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Scope and Limitations of $Pd_2(dba)_3$/P(*i*-BuNCH$_2$CH$_2$)$_3$N-Catalyzed Buchwald−Hartwig Amination Reactions of Aryl Chlorides

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Proazaphosphatrane ligands in combination with $Pd_2(dba)_3$ generate highly active catalysts for Buchwald−Hartwig amination of aryl chlorides. In particular, commercially available P(*i*-BuNCH$_2$CH$_2$)$_3$N is a highly general and efficient ligand, allowing the coupling of an electronically diverse set of aryl chlorides, including chloropyridines, with a wide variety of amines using 1 mol % of Pd at 100 °C. Either a 1:1 or 2:1 ratio of ligand to Pd was found to be effective. This catalyst system performs exceptionally well for sterically hindered substrates, even with only 0.25 mol % of Pd. It is shown that NaOH can also be used as the base (instead of NaO-*t*-Bu) allowing functionalized substrates to participate in these reactions.

Introduction

Over the past decade, one of the foremost accomplishments in the field of catalysis has been the discovery of the palladium-catalyzed carbon−nitrogen bond-forming process commonly known as the Buchwald−Hartwig amination reaction.[1−3] This process generally involves the coupling of aryl halides with amines mediated by a suitable palladium complex as a catalyst to afford arylamines which often are important intermediates in organic synthesis and which occur within the molecular framework of several natural products,[4] dendrimers,[5] ligands,[6−8] and advanced materials.[9] A major impetus to this field was provided by the ability to activate notoriously unreactive but relatively cheap aryl chlorides. Not surprisingly, a plethora of palladium catalyst systems, featuring a palladium-bound ligand, are now accessible for accomplishing the aforementioned transformation involving aryl chlorides. Typically, electronically rich sterically hindered ligands belonging to the trialkylphosphine,[10−13] ferrocenyldialkylphosphine,[14] aryldialkylphosphine,[15−17] heterocyclic carbene,[18−20] palladacycle,[21−23] or phosphinous acid[24] classes have been investigated in these reactions.

Over the past few years, part of our research effort has focused on the design, synthesis, and application of proazaphosphatranes of type **A** to organic methodology.[25] Recently, we have focused on the use of **A** as an ancillary ligand in palladium-mediated coupling reactions. In this regard, we have successfully demonstrated that in contrast to **1** and **2**, the commercially available proazaphosphatrane **3** is highly active in Suzuki,[26] Buchwald−Hartwig amination,[27−29] α-arylation,[30,31] and Stille[32]

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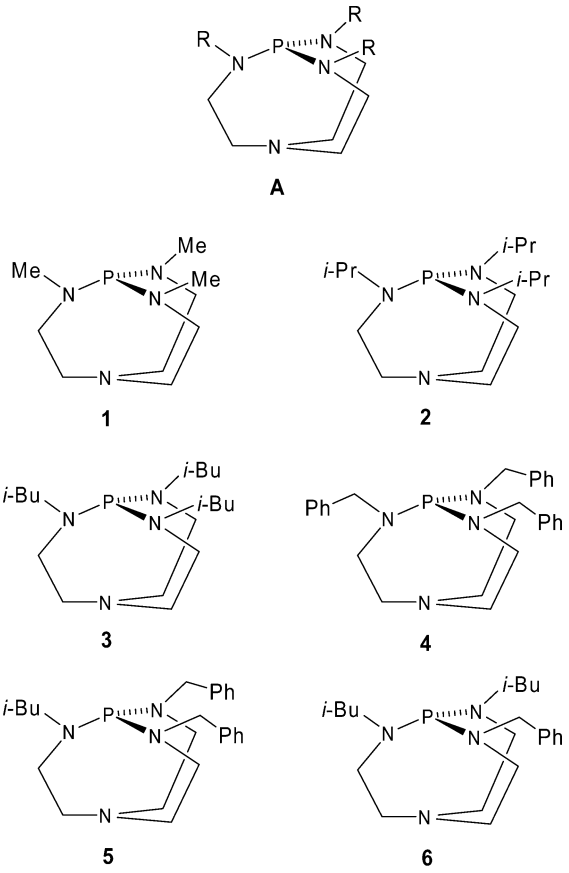
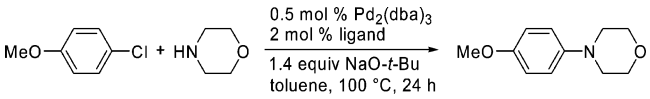
reactions. We have also developed a novel triaminophosphine ligand, P(*i*-BuNCH$_2$)$_3$CMe, which is structurally similar to **3**, for Buchwald−Hartwig amination reactions.[33] A particularly notable feature of this ligand is that, in contrast to **3**, it allows weak base such as Cs_2CO_3 to function in amination reactions.



