examples of Pd(I) dimer complexes as precatalysts. Bottom: Pd(I) dimers synthesized in this work with biaryl phosphine ligands used (**L1-L6**).

In contrast to the halide-bridged Pd(I) dimer complex, Murahashi *et al.* reported the first homoleptic dinucelar Pd(I) complex $[Pd_2MeCN_6][BF_4]_2$ that features a direct Pd–Pd interaction with no bridging ligands.[8a] Hor and coworkers then demonstrated that the $[SbF_6]$ analogue of this dimer, $[Pd_2MeCN_6][SbF_6]_2$, was an active "ligandless" precatalyst for Suzuki-Miyaura cross-coupling reactions (Fig. 1).[8b] In fact, the addition of phosphine ligands was found to enhance catalytic performance, though no phosphine-ligated Pd complexes were isolated in this study. Biaryl phosphine ligands have been shown to improve reactivity and expand the substrate scope for many Pd-based catalytic transformations.[9,1f,2a-d,3a-c] Based on this reasoning, Christmann and colleagues went on to synthesize a Pd(I) dimer that incorporated a bulky biaryl phosphine, $Pd_2X(\mu\text{-}X)(\mu\text{-}P^tBu_2bph)$ (X = Cl, Br; Fig. 1).[10] These Pd(I) dimers were effective precatalysts for amination reactions of aryl halides; however, the synthesis of these

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dimers is lengthy (48 hr reaction time), low-yielding (45-71%), and not general as only one type of biaryl phosphine ligand was used. Similarly, a Pd(I) dimer supported by two biaryl phosphine ligands was reported by Barder and showed promise as a precatalyst for C–C bond-forming reactions, but again, the reported synthesis was not general for other analogous Pd(I) dimer complexes.[11]

We were interested in expanding the class of Pd(I) dimers with biaryl phosphine ligands and studying their performance as precatalysts for cross-coupling reactions. To that end, we have developed a straightforward synthetic route that enables access to numerous Pd(I) dimer complexes *via* the $[Pd_2MeCN_6][BF_4]_2$ precursor. Notably, this method can accommodate several biaryl ligands, and the desired Pd(I) dimer complexes are formed quantitatively within minutes. These Pd(I) dimers behave as excellent precatalysts for Buchwald-Hartwig amination reactions, thus expanding the range of available air-stable Pd-based precatalysts.

Following the procedure reported by Murahashi and coworkers, $[Pd_2MeCN_6][BF_4]_2$ was synthesized by the conproportionation reaction between Pd(0) and Pd(II) (Pd_2dba_3 and $[Pd(MeCN)_4][BF_4]_2$, respectively) on a 0.5 gram scale and served as a competent Pd(I) dimer precursor (Fig. 2A). To generate Pd(I) dimer complexes 1-6, two equivalents of a biaryl phosphine ligand (L1-L6) dissolved in CH_2Cl_2 were added to a slurry of $[Pd_2MeCN_6][BF_4]_2$ in CH_2Cl_2 and stirred at room temperature for up to 30 minutes (Fig. 2A). An immediate color change was observed for all reactions, suggesting rapid ligand exchange between biaryl phosphine ligands L1-L6 and acetonitrile. Reaction progress can be easily monitored *via* ^{31}P NMR as there is a substantial downfield shift upon coordination of the biaryl phosphine ligand to the metal center (Fig. 2B). In some cases, prolonged reaction time results in the formation of Pd-black so shorter reaction times were used to maximize yield (<10 minutes, see ESI for experimental details). This is particularly noticeable in the synthesis of 5: Pd-black forms within minutes of the addition of L5 to $[Pd_2MeCN_6][BF_4]_2$, and the isolated yield of 5 after reacting for 10 minutes is 35% (the yield increases to 91% with ~1 minute reaction time). In contrast, no Pd-black formation was observed during the synthesis of 6, and the isolated yield was quantitative even when the reaction time was 30 minutes. Upon completion, the crude reaction mixtures were filtered through Celite and the filtrates dried *in vacuo* to offer crystalline solids with yields ranging from 72% to 99%.

