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Xantphos is one of the two most common ligands used in palladium catalyzed Buchwald-Hartwig amination reactions, because of its broad scope and high probability of success. It does not, however, work well with unactivated aryl chlorides. Herein NIXANTPHOS is compared to Xantphos and an array of mono- and bidentate phosphines. NIXANTPHOS outperforms Xantphos and all other bidentate ligands examined. Under the optimal reaction conditions, unactivated aryl chlorides afford the expected products in good to excellent yield with as low as 0.05 mol % (500 ppm) palladium loading.

Introduction

Buchwald–Hartwig coupling reactions have emerged as one of the most important methods in the synthesis of pharmaceuticals, agrochemicals, natural products and novel materials.[1] Although many palladium complexes are known to catalyze this C–N bond-forming reaction, a handful of ligands are consistently employed, because of their broad utility, reliability and outstanding performance (Figure 1).[2] In their comprehensive 2016 review on the applications of the Buchwald-Hartwig amination reaction, Ruiz-Castillo and Buchwald[1a] noted: "…BINAP and Xantphos have become the most often used ligands for *N*-arylation reactions." Indeed, van Leeuwen's Xantphos[3] has been used in many successful Buchwald-Hartwig C–N cross-coupling reactions in the last 5 years alone,[1a, 2a, 2b, 3a, 4] including on scale.[5]

Despite the known utility of Pd(Xantphos)-based catalysts in C–N coupling reaction, *unactivated aryl chloride* substrates are poor coupling partners at low temperature due to the high barrier to oxidative addition of these substrates to palladium catalysts bearing bidentate phosphines. Based on recent work from our group with van Leeuwen's NIXANTPHOS ligand, we sought to compare the popular Xantphos to NIXANTPHOS in the Buchwald-Hartwig amination. In the process, we also compared the NIXANTPHOS with a host of other ligands. Herein, we demonstrate that NIXANTPHOS is not only a viable ligand for Buchwald-Hartwig coupling reactions, it outperforms Xantphos with unactivated aryl chloride substrates.

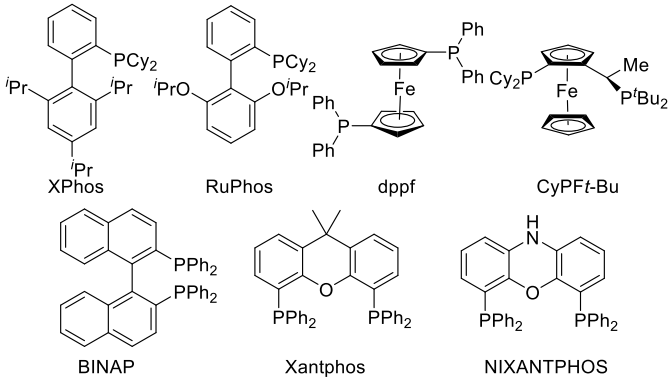

Figure 1. Representative ligand structures in Buchwald–Hartwig coupling reactions.

Results and Discussion

For reasons outlined below, we hypothesized that the Pd(NIXANTPHOS) catalyst system might catalyze *N*-arylation reactions with unactivated aryl chlorides at or just above room temperature. This hypothesis is based, in part, on structural similarities between van Leeuwen's Xantphos (bite angle 111°)[6] and NIXANTPHOS (bite angle 114°),[7] and the efficiency of the Xantphos-based catalyst in the Buchwald-Hartwig coupling with aryl bromides.[4a, 4b] Our hypothesis is also founded upon a dramatic difference in the catalytic performance between M(NIXANTPHOS)- and M(Xantphos)-based catalysts in the room temperature C–C cross-coupling of diarylmethane pronucleophiles with aryl chlorides (M = Pd, Ni).[8] As background information, it is known that the oxidative addition of aryl chlorides proceeds via a low energy Pd-L_1 pathway (where L_1 is a bulky monodentate phosphine).[9] When bidentate phosphines are used, the oxidative addition of Ar–Cl is forced to proceed through the higher energy PdL_2 pathway, and thus oxidative addition typically takes place at temperatures in excess of 90 °C.[10] For this reason, it is not surprising that Pd(Xantphos)-based catalysts cannot promote Buchwald-Hartwig

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Dedicated to Prof. Dick Andersen (UC Berkeley), for his never ending excitement about chemistry and passion for sharing his work with others

coupling reactions with unactivated Ar–Cl substrates near room temperature.

