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# In Situ Formation of Cationic $\pi$ -Allylpalladium Precatalysts in Alcoholic Solvents: Application to the C-N Bond Formation.

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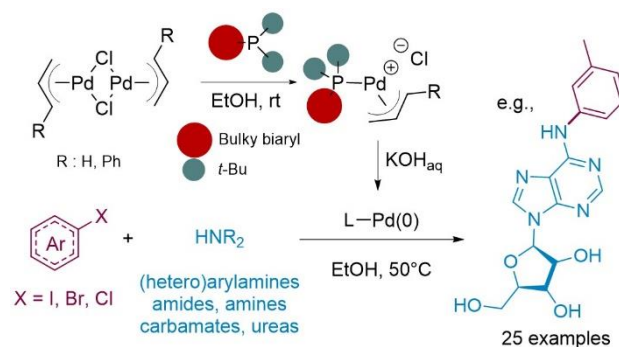
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**Abstract:** We report an efficient Buchwald-Hartwig cross-coupling reaction in alcoholic solvents, in which low catalyst loading showed excellent performance for coupling aryl halides (I, Br, Cl) with a broad set of amines, amides, ureas, or carbamates under mild conditions. Mechanistically speaking, in protic and polar medium, extremely bulky biarylphosphine ligands interact with dimeric precatalyst  $[\text{Pd}(\pi\text{-R-allyl})\text{Cl}]_2$  to form the corresponding cationic complexes  $[\text{Pd}(\pi\text{-R-allyl})(\text{L})\text{Cl}]$  *in situ* and spontaneously. The resulting precatalyst further evolves under basic conditions into the corresponding L-Pd(0) catalyst, which is commonly employed for cross-coupling reactions. This mechanistic study highlights the prominent role of alcoholic solvents for the formation of the active catalyst.

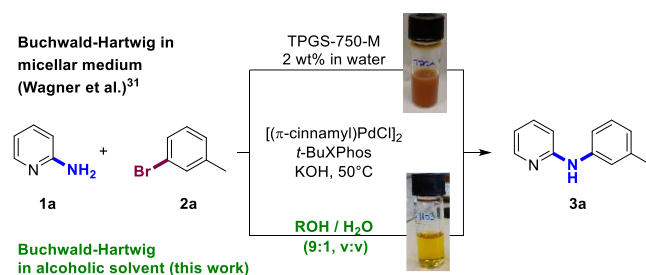
**KEYWORDS:** Buchwald-Hartwig reaction, cross-coupling, catalyst activation, precatalyst formation, palladium, green solvent



## INTRODUCTION

The use of palladium as a catalyst for the formation of  $\text{C}(\text{sp}^2)\text{-N}$  was pioneered in 1983 by Migita et al.,<sup>1</sup> but this seminal work was later independently improved by Stephen L. Buchwald and John F. Hartwig in the 1990s.<sup>2-5</sup> This palladium-catalyzed formation of the  $\text{C}(\text{sp}^2)\text{-N}$  bond is now known as the Buchwald-Hartwig amination reaction,<sup>6,7</sup> which has been a breakthrough for synthetic chemists because of the ubiquitous nature of aryl amines and related heterocycles in natural products, pharmaceuticals, agrochemicals, and materials.<sup>8-11</sup> According to D. G. Brown and J. Bostro, the Buchwald-Hartwig reaction was used at least once in about 10% of all medicinal chemistry papers published in 2014 and was one of the top-20 most used reactions in the pharmaceutical industry.<sup>11,12</sup>

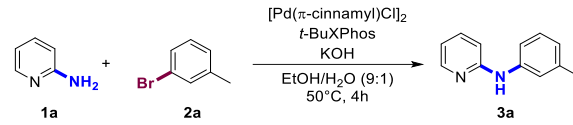
Over the last two decades, considerable efforts have been made to develop more efficient reaction conditions,<sup>6,7,13-26</sup> notably through the development of several generations of catalysts and ligands. In terms of solvents, the Buchwald-Hartwig cross-coupling reaction classically occurs in hydrocarbon solvents (most frequently toluene) or in cyclic ethers such as THF or 1,4-dioxane.<sup>27</sup> During the last decade, pharmaceutical companies such as Pfizer, GSK, and Sanofi have begun to publish selection guides for solvents used by medicinal chemists according to their environmental, health, and safety (EHS) properties.<sup>28</sup> According to these guides, toluene is classified as "usable", but its replacement is recommended by Sanofi. THF is classified as "usable" by Pfizer but has "major issues" according to GSK, while 1,4-dioxane is classified as "undesirable" by all 3 companies. However, other solvents have



**Figure 1.** Buchwald-Hartwig cross-coupling reaction with  $[\text{Pd}(\pi\text{-cinnamyl})\text{Cl}]_2/t\text{-BuXPhos}$  in micellar conditions and in alcoholic solvents

been used successfully, including *tert*-butanol or glycol derivatives (2-methoxyethanol, ethyleneglycol).<sup>27</sup> Nevertheless, alternatives to these solvents are also recommended by pharmaceutical companies.<sup>28</sup>

In 2015, Caille et al. published the synthesis of 12 kg of a Buchwald-Hartwig coupling product using a  $\text{Pd}(\text{OAc})_2/\text{BrettPhos}$  catalytic complex in *i*-PrOH.<sup>29</sup> This secondary alcohol was tagged as "preferred" by Pfizer and Sanofi<sup>28</sup> and was chosen for practical reasons as the low solubility of the product in *i*-PrOH allows it to crystallize directly from the reaction mixture. Water was successfully reported by Lipshutz et al. for the Buchwald-Hartwig reaction under micellar conditions (with TPGS-750-M as a surfactant) through the use of the  $[\text{Pd}(\pi\text{-allyl})\text{Cl}]_2/\text{cBRIDP}$  catalytic system.<sup>30</sup> This micellar amination reaction has since been improved by several groups, including ours.<sup>31-36</sup>

**Table 1. Optimization of the reaction conditions<sup>a</sup>**


Entry	Modifications of the conditions	yield % <sup>b</sup>
1	none	> 98
2	MeOH instead of EtOH	> 98
3	<i>n</i> -PrOH instead of EtOH	> 98
4	<i>i</i> -PrOH instead of EtOH	29
5	<i>n</i> -BuOH instead of EtOH	> 98
6	<i>s</i> -BuOH instead of EtOH	48
7	<i>t</i> -BuOH instead of EtOH	7
8	[Pd(π-allyl)Cl] <sub>2</sub> instead of [Pd(π-cinnamyl)Cl] <sub>2</sub>	> 98
9	XPhos instead of <i>t</i> -BuXPhos	11
10	JohnPhos instead of <i>t</i> -BuXPhos	65
11	<i>t</i> -BuBrettPhos instead of <i>t</i> -BuXPhos	> 98
12	BippyPhos instead of <i>t</i> -BuXPhos	> 98
13	P( <i>t</i> -Bu) <sub>3</sub> .HBF <sub>4</sub> instead of <i>t</i> -BuXPhos	trace