In a recent communication, we reported that by using 2 mol % of Pd$_2$(dba)$_3$ (4 mol % Pd) and 8 mol % of **3** (2L/Pd), a wide array of aryl chlorides can be coupled with a variety of amines at 80 °C.[28] We believed that the level of catalyst loading (4 mol %) used in laboratory-scale experiments in our protocol might render larger scale experiments overly costly in view of the cost of the precious metal catalyst. We speculated that these reactions could be conducted with decreased catalyst loading albeit at higher temperature. Further, since the appearance of our preliminary report on the amination of aryl chlorides employing **3** as an ancillary ligand,[28] we have synthesized three new proazaphosphatranes with benzyl as well as a combination of isobutyl and benzyl substituents on the PN$_3$ nitrogens, namely **4**, **5**, and **6**. Our previous studies on Pd/proazaphosphatrane-catalyzed reactions have revealed that the isobutyl group on the PN$_3$ nitrogen is particularly important for catalyst activity presumably providing a propitious balance of steric and electronic parameters.[26−32] However, recent results from our laboratories on Stille reactions catalyzed by proazaphosphatranes[32] have shown that ligands **4** and **5** also generate quite active palladium catalysts for the coupling of aryl chlorides with organotin compounds. Thus we also wished to explore the usefulness of ligands **4**, **5**, and **6** in amination reactions of aryl chlorides. Here we give a full account of our studies on Pd$_2$(dba)$_3$/**3**-catalyzed Buchwald−Hartwig amination reactions of aryl chlorides.[34]

TABLE 1. Effect of Proazaphosphatrane Ligands on Pd-Catalyzed Amination of 4-Chloroanisole with Morpholine



entry	ligand	yield (%)[a]
1	**1**	10
2	**2**	31
3	**3**	88
4	**4**	<5
5	**5**	47
6	**6**	86

[a] Isolated yields (average of two runs).

Results and Discussion

Ligand Screening. To test the feasibility of the above notions, we initially conducted the reaction of 4-chloroanisole with morpholine at 100 °C, as shown in entry 3 of Table 1. To our delight, using 0.5 mol % of Pd$_2$(dba)$_3$ in combination with 2 mol % of ligand **3** (corresponding to a 4-fold decrease in the catalyst loading from our original protocol) this reaction indeed proceeded smoothly to afford the desired product in 88% isolated yield after 24 h. When Pd(OAc)$_2$ was used as the palladium precursor, this reaction was substantially slower and was not complete in 24 h perhaps because of the induction period required for the reduction of Pd(II) to the catalytically active Pd(0) species.

Encouraged by these results, we evaluated the efficacy of various proazaphosphatranes in the same screening reaction. Five additional ligands in addition to **3** were screened in this study. The results, provided in Table 1, demonstrate that variations of the PN$_3$ nitrogen substituents can have significant impact on catalyst activity. Thus the ligand containing three isobutyl groups (**3**) is much more effective than those with three methyl (**1**), isopropyl (**2**), or benzyl groups (**4**). The selectivity for the formation of product with respect to arene with ligand **3** was found by GC/MS to be 27:1. Interestingly, ligand **4** performed very poorly in the screening reaction whereas it was quite successfully employed in Stille reactions of aryl chlorides.[32] On the other hand, ligand **5** containing one isobutyl and two benzyl groups led to the formation of an appreciable quantity of the amination product.

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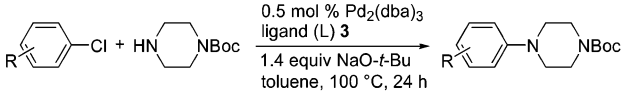
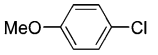
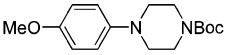
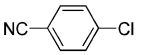
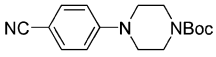
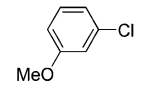
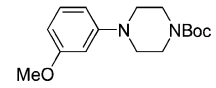
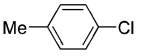
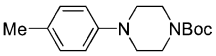
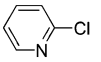
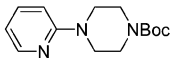
Surprisingly, ligand **6**, containing two isobutyl groups and one benzyl group, afforded the desired amination product in 86% isolated yield, which is comparable to that obtained with ligand **3** (entries 4 and 6, Table 1). These results indicate that catalyst activity is more strongly dependent on the number of isobutyl groups on the PN_3 nitrogens than might have been expected. We now attempt to rationalize the differences in the activities of ligands **1**–**6**.