The most significant difference between van Leeuwen's Xantphos and NIXANTPHOS is the presence of a relatively acidic phenoxazine N–H (pK_a ~21 in DMSO[11]) in the NIXANTPHOS backbone. We have demonstrated that under basic reaction conditions, the N–H is deprotonated and a main group metal is associated with the ligand pi-system.[8c] Based on circumstantial evidence, we proposed that the main group metal cooperates with the palladium center to lower the barrier to oxidative addition of aryl chlorides, such that oxidative addition can take place at room temperature.[8c] In the present study we 1) validate our hypothesis that the Pd(NIXANTPHOS)-based catalyst can promote the amination of aryl chlorides at room temperature, 2) compare the reactivity of Pd(NIXANTPHOS)-based catalyst with Xantphos and a series of mono- and bidentate phosphines ligated palladium catalysts in Buchwald-Hartwig coupling reactions, and 3) explore the scope of the Pd(NIXANTPHOS)-based catalyst in amination reactions.

To initiate our studies, we chose the Pd(NIXANTPHOS) catalyzed cross-coupling reaction between *N*-methyl *o*-toluidine (**1a**) and chlorobenzene (**2a**) at room temperature. *N*-Methyl *o*-toluidine (**1a**) is a sterically hindered aniline derivative, and its *N*-arylation products exhibit interesting biological activity.[12] *N*-Arylation of 1a was previously reported by the Buchwald group employing $LiN(SiMe_3)_2$ or NaO*t*-Bu as base and a palladium RuPhos-based first-generation precatalyst in THF at 85 or 65 °C (Figure 2).[13]

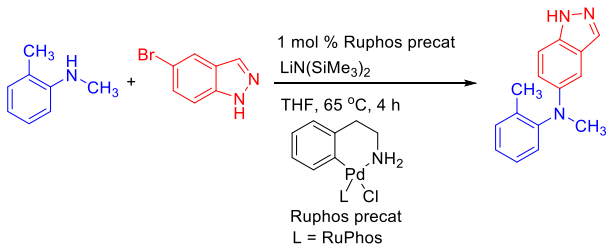
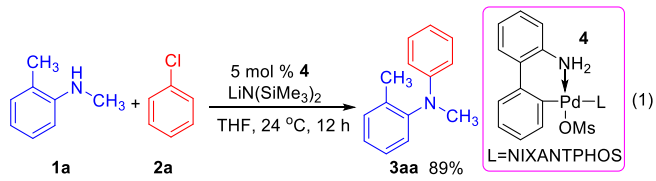
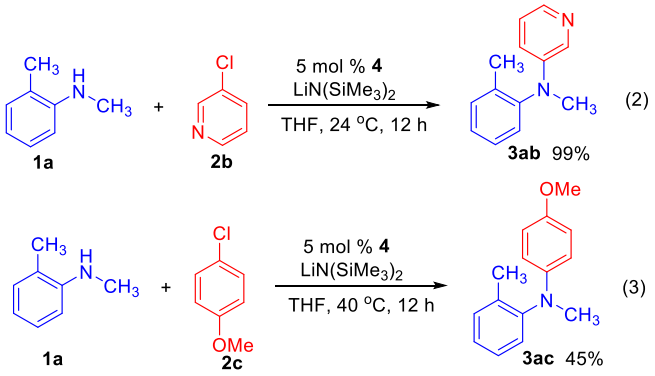


Figure 2. Palladium precatalyst and ligand employed in *N*-arylation of 1a by Buchwald and co-workers.

In our first attempt under typical C–N cross-coupling conditions [1 equiv of *N*-methyl *o*-toluidine (**1a**), 1.5 equiv of $LiN(SiMe_3)_2$, 1 equiv of chlorobenzene (**2a**) and 5 mol % precatalyst 4 in THF at 24 °C],[2l] the *N*-arylation product (**3aa**) was isolated in 89% yield (eq 1).