[a] Reaction conditions: 3-bromotoluene (1 eq, 0.4 mmol), 2-aminopyridine (1.5 eq), [Pd(π-cinnamyl)Cl]<sub>2</sub> (0.5 mol%), *t*-BuXPhos (1.5 mol%), Base (2 eq), solvent (0.2 M), 50°C, 4 h; [b] Average yields of 2 runs determined by HPLC/UV using caffeine as an internal standard

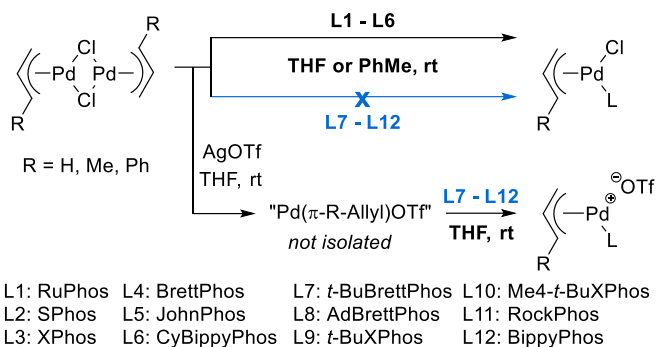
These previous reports led us to hypothesize that the Buchwald-Hartwig reaction is fully compatible with polar protic solvents, and simple alcohols such as ethanol, propanol, or butanol could constitute solvents of high potential in terms of EHS.<sup>28</sup> Furthermore, they have greater ability to solubilize substrates or catalysts in comparison to water. In this report, we describe the optimization of the Buchwald-Hartwig reaction in alcoholic solvents (Figure 1), which allows cross-coupling reactions between a broad scope of nitrogen functions and aryl halides. Furthermore, we discuss the mechanistic aspects of this reaction in alcoholic medium.

## RESULTS AND DISCUSSION

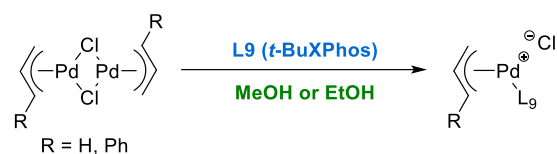
**Reaction development.** 2-aminopyridine **1a** and 3-bromotoluene **2a** were used as prototypical substrates to establish the most suitable reaction conditions in alcoholic solvents (Table 1 and SI-§2). The best catalytic system resulting from our optimization of the Buchwald-Hartwig reaction in micellar medium was [Pd(π-cinnamyl)Cl]<sub>2</sub>/*t*-BuXPhos.<sup>31</sup> Using this system, we screened a series of simple alcohols (Table 1, entries 1-7). All the primary alcohols (MeOH, EtOH, *n*-PrOH, and *n*-BuOH) afforded compound **3a** in quantitative yields after 4 h at 50°C, whereas secondary alcohols such as *i*-PrOH (entry 4) and *s*-BuOH (entry 6) led to lower yields (29% and 48%, respectively), and only 7% yield was obtained with the tertiary alcohol *t*-BuOH (entry 7). Interestingly, [Pd(π-allyl)Cl]<sub>2</sub> instead of [Pd(π-cinnamyl)Cl]<sub>2</sub> led to quantitative yields with all the alcoholic solvents (SI-§2, Table S4). The reaction is compatible with the presence of water (SI-§2, Table S1), allowing the reaction to be performed with technical-grade ethanol (95%), a very cheap solvent.

A set of bases was next screened, and hydroxide salts led to quantitative yields, whereas other mineral bases or K<sub>3</sub>PO<sub>4</sub> appeared less efficient (SI-§2, Table S2). We next evaluated the influence of various phosphines as ligands (Table 1 and SI-§2,

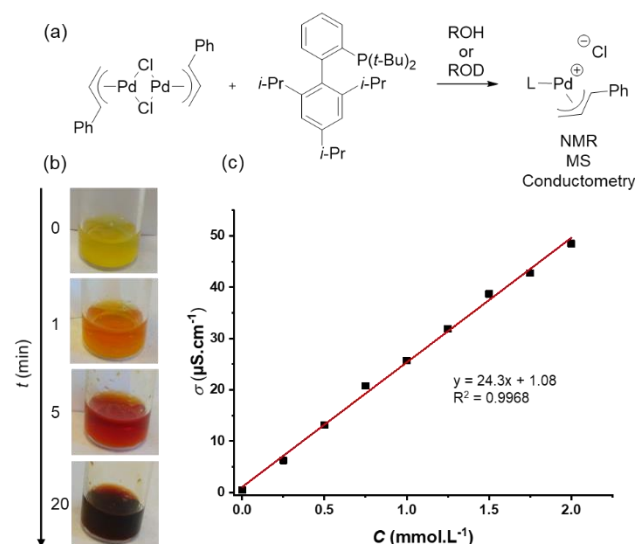
Previous study by Colacot et al.<sup>37</sup>



**Current work:**



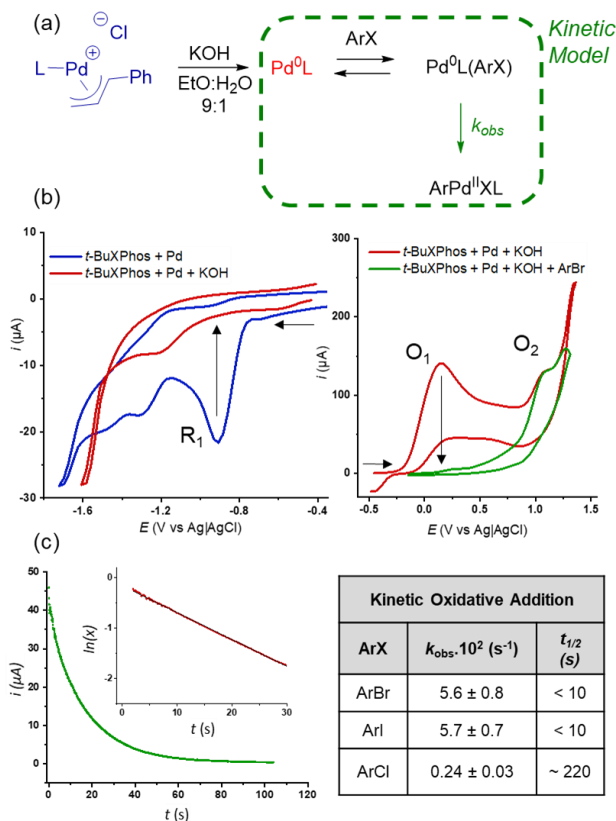
**Figure 2.** Synthesis of cationic R-allylpalladium precatalysts with bi(hetero)arylphosphine ligands



**Figure 3.** Characterization of the precatalyst formation. a) Reaction conditions: [Pd(π-cinnamyl)Cl]<sub>2</sub> (1 eq), *t*-BuXPhos (2 eq), MeOD (for NMR or EtOH (for MS or conductometry)); b) Color change over time; c) Conductivity plotted as a linear function of the amount of [Pd(π-cinnamyl)Cl]<sub>2</sub> + *t*-BuXPhos. Full NMR, MS and conductometry are shown in SI-§6.