A coordinatively unsaturated monophosphine Pd(0) complex is generally accepted as the catalytically active species in palladium-catalyzed cross-coupling reactions and a three-coordinate monophosphine-ligated arylpalladium halide (an example of which was isolated) has been proposed to form after the oxidative addition step.[35] Formation of such complexes is usually favored by sterically hindered ligands. We believe that although ligands **1** and **2** are electronically rich, they lack sufficient steric bulk to form/stabilize monophosphine-ligated PdL species. In contrast, we believe that ligands **3** and **6** (and to some extent ligand **5**) possess a striking balance of electron-richness and steric bulk needed for the generation of active catalyst. In this regard, however, our attempts to isolate a Pd-**3** complex have so far failed. Although we presently do not have a satisfactory explanation for the ineffectiveness of ligand **4**, one possibility is that the electron-rich palladium center of the Pd(0)-**4** complex undergoes intramolecular aromatic C–H bond activation (cyclometalation). Of the three generally accepted mechanistic pathways for such activation (namely, electrophilic metalation, oxidative addition, and the formation of an agostic intermediate[36]) the first option seems unlikely because such a process would involve electrophilic attack of Pd(0) on an ipso carbon of a benzene ring. At this point we are unable to choose between the remaining two possibilities, both of which could be expected to lead to a catalytically inactive species.

Scope of the $Pd_2(dba)_3$/3-Catalyzed Amination Reactions of Aryl Chlorides. Having successfully demonstrated the viability of the $Pd_2(dba)_3$/**3**-catalyzed amination reaction of 4-chloroanisole with morpholine under low palladium loadings, experiments were conducted to determine the scope and limitations of the aforementioned catalyst system. The results are collected in Tables 1–9. The *N*-aryl piperazine moiety is embedded in several pharmacologically interesting targets such as ligands of serotonin (5-HT)-receptors,[37] antifungals,[38] antivirals,[39] antibacterials,[40] and cholesterol ester transfer protein inhibitors.[41] Table 2 summarizes our results on the coupling of various aryl and heteroaryl chlorides with *N*-Boc-protected piperazines. It was shown previously that the ratio of ligand to palladium is an important reaction parameter in palladium-assisted cross-coupling reactions. For example, while the 1:1 ratio of P(*t*-Bu)$_3$ to Pd furnishes a very active catalyst in Suzuki cross-coupling reactions, the use of a 2:1 ratio renders the catalyst inactive.[42] Under the conditions of reduced catalyst loading we report here, either a 1:1 or 2:1 ratio of **3** to Pd generates a very active catalyst that allows coupling of electron-rich, electron-neutral, and electron-poor aryl chlorides. For example, the reaction of 4-chloroanisole with *N*-Boc-protected piperazine gave the expected product in 99% yield (entry 1) with a 2:1 ratio of **3** to Pd, and the use of a 1:1 ratio was equally effective, furnishing the product in 97% yield (entry 2). Notably, the reaction of 2-chloropyridine also proceeded cleanly (entry 7).

TABLE 2. $Pd_2(dba)_3$/3-Catalyzed Amination of Aryl Chlorides with *N*-Boc-piperazine



entry	chloride	L/Pd	product	yield (%)[a]
1		2		99
2		1		97
3		2		90
4		2		96
5		2		95
6		1		94
7		1		92

[a] Isolated yields (average of two runs).

We have also established that under the reduced catalyst loading conditions described here, a broad spectrum of aryl chlorides can be coupled with morpholine (Table 3). With use of a 1:1 ratio of **3** to Pd, yields of the coupled products were 90% or better except in the case of 4-chlorotoluene (entry 4). Interestingly, the coupling of activated 4-chlorobenzonitrile proceeded in slightly lower yield than that of deactivated 4-chloroanisole owing to the observation of more hydrodehalogenation occurring in the former case. It is also possible that coordination of the nitrile group with the alkali metal of the base might also be responsible for the lower yield, as has been observed by Hartwig.[14]

Reactions of the ortho-substituted aryl chlorides 2-chlorotoluene and 2-chloroanisole with morpholine occurred in low yield (<40%). Although deactivated 3-chloropyridine was a suitable substrate, it was necessary in this case to use 1.5 mol % of $Pd_2(dba)_3$ (3 mol % Pd) in combination with 3 mol % of **3**.