Most compounds exhibit one singlet resonance in the ^{31}P NMR, indicating a symmetric structure and chemically equivalent P atoms. As functional group bulk at the *para* position on the bottom ring of the biaryl phosphine ligand increases (L3 and L4), multiple ^{31}P NMR resonances are observed. Specifically, two doublets are observed for 4 (δ 39.26 and 23.15, J^3_{P-P} = 84 Hz, see ESI), suggesting fluctional behavior of the ligand (L4) in solution on the NMR timescale. Steric bulk is increased even more with the replacement of dicyclohexylphosphine (L4) with di-*tert*-butylphosphine (L3). Indeed, multiple resonances are observed in the ^{31}P NMR spectrum for 3, potentially resulting from this increased steric

bulk limiting the ability of the ligands to associate with the Pd(I) centers. Variable temperature (VT) ^{31}P NMR studies on 4 in CD_2Cl_2 reveal new resonances at -80°C, suggesting the presence of multiple conformations due to limited (or slow) fluctionality at low temperature (Fig. S1). After warming this sample back to 25°C, the broad resonances reappear, further reinforcing the proposed fluctional behaviour. Due to low solubility and poor stability of 3 in CD_2Cl_2 solution on the timescale required to acquire ^{31}P NMR spectra (*vide infra*), VT NMR studies were not possible for this sample. Attempts to grow diffraction-quality crystals of 3 and 4 to validate these suggested structures resulted in the formation of metallic Pd.
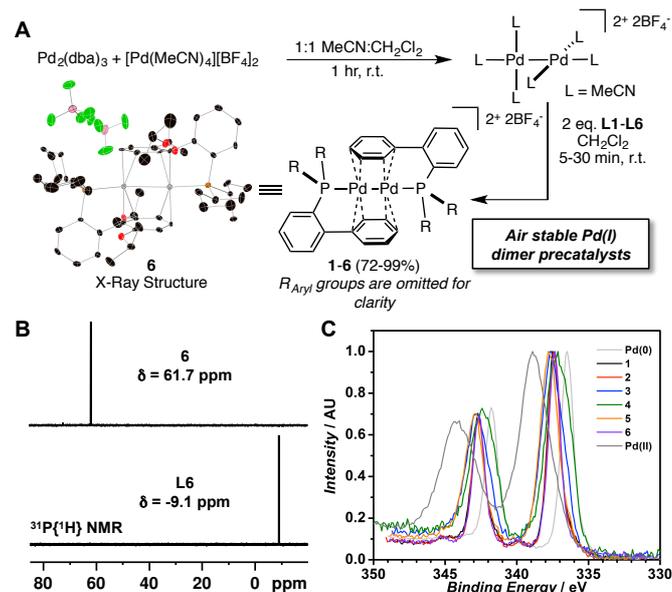

Fig. 2 (A) Synthetic route to Pd(I) dimer complexes 1-6. Left: X-ray crystal structure of 6 drawn with 50% ellipsoid probability (CCDC 1812500). H atoms are omitted for clarity. (B) $^{31}P\{^1H\}$ NMR data for L6 (bottom) and 6 (top), both in CD_2Cl_2. (C) XPS data for compounds 1-6. Pd(0) is Pd_2dba_3, and Pd(II) is $[Pd(MeCN)_4][BF_4]_2$.

On the other hand, compounds 2, 5 and 6 could all be characterized *via* single crystal X-ray diffraction, confirming the propsed dimeric structure (Fig. 1A and Fig. S2). For all of these dimer structures, Pd(I)···Pd(I) distances range from 2.702–2.716 Å in the solid state, slightly greater than the sum of covalent radii for two Pd atoms (2.40 Å).[12] To further probe the oxidation state of Pd in 1-6, we employed X-ray photoelectron spectroscopy (XPS). As anticipated, the binding energies for Pd 3d electrons in 1-6 fall between the binding energies for Pd 3d electrons in Pd(0) (Pd_2dba_3) and Pd(II) ($[PdMeCN_4][BF_4]_2$) standards, suggesting that both Pd atoms are in the +1 formal oxidation state (Fig. 2C and Table S2).

Compounds 1-6 are stable as solids indefinitely when stored in air at 5°C; in contrast, only 5 and 6 exhibit long-term stability in CH_2Cl_2 solution. Solutions of 1-6 in CH_2Cl_2 were stored on the bench top under atmospheric conditions, and within 3 days, metallic Pd films coated the vials containing 1-4, whereas 5 and 6 remained in solution with no observed changes in ^{31}P NMR spectra after 1 week. Compounds 3 and 4, which contain ligands with the greatest amount of steric bulk on the bottom aryl ring (L3 and L4, respectively), exhibit the

lowest stability in CH$_2$Cl$_2$ solution as Pd-black and metallic Pd films both start forming within 30 minutes after dissolution.