Table S3). Only the sterically-hindered monodentate *t*-butyl phosphines bearing biaryl or biheteroaryl moieties (*t*-BuXPhos, *t*-BuBrettPhos, or BippyPhos) led to quantitative yields.

**Mechanistic study.** To investigate the role of the solvent in the catalytic system, the formation of the active Pd(0) catalyst starting from [Pd(π-cinnamyl)Cl]<sub>2</sub> and *t*-BuXPhos was examined in EtOH. In a previous study,<sup>37</sup> Colacot reported that with such hindered phosphine, [Pd(π-cinnamyl)Cl]<sub>2</sub> requires an activation with AgOTf to form a cationic monomer [Pd(π-R-allyl)]OTf in organic solvents (THF or toluene). The latter further reacts with bulky phosphines to give the monoligated cationic [Pd(π-R-allyl)(L)]OTf (Figure 2). In full agreement with Colacot's work, the system [Pd(π-cinnamyl)Cl]<sub>2</sub> / *t*-BuXPhos in dioxane or



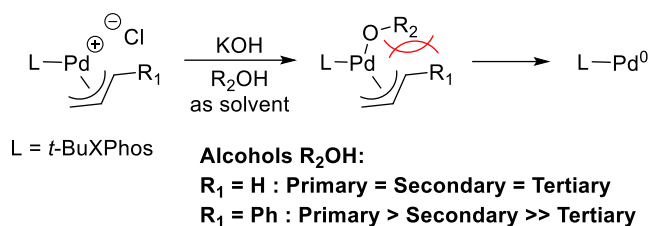
**Figure 4.** Characterization of L-Pd(0) by cyclic voltammetry (panel a & b) and kinetic monitoring of the oxidative addition in the presence of ArBr (10 eq., panel a & c; See SI-9c for experimental details)

toluene did not form any active catalytic complex, leading to traces of compound **3a** (SI-§4). However, in polar protic solvents such as alcohols, silver triflate is not required to preactivate the Pd(II) dimer in presence of the bulky phosphine.

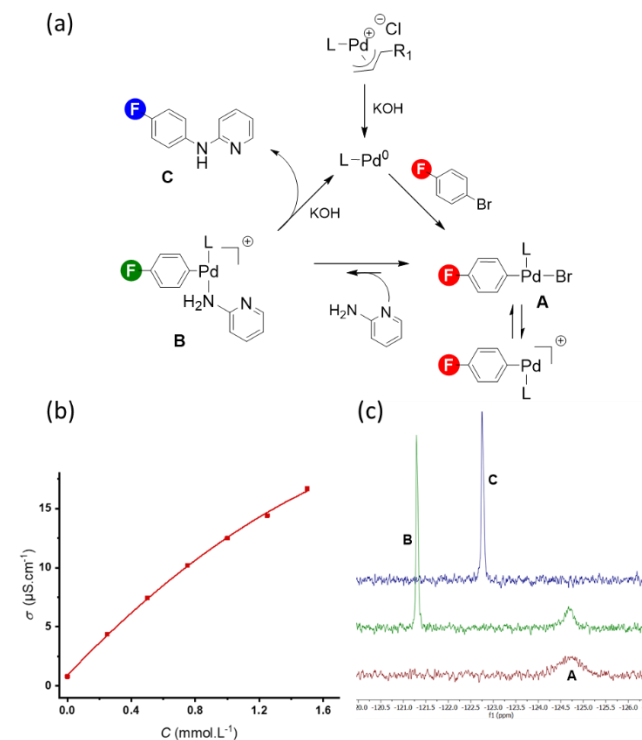
Whereas  $[\text{Pd}(\pi\text{-cinnamyl})\text{Cl}]_2$  is almost insoluble in EtOH (SI-§3), the presence of *t*-BuXPhos (2 eq.) led to its solubilization within a few minutes at 25°C to form a dark red solution (Figure 3b). A  $^{31}\text{P}\{^1\text{H}\}$  NMR signal at 76.3 ppm was detected in MeOD (SI-§6), consistently with the cationic complex  $[\text{Pd}(\pi\text{-cinnamyl})(t\text{-BuXPhos})\text{OTf}]$  reported by Colacot et al. at 76.0 ppm in  $\text{CDCl}_3$ .<sup>37</sup> Conductivity measurements confirmed the presence of ionic species (Figure 3 and SI-§6), and *in situ* characterization by NMR and MS confirmed the formation of both  $[\text{Pd}(\pi\text{-allyl})(t\text{-BuXPhos})\text{Cl}]$  and  $[\text{Pd}(\pi\text{-cinnamyl})(t\text{-BuXPhos})\text{Cl}]$  in alcoholic solvents (SI-§5 and §6, respectively).

We next studied the formation of L-Pd(0) after addition of KOH. Using cyclic voltammetry,  $[\text{Pd}(\pi\text{-cinnamyl})(t\text{-BuXPhos})\text{Cl}]$  was characterized by its reduction potential at -0.90 V vs. Ag/AgCl in EtOH (SI-§6c). Immediately after addition of an excess of aqueous KOH (5 eq.) at 50°C, this reduction peak disappeared, and an  $\text{O}_1$  oxidation peak at +0.13 V was observed and attributed to the corresponding L-Pd(0) (Figure 4b and SI-§7b). As expected,  $\text{O}_1$  rapidly evolves under air (SI-§8b), and its intensity decreased after addition of 4-fluorobromobenzene (10 eq., Figure 4b and SI-§9c).