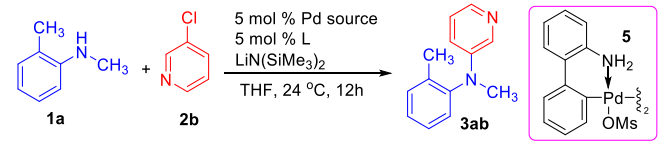
Because we were particularly interested in whether unactivated and heterocyclic aryl chloride substrates were viable cross-coupling partners in this room temperature Pd(NIXANTPHOS) catalyzed C–N cross-coupling reaction, we next examined 3-chloropyridine (**2b**)[14] and 4-chloroanisole (**2c**) under the "unoptimized" reaction conditions in eq 1. Fortunately, heteroaryl chloride (**2b**) underwent efficient C–N cross-coupling to give **3ab** in 99% yield (eq 2). However, with a more electron-rich 4-chloroanisole (**2c**), raising the temperature to 40 °C resulted in formation of **3ac** in 45% yield (eq 3). This result inspired us to examine different variables on the amination reaction.

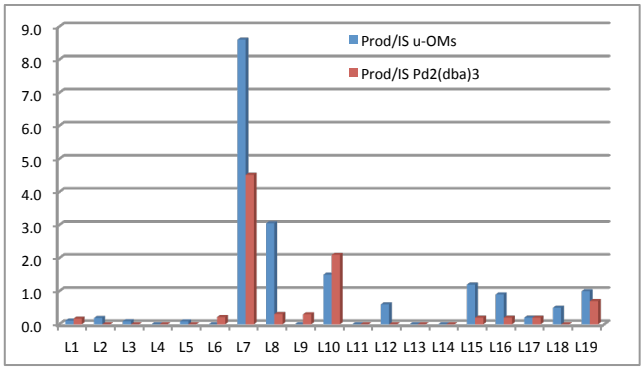


Ligand Comparison in C–N Cross-Couplings with Aryl Chlorides.

We next focused on comparing the catalyst performance in C–N cross-couplings using NIXANTPHOS and a variety of *bidentate* ligands. To compare the reactivity, 1 equiv of aniline (**1a**), 1.5 equiv of $LiN(SiMe_3)_2$, and 1 equiv of 3-chloropyridine (**2b**), in the presence of two palladium sources with 5 mol % Pd (2.5 mol % dimers) and 5 mol % **L1–L19** in THF were examined at 24 °C for 12 h. The results presented in Figure 3 are derived from product/internal standard ratios determined by HPLC (see Supporting Information for details).

In agreement with the large difference in reactivity between NIXANTPHOS and Xantphos in our previous base mediated C–C cross-couplings with aryl chlorides and diphenylmethane pronucleophiles to form triarylmethanes,[8a, 8c] a dramatic difference was observed in the Buchwald–Hartwig coupling.[8c] Among the bidentate ligands examined (**L1–L19**), NIXANTPHOS (**L7**) showed the highest catalytic activity followed by Xantphos (**L8**). These two ligands were both significantly better than the other bidentate ligands. Another bidentate ligand CyPF*t*-Bu (**L20**) was not included in the original screening, but in a separate examination under the same conditions gave traces of coupled product (**3ab**). This result is not surprising, because it is known that the Pd-CyPF*t*-Bu system is less reactive toward secondary amines than with primary amines.[14-15] Using Buchwald's μ-OMs dimer **5** as palladium source generally gave better reactivity than $Pd_2(dba)_3$. The μ-OMs dimer **5**/NIXANTPHOS combination translated to an excellent yield (94%) of **3ab** under the same conditions on laboratory scale (0.2 mmol).