We observed that for certain substrate combinations, catalyst loading can be lowered to 0.1 mol % of Pd to give

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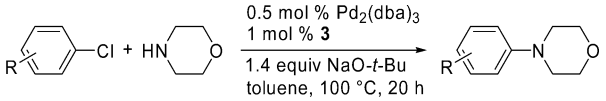
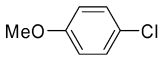
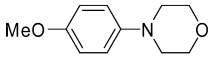
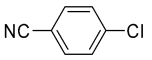
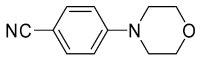
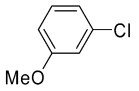
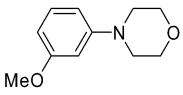
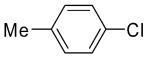
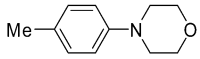
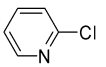
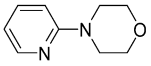
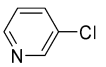
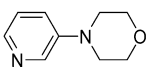
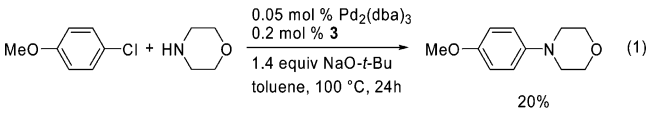
TABLE 3. $Pd_2(dba)_3$/3-Catalyzed Amination of Aryl Chlorides with Morpholine



entry	chloride	product	yield (%)[a]
1			92
2			90
3			95
4			89
5			98
6			88[b]

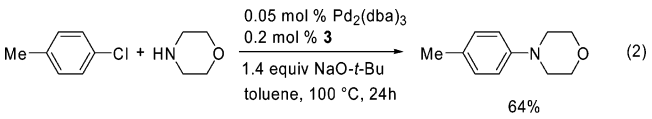
[a] Isolated yields (average of two runs). [b] 1.5 mol % of $Pd_2(dba)_3$ was employed.

the desired products in reasonable yields. For example, with use of 0.05 mol % of $Pd_2(dba)_3$ and 0.2 mol % of **3**, the coupling of deactivated 4-chloroanisole with morpholine proceeded in 20% isolated yield after 24 h (eq 1)



(1)

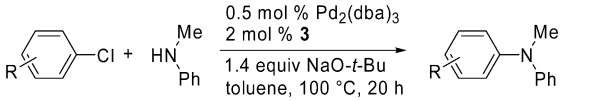
whereas the reaction of electron-neutral 4-chlorotoluene with morpholine afforded the desired product in 64% isolated yield (eq 2).

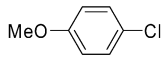
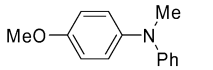
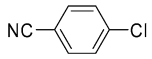
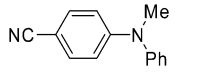
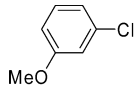
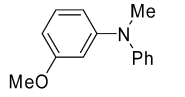
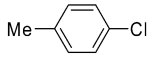
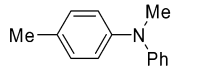
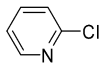
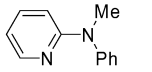
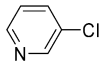
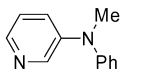


(2)

Results from the coupling of various aryl chlorides with the secondary aniline *N*-methylaniline are summarized in Table 4. Chloropyridines as well as electron-poor, electron-neutral, and electron-rich aryl chlorides all reacted to afford good to excellent product yields. The scope of the reaction of aryl chlorides with diphenylamine is illustrated in Table 5. In many of the reactions examined, we employed both a 1:1 and a 2:1 ratio of **3** to Pd. Although no general correlation of the reactivity of aryl chlorides with these ratios emerged, it is interesting to note that some aryl chlorides coupled in higher yields when a 1:1 ratio of **3** to Pd was employed while others reacted more successfully with a 2:1 ratio. For example, the reaction of electron-rich 4-chloroanisole with diphenylamine afforded the corresponding product in 89% yield (entry 2, Table 5) with a 1:1 ratio of **3** to Pd as compared to a 71% yield (entry 1, Table 5) when a 2:1 ratio of **3** to Pd was used. The coupling of electron-neutral 4-chlorotoluene occurred in higher yield with a 2:1 ratio of **3** to Pd (compare entries 6 and 7, Table 5). *o*-Chlorotoluene also reacted with diphenylamine in excellent yields (entries 11 and 12, Table 5).