The formation of L-Pd(0) was also followed by  $^{31}\text{P}\{^1\text{H}\}$  NMR starting from  $[\text{Pd}(\pi\text{-allyl})(t\text{-BuXPhos})\text{Cl}]$ , and after addition of KOH, the major peak at 58.6 ppm was attributed to L-Pd(0) (SI-§7a). In the presence of oxygen, L-Pd(0) was rapidly oxidized to form the peroxy complex  $\text{Pd}(t\text{-BuXPhos})(\text{O}_2)$ , as well as *t*-BuXPhos oxide (SI-§8a). Surprisingly, the attempt to



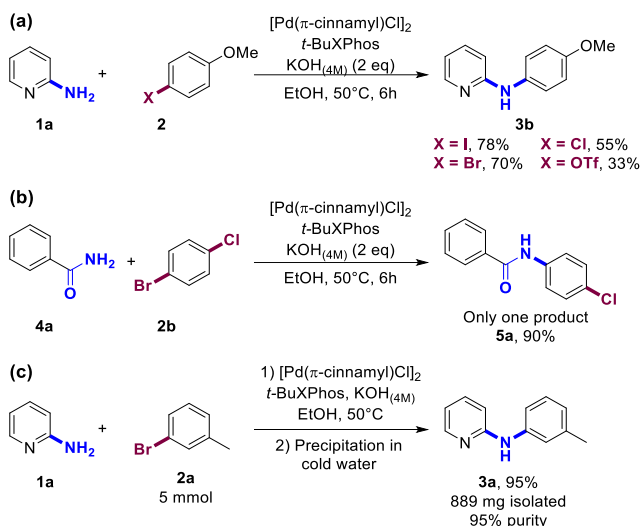
**Figure 5.** Potential role of the alcoholic solvent in the formation of L-Pd(0)



**Figure 6.** Characterization of the partially dissociated complex L-Pd(Ph)(Br) by conductometry (b), and observation of the reductive elimination by  $^{19}\text{F}$  NMR (c)

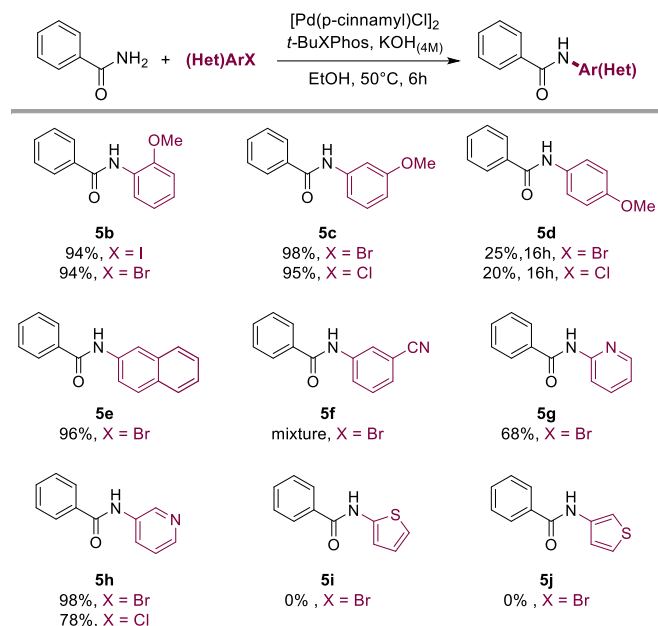
stabilize L-Pd(0) by 1,3-1,1,3,3-tetramethyldisiloxane (TVTMS, 10 eq.) resulted into the fast degradation to black palladium, and this phenomenon was observed with other alkenes such as allylbenzene or 1-hexene. Recently, N. Hazari and A. Nova reported a mechanistic study in which methanol could facilitate reduction of neutral NHC-ligated Pd(II),  $\text{Pd}(\pi\text{-allyl})(i\text{Pr})(\text{Cl})$ , to Pd(0) through the formation of a key-intermediate  $\text{Pd}(\pi\text{-R-allyl})(i\text{Pr})(\text{OMe})$ .<sup>38</sup> In our case, starting with the cationic  $[\text{Pd}(\pi\text{-R-allyl})(t\text{-BuXPhos})\text{Cl}]$ , the formation of a similar intermediate  $\text{Pd}(\pi\text{-R-allyl})(t\text{-BuXPhos})(\text{OR})$  could arise after deprotonation of a solvent molecule ligated to the cationic Pd(II) complex (Figure 5). The resulting neutral intermediate could further evolve through either the reductive elimination of the corresponding ether or an inner sphere hydride transfer to form the active Pd(0).

As shown in Table 1, the  $[\text{Pd}(\pi\text{-cinnamyl})\text{Cl}]_2 / t\text{-BuXPhos}$  system led to quantitative yields in primary alcohols, whereas secondary and tertiary alcohols appeared less efficient. In contrast,  $[\text{Pd}(\pi\text{-allyl})\text{Cl}]_2 / t\text{-BuXPhos}$  led to quantitative yields with all alcoholic solvents (Table S4). These differences of reactivity between  $(\pi\text{-allyl})$  and  $(\pi\text{-cinnamyl})$  palladium complexes in primary, secondary, and tertiary alcohols could be attributed to the steric hindrance of the cinnamyl group that



**Figure 7.** (a) Cross-coupling of aryl iodide, bromine, chlorine, and triflate (b) Cross-coupling of 1-chloro-4-bromobenzene (c) Scale-up of the reaction without chromatography