We turned our attention to the use of the synthesized Pd(I) dimers **1**-**6** as air-stable precatalysts for Buchwald-Hartwig amination reactions. For the initial optimization studies, 4-bromotoluene and morpholine were chosen as a reagent system (Table 1). We first evaluated **1**-**6** as precatalysts at 0.5 mol% loading with 0.5 mol% corresponding ligand (**L1**-**L6**) using KO^{t}Bu as the base (entries 1-6). These Pd(I) dimer complexes are thought to disproportionate to form a Pd(II) species and a catalytically active Pd(0) species after thermal activation;[11] therefore, the role of the base in this system is limited to deprotonating the amine adduct of palladium that forms during the transmetallation step.

Table 1 Optimization of reaction conditions for **7**.
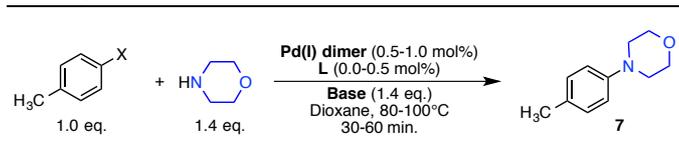
Entry	Pd(I) Precat. (mol%)	L (mol %)	Base	X	Temp (°C)	Time (min.)	Yield^a (%)
1	**1**, 0.5	**L1**, 0.5	KO^{t}Bu	Br	100	30	46
2	**2**, 0.5	**L2**, 0.5	KO^{t}Bu	Br	100	30	25
3	**3**, 0.5	**L3**, 0.5	KO^{t}Bu	Br	100	30	12
4	**4**, 0.5	**L4**, 0.5	KO^{t}Bu	Br	100	30	45
5	**5**, 0.5	**L5**, 0.5	KO^{t}Bu	Br	100	30	60
6	**6**, 0.5	**L6**, 0.5	KO^{t}Bu	Br	100	30	64
7	**6**, 1.0	**L6**, 0.5	KO^{t}Bu	Br	100	30	>99
8	**6**, 0.5	**L6**, 0.5	KO^{t}Bu	Br	100	60	>99
9	**6**, 0.5	**L6**, 0.5	KO^{t}Bu	Br	80	60	>99
10	**6**, 0.5	–	KO^{t}Bu	Br	80	60	>99
11	**6**, 0.5	–	NaO^{t}Bu	Br	80	60	>99
12	**6**, 0.5	–	NaO^{t}Bu	Cl	80	60	>99
13	**6**, 0.5	–	NaO^{t}Bu	I	80	60	40^b
14	**5**, 0.5	–	NaO^{t}Bu	Br	80	60	>99

Pd(I) dimers **1**-**6** were initially screened to find the most optimal precatalyst. Optimization of the reaction conditions proceeded with **6** (optimized conditions in entry 11). ^{a}Yield determined using GC-MS analysis. ^{b}Full conversion of 4-iodotoluene was observed by GC-MS.

After reacting for 30 minutes at 100°C in 1,4-dioxane, **5** and **6** offered the highest GC-MS yields of product **7** (60% and 64%, respectively). Due to the relative ease of synthesis of **6** compared to **5** (*vide supra*), we therefore decided to move forward with **6** as the model Pd(I) dimer precatalyst. Full conversion of 4-bromotoluene was achieved both when the precatalyst loading was doubled to 1.0 mol% (entry 7) and when the reaction time was increased to 1 hour (entry 8), demonstrating that increasing the catalyst loading was not necessary as lower catalyst loadings with longer reaction times were sufficient for full conversion. The temperature was decreased from 100°C to 80°C during the subsequent optimization with no observed yield, and inclusion of extra supporting ligand **L6** was deemed unnecessary (entries 9 and 10, respectively). NaO^{t}Bu was successfully substituted for KO^{t}Bu as the yield remained >99% for this experiment (entry

11). No significant change in performance was observed when varying the halide from bromide to chloride (entry 12), but there was a precipitous drop in the observed yield when 4-iodotoluene was employed (entry 13). This is consistent with previously observed trends in Pd-catalyzed cross-coupling with systems featuring electron-rich biaryl ligands where transmetallation is a rate-determining step.[13] Finally, the use of precatalyst **5** under the optimized conditions still results in GC-MS yields >99% (entry 14).
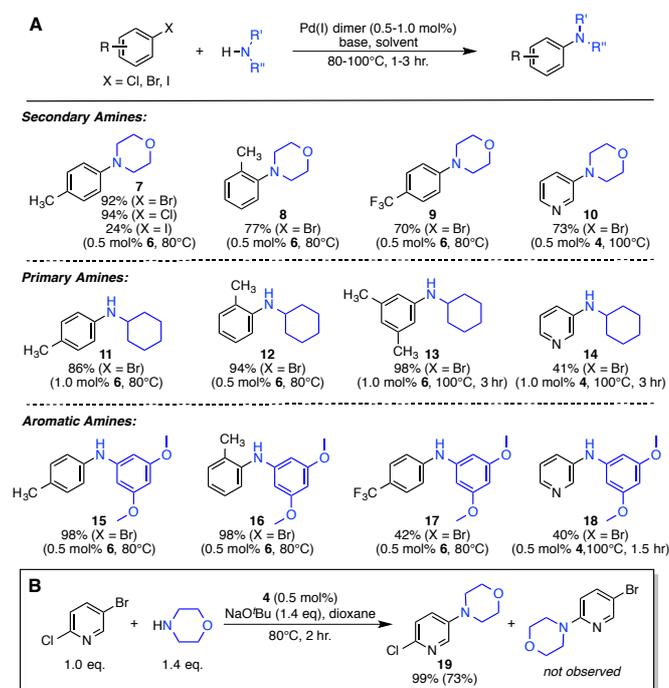