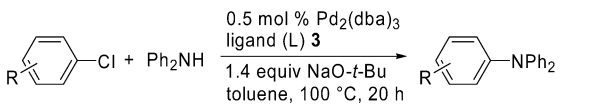
TABLE 4. $Pd_2(dba)_3$/3-Catalyzed Amination of Aryl Chlorides with *N*-Methylaniline

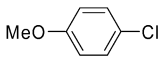
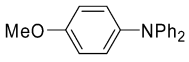
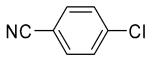
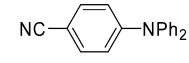
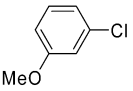
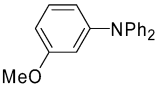
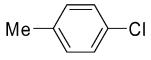
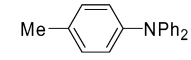
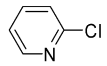
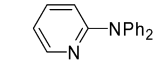
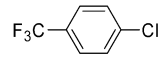


entry	chloride	product	yield (%)[a]
1			95
2			89
3			86[b]
4			88[b]
5			98
6			80

[a] Isolated yields (average of two runs). [b] A 1:1 ratio of **3** to Pd was used.

TABLE 5. $Pd_2(dba)_3$/3-Catalyzed Amination of Aryl Chlorides with Diphenylamine

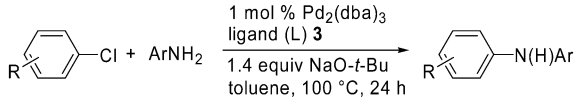


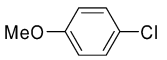
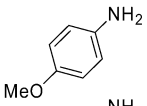
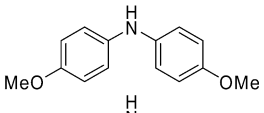
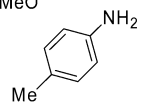
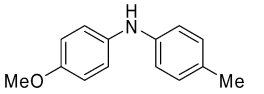
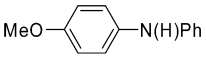
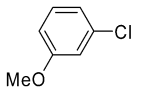
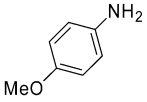
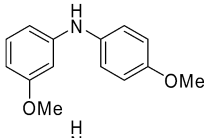
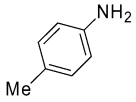
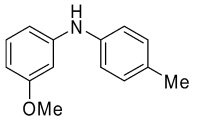
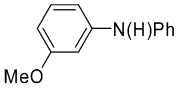
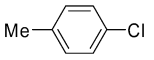
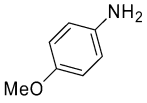
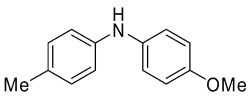
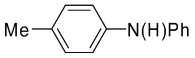
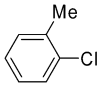
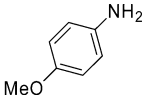
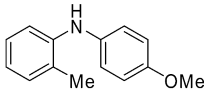
entry	chloride	L/Pd	product	yield (%)[a]
1		2		71
2		1		89
3		2		92
4		2		92
5		1		93
6		2		98
7		1		88
8		2		98
9		1		quant.
10		1		99
11		2		99
12		1		94

[a] Isolated yields (average of two runs).

Results of reactions of aryl chlorides with simple anilines to provide diarylamines are given in Table 6. Substituted anilines as well as aniline itself could be

TABLE 6. $Pd_2(dba)_3$/3-Catalyzed Amination of Aryl Chlorides with Simple Anilines



entry	chloride	amine	L/Pd	product	yield (%)[a]
1			2		78
2			1		65
3			2		78
4		$PhNH_2$	2		84
5			2		72
6			1		77
7			1		86
8			2		84
9		$PhNH_2$	2		86
10			2		84
11		$PhNH_2$	2		86
12			2		99

[a] Isolated yields (average of two runs).

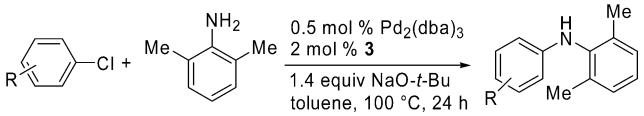
arylated with electronically diverse aryl chlorides. These reactions proceeded best with 1 mol % of $Pd_2(dba)_3$ while the reaction was much slower when 0.5 mol % of $Pd_2(dba)_3$ was employed. As revealed in this table, the presence of an ortho-substituent on the aryl chloride had no deleterious effect and in fact, coupling occurred in nearly quantitative yield (entry 12, Table 6). We also examined amination reactions of aryl chlorides with sterically hindered 2,6-dimethylaniline (Table 7). Only 1 mol % of Pd was sufficient for these couplings to occur in high yields.