**Table 2. Scope of the reaction using various aryl or heteroaryl halides<sup>a,b</sup>**

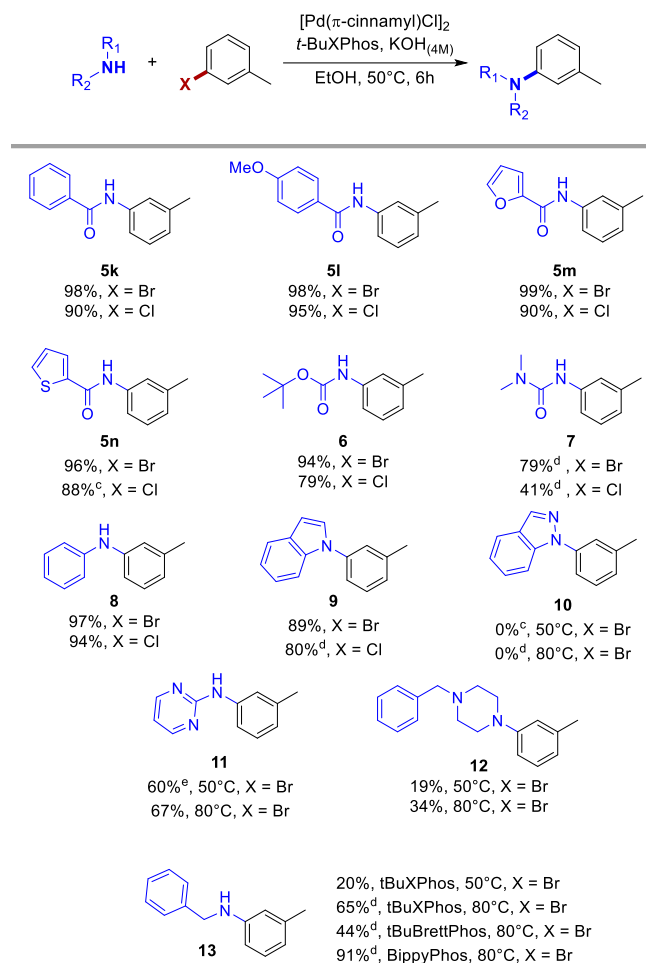


[a] Reaction conditions: (Het)ArX (1 eq, 0.4 mmol), benzamide (1.5 eq), [Pd(π-cinnamyl)Cl]<sub>2</sub> (0.5 mol%), t-BuXPhos (1.5 mol%), KOH (4 M in water, 2 eq, 200 μL), EtOH (1.8 mL), 50°C, 6 h; [b] % refers to isolated yield.

would disfavor the formation of Pd(0) in tertiary alcohols compared to primary ones (Figure 5). Moreover, the comproportionation between L-Pd(0) and neutral Pd(II)(π-R-allyl)(L)(Cl) to form the Pd(I) dimer (μ-R-allyl)(μ-Cl)Pd<sub>2</sub>(L) has largely been described in the literature,<sup>19,20,37–42</sup> but starting from cationic [Pd(π-R-allyl)(t-BuXPhos)]Cl in alcoholic solvents, the corresponding Pd(I) dimers were only detected as traces by MS. This observation is consistent with a previous report concerning the steric hindrance of both the phosphine and the substituted allyl moiety that would disfavor the formation of Pd(I) dimers.<sup>37</sup>

The addition of 4-fluorobromobenzene to L-Pd(0) triggered the oxidative addition with the appearance of a new signal at 56.6 ppm by <sup>31</sup>P{<sup>1</sup>H} NMR (see SI-§9b). Kinetic monitoring of the

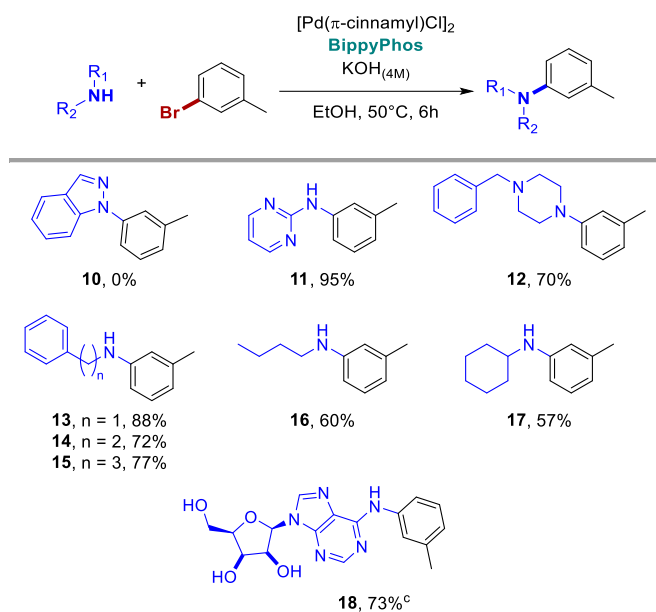
**Table 3. Scope of the reaction using various NH functional groups<sup>a,b</sup>**



[a] Reaction conditions: 3-bromotoluene (1 eq, 0.4 mmol), "NH" compound (1.5 eq), [Pd(π-cinnamyl)Cl]<sub>2</sub> (0.5 mol%), t-BuXPhos (1.5 mol%), KOH (4 M in water, 2 eq, 200 μL), EtOH (1.8 mL), 50°C; [b] % refers to isolated yield; [c] reaction time: 12 h [d] reaction time: 16 h; [e] reaction time: 8 h.

oxidative addition with PhBr (10 eq.) was performed by chronoamperometry at 50°C using a rotating disk electrode (Figure 4c and SI-§9c). This step proceeds rapidly with a pseudo-first order rate constant of 5.6 10<sup>-2</sup> s<sup>-1</sup> and a half-reaction time of about 10 s. Kinetics performed with various amounts of PhBr led to similar rate constants, consistently with zero order for PhBr. This result suggests a pre-complexation of the aryl bromide with an intramolecular oxidative addition, as already reported for similar Buchwald phosphines.<sup>43</sup> Increasing the amount of phosphine does not modify the kinetics of the oxidative addition, which further confirms the formation of L-Pd(0) as the sole Pd(0) species.

Based on these results, we proposed the classical kinetic model for the oxidative addition displayed in Figure 6a. Aryl iodides behave similarly with rate constants that are close to those determined for PhBr, and PhCl proceeds with a rate constant that is one order lower (Figure 4c and SI-§9c). Finally, we performed conductivity measurements proving that in EtOH:H<sub>2</sub>O (9:1) at the concentration of the catalyst, the complex Pd(t-BuXPhos)(4-F-Ph)(Br) is partially dissociated, as shown by the non-linearity between its concentration and conductivity (Figure 6b and SI-§9d). By <sup>19</sup>F{<sup>1</sup>H} NMR, the oxidative addition complex **A** in EtOH:H<sub>2</sub>O (9:1) features a broad signal at -124.7 ppm (Figure 6c).

**Table 4. Scope of the reaction with BippyPhos as ligand<sup>a,b</sup>**

[a] Reaction conditions: 3-bromotoluene (1 eq, 0.4 mmol), "NH" compound (1.5 eq),  $[Pd(\pi\text{-cinnamyl})Cl]_2$  (0.5 mol%), BippyPhos (1.5 mol%), KOH (4 M in water, 2 eq, 200  $\mu$ L), EtOH (1.8 mL), 50°C, 6 h; [b] % refers to isolated yield; [c] reaction time: 16 h.

After addition of 2-aminopyridine (10 eq.) at 50°C, a new signal appeared at -121.3 ppm, which was attributed to the amino ligated complex **B**. Then, the addition of KOH (10 eq.) provoked the instantaneous formation of the coupling product **C**, as attested by the signal at -122.7 ppm, along with disappearance of **B**. As no intermediate could be detected, both the deprotonation of the ligated amine and the reductive elimination should not be rate-limiting at this temperature.