Fig. 3 (A) Substrate scope for the amination of aryl and heterocyclic halides. Conditions: Aryl halide (2.5 mmol), amine (3.5 mmol), NaO^{t}Bu (3.5 mmol), Pd(I) dimer precatalyst (0.5-1.0 mol%), dioxane (2.5 mL), 80-100°C, 1-3 hr. Isolated yields represent the average of two runs. (B) Amination of a mixed-halide heterocycle demonstrates selectivity for bromide (99% conversion of 5-bromo-2-chloropyridine, 73% isolated yield or **19**).

The optimized conditions presented in entry 11 were adopted for further experiments to expand the substrate scope. Precatalyst **6** was found to work with a range of aryl bromides and multiple types of nucleophiles, including secondary amines (**7**-**10**), primary amines (**11**-**14**), and aromatic amines (**15**-**18**, Fig. 3A). Reactions between 4-bromotoluene and both cyclohexylamine and 3,5-dimethoxyaniline (**7** and **11**, respectively) proceeded with 0.5-1.0 mol% loading of **6**. Using this catalytic system, aryl bromides with electron-withdrawing trifluoromethyl groups in the *para*- position were found to work with secondary amines and anilines (**9**, **17**). Reactions with *ortho*-substituted aryl bromides proceeded efficiently with all three classes of amines, and products were isolated in yields of up to 98% (**8**, **12**, **16**). In all cases, reactions involving a heterocyclic electrophile (3-bromopyridine) proceeded sluggishly with GC-MS yields <30% when the standard reaction conditions were employed with **6** as a precatalyst. However, precatalyst **4** proved competent for the transformation between all three

classes of amines and 3-bromopyridine (**10**, **14**, **18**), demonstrating the potential utility of this class of Pd(I) dimer precatalysts. This observation is consistent with previous reports that suggest the increased bulk of **L4** leads to greater efficiency of aminations of heteroaryl halides.[2a,9g]

Finally, a reaction between morpholine and a 2-chloro-5-bromopyridine was performed to test halide selectivity and confirm that this transformation proceeds *via* cross-coupling and not through an aromatic nucleophilic substitution (S$_N$Ar) pathway (Fig. 3B). Full conversion of the electrophile was achieved after 2 hours, but no chloro-substituted product could be detected by GC-MS. In fact, only the desired product (**19**) was observed by GC-MS and isolated yield in 73% yield, confirming the selectivity of this class of precatalysts for bromide. Moreover, this selectivity potentially enables the use of orthogonal methods that are reactive towards chlorides,[14] enhancing the prospective scope of transformations available with this precatalyst system.

In conclusion, we have synthesized and characterized a series of air-stable Pd(I) dimer complexes incorporating biaryl phosphine ligands. A conproportionation reaction between commercially-available Pd(0) and Pd(II) sources followed by the addition of biaryl phosphine ligands results in a nearly quantitative strategy towards the synthesis of these complexes. Single crystal X-ray diffraction studies on several Pd(I) dimers supported by the biaryl phosphine ligands confirm the proposed dimeric structure of these complexes in the solid state, and XPS data suggests the +1 formal oxidation state of the Pd atoms in each dimer complex. Synthesized Pd(I) dimer**s** can efficiently catalyze Buchwald-Hartwig amination reactions involving aliphatic or aromatic amines with aryl halides, including 6-membered heterocyclic substrates. Overall, this work presents a direct and simple route to a potentially large class of air-stable Pd(I) dimer precatalysts which, by further tailoring the biaryl phosphine ligand, can be used for other cross-coupling transformations.

Conflicts of interest

There are no conflicts to declare.

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