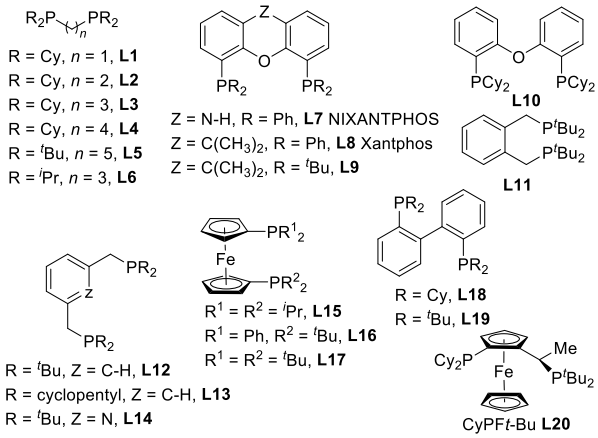


Figure 3. Bidentate phosphine ligand comparison in C–N bond-formation reactions

Given the high reactivity of the NIXANTPHOS catalyst system with respect to bidentate ligands, we were interested in comparing it with the prevailing Buchwald dialkylbiaryl phosphine ligands **L21–L27** as well as other highly regarded monodentate ligands **L28–L31**. As shown in Figure 4, the coupling with 3-chloropyridine using NIXANTPHOS gave comparable results to the Buchwald family of ligands (**L21–L25**), including XPhos (**L21**), SPhos (**L22**), and RuPhos (**L25**) when 5 mol % Pd was used.

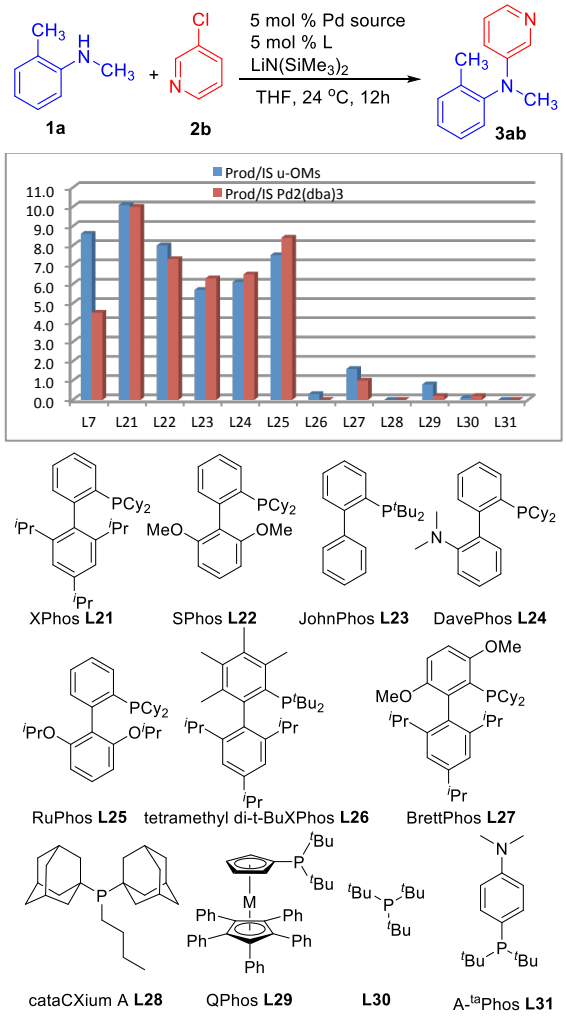


Figure 4. Comparison NIXANTPHOS with commonly used monodentate ligands in Buchwald-Hartwig coupling

To summarize the results of the proceeding section, direct comparisons between μ-OMs dimer **5** as palladium source with $Pd_2(dba)_3$ show that Buchwald precatalyst **5** is better. NIXANTPHOS was the best ligand among the bidentate ligands for Buchwald–Hartwig cross-coupling of *N*-methyl-*o*-toluidine (**1a**) with 3-chloropyridine (**2b**) followed by Xantphos. Three monodentate ligands (XPhos, SPhos, RuPhos) showed excellent catalytic reactivity. For the next screening the reaction of *N*-methyl *o*-toluidine (**1a**) with 4-chloroanisole (**2c**), a less reactive aryl chloride substrate towards oxidative addition, was undertaken to compare the catalytic reactivity of NIXANTPHOS and state of the art Buchwald dialkylbiaryl phosphine ligands.

Two palladium sources [Buchwald's precatalyst **5** and $Pd_2(dba)_3$] and 10 diverse monodentate phosphine ligands **L21**–**L31** and NIXANTPHOS **L7** were examined using 1 equiv of *N*-methyl *o*-toluidine (**1a**), 1.5 equiv of $LiN(SiMe_3)_2$, and 1 equiv of 4-chloroanisole (**2c**), in the presence of 5 mol % palladium source (2.5 mol % dimers) and 5 mol % ligand in THF at 24 °C. The HTE results are presented in Figure 5. According to Figure 5 NIXANTPHOS is less reactive than the most active members of the Buchwald family of dialkylbiaryl phosphine ligands (**L21**–**L25**).