**Scope of the reaction.** As shown previously, different halides are able to undergo oxidative addition. Next, we compared the efficiencies of the whole reaction between aryl iodide, bromide, chloride, and triflate (Figure 7a). The 4-methoxybenzene was selected as the aromatic platform because the presence of an electron-donating group at the *para* position of the (pseudo)halide could allow us to discriminate between the various electrophiles. Aryl bromides and iodides displayed similar reactivity (78% and 70% yield, respectively), while the aryl chloride appeared slightly less reactive with 55% yield. Unsurprisingly, the aryl triflate led to only 33% yield as it was not stable in this basic hydroalcoholic environment (Figure 7a).

Based on these results, 1-chloro-4-bromobenzene was chemoselectively functionalized with benzamide at the bromo-position (Figure 7b). The reaction could be easily scaled-up using 5 mmol of 3-bromotoluene (Figure 7c). The addition of ice water at the end of the reaction precipitated the expected product **3a** as a white powder with a yield of 95% and HPLC purity above 98% (254 nm). This procedure avoids the use of any organic solvents such as EtOAc or DCM for work-up or any purification on silica gel, which is consistent with the criteria of green chemistry.

The scope of the reaction was then assessed by coupling the benzamide with various (hetero)aryl halides (Table 2). Azaheterocycles (**5g**, **5h**), naphthyl (**5e**), and aromatic rings bearing methoxy groups at *ortho* or *meta* positions (**5b**, **5c**) were coupled in good to excellent yields, whereas the *para*-substituted product (**5d**) was obtained with modest yields below 25%. The cyano group in the *meta* position (**5f**) led to a

complex mixture, likely due to the hydrolysis of the cyano moiety. No reaction occurred with both 2- and 3-bromothiophenes (**5i**, **5j**).

Next, we evaluated the coupling of 3-bromo- or 3-chlorotoluene with various reactants bearing an "NH" functional group (Table 3). Aryl- and heteroaryl amines (**5k-n**), carbamates (**6**), urea (**7**), aniline (**8**), indole (**9**), and 2-aminopyrimidine (**11**) were all successfully coupled in good to excellent yields. No reaction was observed with indazole (**10**), but this heteroaromatic amine is known as a poorly reactive substrate in Buchwald-Hartwig CCR.<sup>44</sup>

With primary and secondary amines (**12**, **13**), yields were rather low (< 20%) at 50°C.

At 80°C, **14** was isolated in 65% yield, but the temperature had only a small effect for piperazine **11** (34% yield at 80°C instead of 19% yield). For these less efficient partners, several ligands that have already been identified during the optimization process were screened, and BippyPhos featured excellent results, affording **13** in 91% yield (Table 3). Developed by R. A. Singer in 2006,<sup>45</sup> BippyPhos is considered as one of the most appropriate ligands for  $[Pd(\pi\text{-cinnamyl})Cl]_2$ .<sup>46</sup> At 50°C in EtOH, the  $[Pd(\pi\text{-cinnamyl})Cl]_2$ /BippyPhos catalytic system allowed us to couple a broad scope of amines (**11-18**) with yields ranging from 57% to 95% (Table 4). No reaction was observed with indazole (**10**), but adenosine without any protecting groups on the sugar moiety was successfully coupled to 3-bromotoluene to afford **18** in 73% yield.

## CONCLUSIONS

We have developed an efficient catalytic system for the Buchwald-Hartwig cross-coupling reaction in "green" alcoholic solvents. The ability of  $[Pd(\pi\text{-R-allyl})Cl]_2$  to interact spontaneously with extremely bulky biarylphosphine ligands **L** in alcohols led to the *in-situ* formation of cationic  $[Pd(\pi\text{-R-allyl})(L)Cl]$  palladium complexes. To date, these kinds of cationic precatalysts have been only described with a triflate as a counter-anion, involving a pretreatment of  $[Pd(\pi\text{-R-allyl})Cl]_2$  with silver triflate.<sup>37</sup> In alcoholic solvents, the cationic  $[Pd(\pi\text{-R-allyl})(L)Cl]$  precatalyst spontaneously formed *in situ* and can be easily activated under mild conditions into the corresponding L-Pd(0) catalyst, which is commonly employed for cross-coupling reactions. In typical cases, the  $[Pd(\pi\text{-allyl})Cl]_2$  / tBuXPhos system will be preferred as it is cheaper, easy to access, compatible with all alcoholic solvents, and it allows the coupling of a wide range of nitrogen groups. However, for challenging cases such as the coupling of primary or secondary amines, the use of the BippyPhos as ligand will be preferred. A broad scope of C-N coupling reactions with low catalyst loading and short reaction times highlights the practicability of this catalytic system under conditions that are more respectful of the principles of green chemistry.

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## Notes

The authors declare no competing financial interest.

## ■ SUPPORTING INFORMATION

The supporting information is available free of charge at ...

Materials and methods, detailed experimental procedures, tables of optimization, characterization of the palladium complexes (NMR, MS, conductometry, cyclic voltammetry, amperometry), solubility of the palladium complexes. <sup>1</sup>H and <sup>13</sup>C NMR spectra for new compounds.