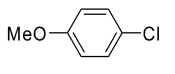
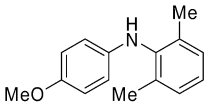
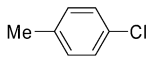
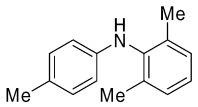
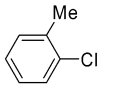
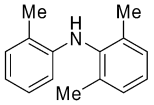
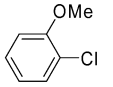
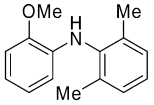
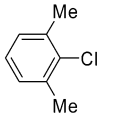
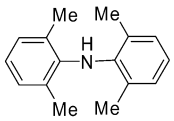
Interestingly, the reaction of 2-chloro-*m*-xylene with 2,6-dimethylaniline provided tetra-ortho-substituted diarylamine in 89% isolated yield at 100 °C in the presence of only 0.5 mol % of Pd (entry 5, Table 7). Remarkably, when the catalyst loading was lowered to 0.25 mol % of Pd, the desired coupling product was still obtained in high (85%) isolated yield (entry 6, Table 7). Although the aforementioned reaction is quite challenging, the result obtained is not totally surprising. Mechanistically, such a class of substrates would involve a highly hindered aryl amidopalladium intermediate of type ArNPd(L)Ar′, for which the product-forming reductive elimination step would be expected to be facile in the presence of a bulky ligand such as **3** owing to relief of strain.[43] Comparison of our yield with yields previously reported for the same reaction conducted at 120 °C over 20 h with 0.5 mol % of Pd in the presence of the ligands PCy_3[13] (96%) and DMAPPAd$_2$ [di(1-adamantyl)-3-(*N*,*N*-dimethylamino)propylphosphine][13] (96%) revealed that the activity of these ligands is comparable to that of **3** (95%, entry 7, Table 7). However, catalysts based on $PhPCy_2$ (90%), P(*t*-Bu)$_3$[13] (77%), (*o*-biphenyl)PCy_2[13] (42%), and $BuPCy_2$[13] (78%) were inferior to the $Pd_2(dba)_3$/**3** catalyst system.

It is well-known that reactions of acyclic secondary amines and primary aliphatic amines with aryl chlorides are not commonplace in amination chemistry. Nevertheless, catalysts bearing (*o*-biphenyl)P(*t*-Bu)$_2$,[15] Q-phos (di-*tert*-butylphosphino pentaphenylferrocene),[14] P(*t*-Bu)$_3$,[11] *n*-BuPAd$_2$ [di(1-adamantyl)-*n*-butylphosphine],[13] 2-(2′-dicyclohexylphosphinophenyl)-2-methyl-1,3-dioxolane,[17] and unsaturated imidazolium[20] as ligands did allow such couplings in good to excellent yields. We have also investigated the efficacy of **3** in the arylation of these

(43) For mechanistic studies, see: (a) Singh, U. K.; Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14104. (b) Alcazar-Roman, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 12905. (c) Alcazar-Roman, L. M.; Hartwig, J. F.; Rheingold, A. L.; Liable-Sands, L. M.; Guzei, I. A. *J. Am. Chem. Soc.* **2000**, *122*, 4618 and references therein. Also, see ref 35.

TABLE 7. $Pd_2(dba)_3$/3-Catalyzed Amination of Aryl Chlorides with Sterically Hindered 2,6-Dimethylaniline

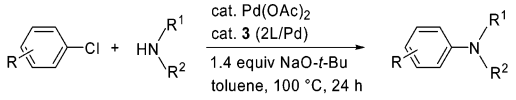


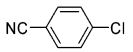
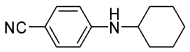
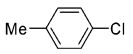
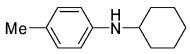
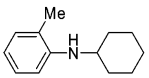
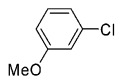
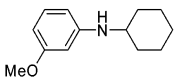
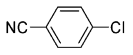
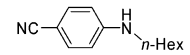
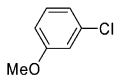
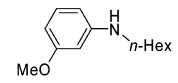
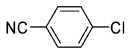
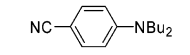
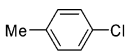
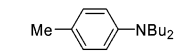
entry	chloride	product	yield (%)[a]
1			86
2			88
3			94
4			85
5			89[b]
6			85[c]
7			95[d]

[a] Isolated yields (average of two runs). [b] 0.25 mol % of $Pd_2(dba)_3$ and 1 mol % of **3** was employed. [c] 0.125 mol % of $Pd_2(dba)_3$ and 0.5 mol % of **3** was employed. [d] The reaction was conducted at 120 °C for 20 h.