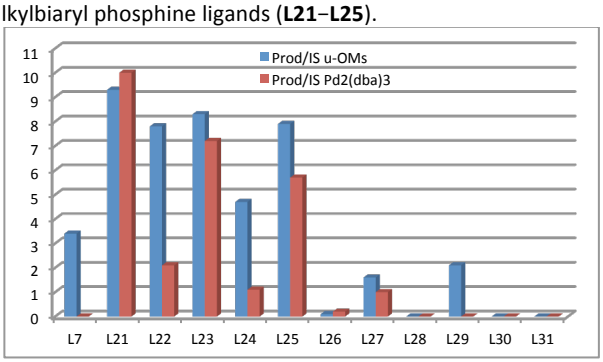
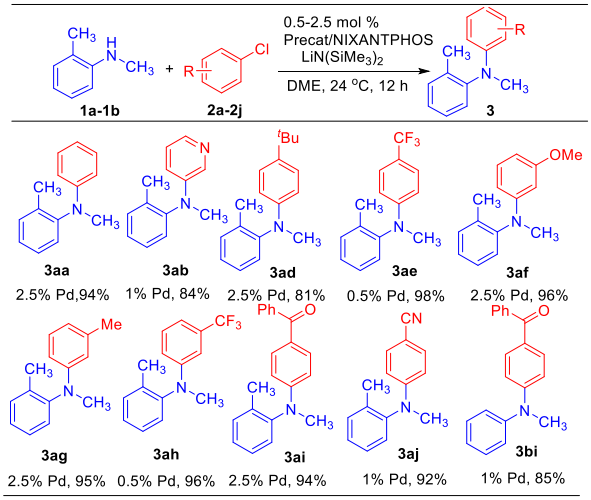


Figure 5. Comparison of NIXANTPHOS with commonly used monodentate ligands in the Buchwald-Hartwig coupling reaction.

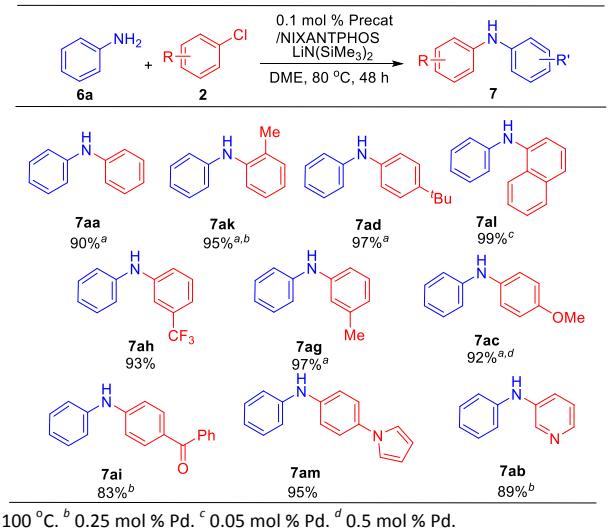
After demonstrating that the Pd(NIXANTPHOS)-based catalyst is competitive among a broad range of catalysts in C–N bond-forming reactions, we next moved to examine the scope of the electrophiles in the presence of 1 equiv of **1a**, 1.2 equiv of $LiN(SiMe_3)_2$, 1.2 equiv of aryl chloride and 0.5–2.5 mol % precatalyst **4** in DME at 24 °C (see Supporting Information for the optimization of the solvent). With 2.5 mol % palladium loading, the parent chlorobenzene underwent this transformation to afford the desired product in 94% isolated yield (**3aa**, Table 1). Heterocyclic 3-chloropyridine was a good substrate under these conditions, delivering the product in 81% yield (**3ab**). Aryl chlorides containing slightly electron-donating groups, such as 4-*t*-Bu, exhibited good reactivity, affording the product in 81% yield (**3ad**). 4-Chlorobenzotrifloride outperformed other electrophiles, delivering the product in 98% yield with as low as 0.5 mol % Pd loading (**3ae**). Excellent yields (≥95%) were obtained with the aryl chlorides bearing methyl, methoxy, and trifluoromethyl groups in the *meta* positions (**3af–3ah**). Aryl chlorides bearing ketones, or nitriles were all tolerated under these conditions, delivering the products in 85–94% yields (**3ai–3aj**, and **3bi**).