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## ■ REFERENCES

- (1) Kosugi, M.; Kameyama, M.; Migita, T. Palladium-Catalyzed Aromatic Amination of Aryl Bromides with N,N-Di-Ethylaminotributyltin. *Chem. Lett.* **1983**, *12* (6), 927–928.
- (2) Guram, A. S.; Buchwald, S. L. Palladium-Catalyzed Aromatic Aminations with in Situ Generated Aminostannanes. *J. Am. Chem. Soc.* **1994**, *116* (17), 7901–7902.
- (3) Paul, F.; Patt, J.; Hartwig, J. F. Palladium-Catalyzed Formation of Carbon-Nitrogen Bonds. Reaction Intermediates and Catalyst Improvements in the Hetero Cross-Coupling of Aryl Halides and Tin Amides. *J. Am. Chem. Soc.* **1994**, *116* (13), 5969–5970.
- (4) Louie, J.; Hartwig, J. F. Palladium-Catalyzed Synthesis of Arylamines from Aryl Halides. Mechanistic Studies Lead to Coupling in the Absence of Tin Reagents. *Tetrahedron Lett.* **1995**, *36* (21), 3609–3612.
- (5) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. A Simple Catalytic Method for the Conversion of Aryl Bromides to Arylamines. *Angew. Chem. Int. Ed. Engl.* **1995**, *34* (12), 1348–1350.
- (6) Forero-Cortés, P. A.; Haydl, A. M. The 25th Anniversary of the Buchwald–Hartwig Amination: Development, Applications, and Outlook. *Org. Process Res. Dev.* **2019**, *23* (8), 1478–1483.
- (7) Dorel, R.; Grugel, C. P.; Haydl, A. M. The Buchwald–Hartwig Amination After 25 Years. *Angew. Chem. - Int. Ed.* **2019**, *17118*–17129.
- (8) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116* (19), 12564–12649.
- (9) Roughley, S. D.; Jordan, A. M. The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J. Med. Chem.* **2011**, *54* (10), 3451–3479.
- (10) Schneider, N.; Lowe, D. M.; Sayle, R. A.; Tarselli, M. A.; Landrum, G. A. Big Data from Pharmaceutical Patents: A Computational Analysis of Medicinal Chemists' Bread and Butter. *J. Med. Chem.* **2016**, *59* (9), 4385–4402.
- (11) Brown, D. G.; Bostro, J. Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem.* **2016**, *59*, 4443–4458.
- (12) Buskes, M. J.; Blanco, M.-J. Impact of Cross-Coupling Reactions in Drug Discovery and Development. *Molecules* **2020**, *25* (15), 3493.
- (13) McCann, S. D.; Reichert, E. C.; Arrechea, P. L.; Buchwald, S. L. Development of an Aryl Amination Catalyst with Broad Scope Guided by Consideration of Catalyst Stability. *J. Am. Chem. Soc.* **2020**, *142* (35), 15027–15037.
- (14) Surry, D. S.; Buchwald, S. L. Dialkylbiaryl Phosphines in Pd-Catalyzed Amination: A User's Guide. *Chem. Sci.* **2011**, *2* (1), 27–50.
- (15) Ingoglia, B. T.; Wagen, C. C.; Buchwald, S. L. Biaryl Monophosphine Ligands in Palladium-Catalyzed C–N Coupling: An Updated User's Guide. *Tetrahedron* **2019**, *75* (32), 4199–4211.
- (16) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. Unparalleled Rates for the Activation of Aryl Chlorides and Bromides: Coupling with Amines and Boronic Acids in Minutes at Room Temperature. *Angew. Chem. Int. Ed.* **2002**, *41* (24), 4746–4748.
- (17) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. Modified (NHC)Pd(Allyl)Cl (NHC = N-Heterocyclic Carbene) Complexes for Room-Temperature Suzuki-Miyaura and Buchwald-Hartwig Reactions. *J. Am. Chem. Soc.* **2006**, *128* (12), 4101–4111.
- (18) Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Sayah, M.; Valente, C. Pd-Catalyzed Aryl Amination Mediated by Well Defined, N-Heterocyclic Carbene (NHC)–Pd Precatalysts, PEPPSI. *Chem. - Eur. J.* **2008**, *14* (8), 2443–2452.
- (19) Hill, L. L.; Crowell, J. L.; Tutwiler, S. L.; Massie, N. L.; Hines, C. C.; Griffin, S. T.; Rogers, R. D.; Shaughnessy, K. H.; Grasa, G. A.; Johansson Seechurn, C. C. C.; Li, H.; Colacot, T. J.; Chou, J.; Woltermann, C. J. Synthesis and X-Ray Structure Determination of Highly Active Pd(II), Pd(I), and Pd(0) Complexes of Di(Tert -Butyl)Neopentylphosphine (DTBNpP) in the Arylation of Amines and Ketones. *J. Org. Chem.* **2010**, *75* (19), 6477–6488.
- (20) Seechurn, C. C. C. J.; Parisel, S. L.; Colacot, T. J. Air-Stable Pd(R-Allyl)Cl (L= Q-Phos, P(t-Bu) 3, Etc.) Systems for C–C/N Couplings: Insight into the Structure - Activity Relationship and Catalyst Activation Pathway. *J. Org. Chem.* **2011**, *76* (19), 7918–7932.
- (21) Chartoire, A.; Lesieur, M.; Slawin, A. M. Z.; Nolan, S. P.; Cazin, C. S. J. Highly Active Well-Defined Palladium Precatalysts for the Efficient Amination of Aryl Chlorides. *Organometallics* **2011**, *30* (16), 4432–4436.
- (22) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. A New Class of Easily Activated Palladium Precatalysts for Facile C–N Cross-Coupling Reactions and the Low Temperature Oxidative Addition of Aryl Chlorides. *J. Am. Chem. Soc.* **2008**, *130* (21), 6686–6687.
- (23) Bruneau, A.; Roche, M.; Alami, M.; Messaoudi, S. 2-Aminobiphenyl Palladacycles: The "Most Powerful" Precatalysts in C–C and C–Heteroatom Cross-Couplings. *ACS Catal.* **2015**, *5* (2), 1386–1396.
- (24) Lau, S. H.; Yu, P.; Chen, L.; Madsen-Duggan, C. B.; Williams, M. J.; Carrow, B. P. Aryl Amination Using Soluble Weak Base Enabled by a Water-Assisted Mechanism. *J. Am. Chem. Soc.* **2020**, *142* (47), 20030–20039.
- (25) MacLean, M. A.; Wheaton, C. A.; Stradiotto, M. Developing Backbone-Modified Mor-DalPhos Ligand Variants for Use in Palladium-Catalyzed C–N and C–C Cross-Coupling. *Can. J. Chem.* **2018**, *96* (7), 712–721.
- (26) Ouyang, J.-S.; Liu, S.; Pan, B.; Zhang, Y.; Liang, H.; Chen, B.; He, X.; Chan, W. T. K.; Chan, A. S. C.; Sun, T.-Y.; Wu, Y.-D.; Qiu, L. A