amines (Table 8). In the examples presented in this table, the use of $Pd(OAc)_2$ as a precatalyst instead of $Pd_2(dba)_3$ was found to be beneficial. For cyclohexylamine and dibutylamine (representative members of cyclic hindered primary aliphatic amines and acyclic secondary amines, respectively) it was necessary to increase catalyst loading to 3 mol % of Pd to achieve the coupling products in good yields. These slightly modified conditions were effective for the amination of 4-chlorobenzonitrile, 4-chlorotoluene, and even the strongly electron-donating methoxide substituent in the meta-position of chlorobenzene with cyclohexylamine, providing the corresponding products in 65−67% yield (entries 1, 2, and 4, Table 8). Under these conditions no diarylation product was observed. Reactions of hindered aryl halides with hindered primary aliphatic amines often proceed in high yields as compared with unhindered systems because of reduced formation of hydrodehalogenation side product. In accord with this observation, we found that the coupling of 2-chlorotoluene with cyclohexylamine also occurred in high yield (entry 3, Table 8). Reactions of the unhindered primary aliphatic amine *n*-hexylamine required 6 mol % of Pd and still the reaction proceeded in only moderate yield (entries 5 and 6, Table 8) owing to significant hydrodehalogenation and diarylation. Attempts to minimize diarylation side products by using 1.5−2 equiv of *n*-hexylamine (relative to aryl chloride) were not successful. Acceptable yields were obtained for the arylation of dibutylamine with aryl

TABLE 8. $Pd(OAc)_2$/3-Catalyzed Amination of Aryl Chlorides with Aliphatic Amines



entry	chloride	mol % Pd	product	yield (%)[a]
1		3		67
2		3		67
3		3		87
4		3		65
5		6		68
6		6		68
7		3		66
8		3		55

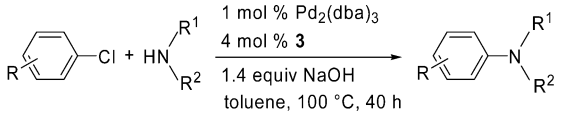
[a] Isolated yields (average of two runs).

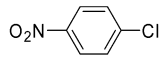
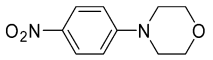
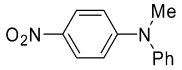
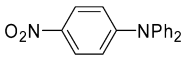
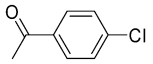
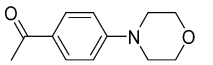
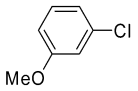
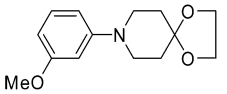
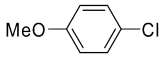
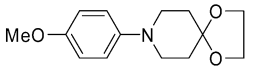
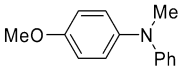
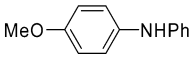
chlorides possessing electron-poor or electron-neutral groups. Unfortunately, reactions of electron-rich 4-chloroanisole with primary aliphatic amines and acyclic secondary amines were inefficient.

We also briefly examined the use of NaOH[20,44] as the stoichiometric base in $Pd_2(dba)_3$/**3**-catalyzed amination reactions of aryl chlorides (Table 9). Although these reactions were slower than those with NaO-*t*-Bu, probably because of the poor solubility of NaOH in toluene, the reaction did provide good to excellent product yields and it did not require a phase-transfer catalyst. In contrast, Hartwig's use of alkali metal hydroxides (NaOH and KOH) as bases in amination reactions did require a phase-transfer catalyst.[44] Our protocol was applicable to aryl chlorides bearing base-sensitive functional groups, such as nitro and enolizable ketones, and required 2 mol % of palladium. These substrates were not compatible when strongly basic NaO-*t*-Bu was used as the stoichiometric base. The electron-rich aryl chloride 4-chloroanisole was also amenable to our protocol. Cyclic secondary amines, the secondary aniline diphenylamine, and aniline were suitable substrates. For the reaction of 4-chloroanisole with aniline, the catalyst loading had to be increased to 2 mol % of $Pd_2(dba)_3$ to obtain the desired product in good yield (entry 9, Table 9). In a singular case, we found that the desired reaction occurred even in the presence of added water and a phase-transfer catalyst. Thus, the reaction of 1-chloro-4-nitrobenzene with diphenylamine proceeded in 87% isolated yield in the presence of NaOH, H_2O, **3** (cat.) $Pd_2(dba)_3$ (cat.), and Bu_4NBr (cat.) (entry 3, Table 9). It should be noted that

(44) For the use of alkali metal hydroxides as bases in amination chemistry, see: Kuwano, R.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 6479.