Table 1. Room temperature arylation of secondary anilines with Pd(NIXANTPHOS)-based catalyst



Diphenylamine derivatives have found applications in agrochemicals.[16] We discovered that the NIXANTPHOS-based catalyst exhibits good to excellent reactivity for primary anilines at 80 °C. We first explored the reaction of aniline in couplings with a range of aryl chlorides with low palladium loadings. In general, fair to excellent reactivity was exhibited with aryl chlorides bearing various substituents, affording the desired products in 83–99% yield (Table 2). Thus, 2-methyl, and 4-*tert*-butyl chlorobenzene gave **7ak** and **7ad** in 95 and 97% yield, respectively (0.25 mol % palladium loading). The sterically hindered 1-chloronaphthalene is an outstanding coupling partner, affording the product (**7al**) in 99% yield with as low as 0.05 mol % (500 ppm) palladium loading. Aryl chlorides bearing trifluoromethyl or methyl at the *meta* position provided products **7ah** and **7ag** in 93 and 97% yields, respectively. Substrates with electron donating groups, such as 4-chloroanisole, required higher palladium loadings (0.5 mol %) to give **7ac** in 92% yield. Although benzophenone can undergo additions with $Li(SiMe_3)_2$,[17] no problems were encountered in the amination. Thus, 4-chlorobenzophenone underwent coupling to provide diarylamine derivative **7ai** in 83% yield. Heteroaryl chlorides 4-pyrrolylchlorobenzene and 3-chloropyridine are both good substrates and furnished products in 89–95% yields (**7am** and **7ab**).

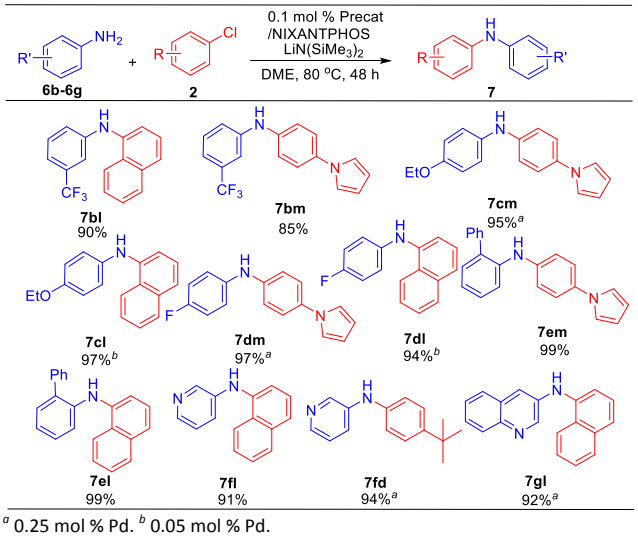
Table 2. Scope and reactivity in arylations of aniline



[a] 100 °C. [b] 0.25 mol % Pd. [c] 0.05 mol % Pd. [d] 0.5 mol % Pd.

We next tested aniline derivatives bearing various functional groups and heteroatoms as shown in Table 3. Anilines containing electron-withdrawing groups are known to exhibit reduced reactivity.[18] In this study, 3-trifluoromethyl aniline was a fine substrate, affording the desired products in 85–90% yield (**7bl**, **7bm**). 4-Ethoxy aniline was an excellent substrate generating coupling products **7cm** and **7cl** in 95 and 97% yield, respectively. It is noteworthy that the 4-fluoroaniline coupled with sterically hindered 1-chloronaphthalene with as low as 500 ppm palladium loading (97% yield). *N*-Substituted 2-aminobiphenyls have found applications in the preparation of palladium precatalysts.[19] 2-Aminobiphenyl derivatives could be efficiently synthesized using the Pd(NIXANTPHOS) system with 0.1 mol % palladium loading (**7em** and **7el**). Heteroaryl anilines are common motifs of pharmaceuticals.[20] Both 3-aminopyridine and 3-aminoquinoline were well-tolerated coupling partners, rendering the desired products in 92–94% yield.