- Bulky and Electron-Rich *N*-Heterocyclic Carbene–Palladium Complex (SIPr)<sup>Ph</sup><sub>2</sub> Pd(Cin)Cl: Highly Efficient and Versatile for the Buchwald–Hartwig Amination of (Hetero)Aryl Chlorides with (Hetero)Aryl Amines at Room Temperature. *ACS Catal.* **2021**, *11* (15), 9252–9261.
- (27) Sherwood, J.; Clark, J. H.; Fairlamb, I. J. S.; Slattery, J. M. Solvent Effects in Palladium Catalysed Cross-Coupling Reactions. *Green Chem.* **2019**, *21* (9), 2164–2213.
- (28) Byrne, F. P.; Jin, S.; Paggiola, G.; Petchey, T. H. M.; Clark, J. H.; Farmer, T. J.; Hunt, A. J.; Robert McElroy, C.; Sherwood, J. Tools and Techniques for Solvent Selection: Green Solvent Selection Guides. *Sustain. Chem. Process.* **2016**, *4* (1), 7.
- (29) Affouard, C.; Crockett, R. D.; Diker, K.; Farrell, R. P.; Gorins, G.; Huckins, J. R.; Caille, S. Multi-Kilo Delivery of AMG 925 Featuring a Buchwald–Hartwig Amination and Processing with Insoluble Synthetic Intermediates. *Org. Process Res. Dev.* **2015**, *19* (3), 476–485.
- (30) Isley, N. A.; Dobarco, S.; Lipshutz, B. H. Installation of Protected Ammonia Equivalents onto Aromatic & Heteroaromatic Rings in Water Enabled by Micellar Catalysis. *Green Chem.* **2014**, *16* (3), 1480–1488.
- (31) Wagner, P.; Bollenbach, M.; Doebelin, C.; Bihel, F.; Bourguignon, J.-J.; Salomé, C.; Schmitt, M. T-BuXPhos: A Highly Efficient Ligand for Buchwald–Hartwig Coupling in Water. *Green Chem.* **2014**, *16* (9), 4170.
- (32) Salomé, C.; Wagner, P.; Bollenbach, M.; Bihel, F.; Bourguignon, J. J.; Schmitt, M. Buchwald–Hartwig Reactions in Water Using Surfactants. *Tetrahedron* **2014**, *70* (21), 3413–3421.
- (33) Zhang, Y.; Takale, B. S.; Gallou, F.; Reilly, J.; Lipshutz, B. H. Sustainable Ppm Level Palladium-Catalyzed Aminations in Nanoreactors under Mild, Aqueous Conditions. *Chem. Sci.* **2019**, 10556–10561.
- (34) Ansari, T. N.; Taussat, A.; Clark, A. H.; Nachtegaal, M.; Plummer, S.; Gallou, F.; Handa, S. Insights on Bimetallic Micellar Nanocatalysis for Buchwald–Hartwig Aminations. *ACS Catal.* **2019**, *9* (11), 10389–10397.
- (35) Bollenbach, M.; Lecroq, W.; Wagner, P.; Fessard, T.; Schmitt, M.; Salomé, C. On Water *N*-Arylation of Oxetanylamines for the Preparation of *N*-Aryl-Oxetanylamines; Potentially Useful Aryl-Amide Isosteres. *Chem. Commun.* **2019**, 55 (11), 1623–1626.
- (36) Cosgrove, S. C.; Thompson, M. P.; Ahmed, S. T.; Parmeggiani, F.; Turner, N. J. One-Pot Synthesis of Chiral *N*-Arylamines by Combining Biocatalytic Aminations with Buchwald–Hartwig *N*-Arylation. *Angew. Chem. - Int. Ed.* **2020**, *59* (41), 18156–18160.
- (37) Deangelis, A. J.; Gildner, P. G.; Chow, R.; Colacot, T. J. Generating Active L-Pd(0) via Neutral or Cationic  $\pi$ -Allylpalladium Complexes Featuring Biaryl/Bipyrazolyphosphines: Synthetic, Mechanistic, and Structure-Activity Studies in Challenging Cross-Coupling Reactions. *J. Org. Chem.* **2015**, *80* (13), 6794–6813.
- (38) Melvin, P. R.; Balcells, D.; Hazari, N.; Nova, A. Understanding Precatalyst Activation in Cross-Coupling Reactions: Alcohol Facilitated Reduction from Pd(II) to Pd(0) in Precatalysts of the Type ( $\eta^3$ -Allyl)Pd(L)(Cl) and ( $\eta^3$ -Indenyl)Pd(L)(Cl). *ACS Catal.* **2015**, *5* (9), 5596–5606.
- (39) Hruszkewycz, D. P.; Guard, L. M.; Balcells, D.; Feldman, N.; Hazari, N.; Tilset, M. Effect of 2-Substituents on Allyl-Supported Precatalysts for the Suzuki–Miyaura Reaction: Relating Catalytic Efficiency to the Stability of Palladium(I) Bridging Allyl Dimers. *Organometallics* **2015**, *34* (1), 381–394.
- (40) Melvin, P. R.; Nova, A.; Balcells, D.; Dai, W.; Hazari, N.; Hruszkewycz, D. P.; Shah, H. P.; Tudge, M. T. Design of a Versatile and Improved Precatalyst Scaffold for Palladium-Catalyzed Cross-Coupling: (H<sub>3</sub>-1-TBu-Indenyl)<sub>2</sub>( $\mu$ -Cl)<sub>2</sub>Pd<sub>2</sub>. *ACS Catal.* **2015**, *5* (6), 3680–3688.
- (41) Hazari, N.; Hruszkewycz, D. P. Dinuclear PdI Complexes with Bridging Allyl and Related Ligands. *Chem. Soc. Rev.* **2016**, *45* (10), 2871–2899. <https://doi.org/10.1039/c5cs00537j>.
- (42) Scott, N. W. J.; Ford, M. J.; Husbands, D. R.; Whitwood, A. C.; Fairlamb, I. J. S. Reactivity of a Dinuclear Pd<sup>I</sup> Complex [Pd<sub>2</sub>( $\mu$ -PPh<sub>2</sub>)( $\mu$ -OAc)(PPh<sub>3</sub>)<sub>2</sub>] with PPh<sub>3</sub>: Implications for Cross-Coupling Catalysis Using the Ubiquitous Pd(OAc)<sub>2</sub>/NPPH<sub>3</sub> Catalyst System. *Organometallics* **2021**, *40* (17), 2995–3002.
- (43) Wagschal, S.; Perego, L. A.; Simon, A.; Franco-Espejo, A.; Tocqueville, C.; Albaneze-Walker, J.; Jutand, A.; Grimaud, L. Formation of XPhos-Ligated Palladium(0) Complexes and Reactivity in Oxidative Additions. *Chem. – Eur. J.* **2019**, *25* (28), 6980–6987.
- (44) Ayothiraman, R.; Rangaswamy, S.; Maity, P.; Simmons, E. M.; Beutner, G. L.; Janey, J.; Treitler, D. S.; Eastgate, M. D.; Vaidyanathan, R. Zinc Acetate-Promoted Buchwald–Hartwig Couplings of Heteroaromatic Amines. *J. Org. Chem.* **2017**, *82* (14), 7420–7427.
- (45) Singer, R. A.; Doré, M.; Sieser, J. E.; Berliner, M. A. Development of Nonproprietary Phosphine Ligands for the Pd-Catalyzed Amination Reaction. *Tetrahedron Lett.* **2006**, *47* (22), 3727–3731.
- (46) Crawford, S. M.; Lavery, C. B.; Stradiotto, M. BippyPhos: A Single Ligand With Unprecedented Scope in the Buchwald–Hartwig Amination of (Hetero)Aryl Chlorides. *Chem. – Eur. J.* **2013**, *19* (49), 16760–16771.