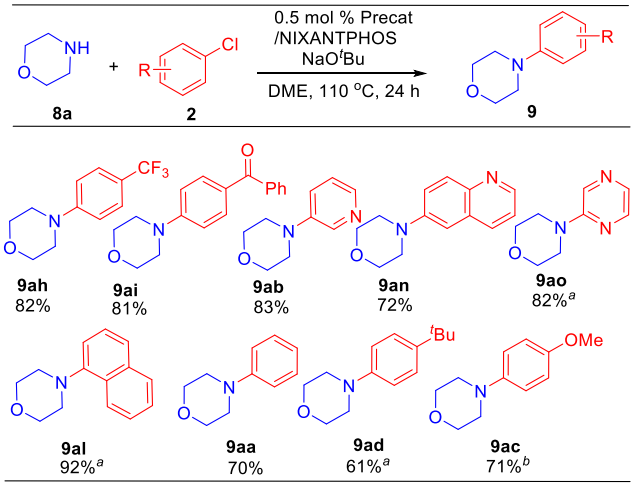
Table 3. Scope and reactivity in arylations of aniline variants



[a] 0.25 mol % Pd. [b] 0.05 mol % Pd.

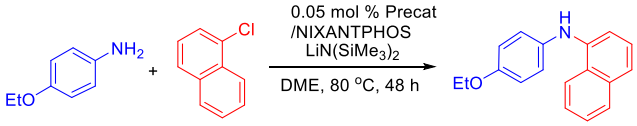
As exemplified above, the Pd(NIXANTPHOS) system could efficiently catalyze the *N*-arylations of primary and secondary aniline derivatives, which encouraged us to ask if this catalyst can also arylate secondary alkyl amines. We next examined the arylations of morpholine using the Pd(NIXANTPHOS) system, because morpholine derivatives bearing heteroarenes exhibit bioactivity.[21] In this study, we examined aryl chlorides with both electron-withdrawing and donating groups as well as heteroaryl chlorides (Table 4). The Pd(NIXANTPHOS) system exhibited good reactivity, affording the products in 61–92% yield. 4-Chloroanisole required higher palladium loading (2.5 mol %), rendering the desired product **9ac** in 71% yield.

Table 4. Palladium catalyzed arylation of morpholine with more elaborated aryl chlorides.



[a] 1 mol % Pd. [b] 2.5 mol % Pd

For a method to be useful, it must be scalable. To test the scalability, 4.0 mmol of **2l** was utilized in the cross-coupling with **6c** to provide 95% yield of **7cl** (1.0 g) (Scheme 1).



Scheme 1. Gram scale synthesis of *N*-(4-ethoxyphenyl)naphthalen-1-amine with 500 ppm palladium loading

Conclusions

A reactivity comparison of the Pd(NIXANTPHOS)-based catalyst for coupling of sterically hindered secondary anilines was made with the analogous Xantphos system and various mono- and bidentate phosphine ligands using unactivated aryl chloride substrates. It was found that the NIXANTPHOS-based catalyst outperformed the parent ligand Xantphos. The Pd(NIXANTPHOS) system exhibited excellent reactivity in *N*-arylations of primary aniline derivatives with as low as 0.05 mol % palladium loading. The data presented herein indicate that when screening and optimizing the palladium catalyzed Buchwald-Hartwig coupling reaction of amines with *aryl chlorides*, NIXANTPHOS is likely a better choice than the commonly used Xantphos.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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TOC entry for:

NIXANTPHOS: A Highly Active Ligand for Palladium Catalyzed Buchwald-Hartwig Amination of Unactivated Aryl Chlorides

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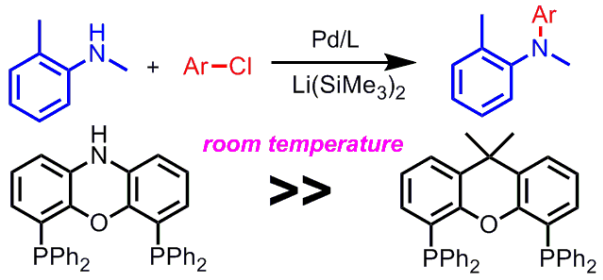

The NIXANTPHOS-based catalyst outperformed the parent ligand Xantphos in Pd-catalyzed amination reaction of aryl chlorides at room temperature.