TABLE 9. $Pd_2(dba)_3$/3-Catalyzed Amination of Aryl Chlorides with NaOH as the Base



entry	chloride	product	yield (%)[a]
1			>99
2			92
3			90
4			87[b]
5			95
6			91
7			89
8			98
9			82[c]

[a] Isolated yields (average of two runs). [b] 1.4 equiv of H_2O and 0.2 equiv of Bu_4NBr was also added to the reaction. [c] 2 mol % of Pd_2 (dba)$_3$ was employed.

palladium-catalyzed amination reactions using NaOH or KOH as bases have also been performed in aqueous media in the absence of a phase-transfer reagent and with or without the use of a co-solvent.[16,45]

A Comment on Assembly of the Reaction Components. Except for the screening of the ligands, for which the glovebox (Table 1) was used, weighing of the reaction components (palladium catalyst precursor, base, and solid substrates) was carried out in air (Tables 2–9) and standard Schlenk-line techniques were employed. When moisture-sensitive NaO-*t*-Bu was employed, small quantities of it in a vial were removed from the glovebox (where the bottle of NaO-*t*-Bu was stored) and then weighed in air for the reaction. Because ligand **3** is air- and moisture-sensitive, we prepared a stock solution of it in toluene (2 mM) and stored it under argon outside the glovebox.

Conclusions

By building on our previous findings, we have shown that more economical protocols for palladium-catalyzed Buchwald–Hartwig amination reactions of aryl chlorides can be developed using commercially available ligand **3**. We have determined that the isobutyl group on the PN_3 nitrogens of the proazaphosphatrane framework is important for maximizing activity of the proazaphosphatrane/$Pd_2(dba)_3$ catalyst system, but that ligand **6**, with two isobutyl groups and one benzyl group on PN_3 nitrogens, also functions as a potent ligand in this system. The $Pd_2(dba)_3$/**3** combination allows coupling of electronically diverse aryl chlorides with an array of amines to proceed in high yields. The majority of these reactions were conducted with 1 mol % of Pd. For the reaction of 2-chloro-*m*-xylene with 2,6-dimethylaniline, catalyst loading can be lowered to as little as 0.25 mol % of Pd without significantly compromising product yield. Either a 1:1 or a 2:1 ratio of L:Pd was found to be effective in this reaction. The $Pd_2(dba)_3$/**3** catalyst system also permitted amination reactions to occur (although slowly) in the presence of NaOH as the stoichiometric base, with aryl functional groups such as nitro and enolizable ketone being tolerant to these conditions.

Experimental Section

General Procedure for the Screening of Ligands (Table 1). An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd_2(dba)_3$ (0.5 mol %) and NaO-*t*-Bu (1.4 mmol) inside a nitrogen-filled glovebox. Ligands that were solids, namely, **1**, **4**, and **5** (2 mol %), were also added at this time. The flask was capped with a rubber septum and removed from the glovebox. This cycle was repeated three times. Ligands that were liquids, namely, **2**, **3**, and **6** (2 mol %), were then added via syringe from a stock solution (2 mM in toluene). Morpholine (1.2 mmol), 4-chloroanisole (1.0 mmol), and toluene (3 mL) were then successively added by syringe. The reaction mixture was heated at 100 °C for 24 h after which the mixture was cooled to room temperature, adsorbed onto silica gel, and then purified by column chromatography (hexanes/ethyl acetate as eluent).

General Procedure for the $Pd_2(dba)_3$/3-Catalyzed Amination Reactions of Aryl Chlorides (Tables 2–7). An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd_2(dba)_3$ (x mol %, see Tables 2–7) and NaO-*t*-Bu (1.4 mmol) in air. Amine (1.2 mmol) and aryl chloride (1.0 mmol) were also added at this time if they were solids. The flask was capped with a rubber septum, evacuated, and then flushed with argon. This cycle was repeated three times. Ligand **3** ($x - 2x$ mol %, see Tables 2–7) was then added via syringe from a stock solution (2 mM in toluene). Aryl chloride (if a liquid, 1.0 mmol), amine (if a liquid, 1.2 mmol), and toluene (3 mL) were then successively added by syringe. The reaction mixture was then heated at 100 °C until the starting material had been completely consumed as judged by TLC (20–24 h). The mixture was cooled to room temperature, adsorbed onto silica gel, and then purified by column chromatography (hexanes/ethyl acetate as eluent).

General Procedure for the $Pd(OAc)_2$/3-Catalyzed Amination Reactions of Aryl Chlorides with Aliphatic Amines (Table 8). An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd(OAc)_2$ (3–6 mol %) and NaO-*t*-Bu (1.4 mmol) in air. Amine (1.2 mmol) and aryl chloride (1.0 mmol) were also added at this time if they were solids. The flask was capped with a rubber septum, evacuated, and then flushed with argon. This cycle was repeated three times. Ligand **3** (6–12 mol %) was then added via syringe from a stock solution (2 mM in toluene). Aryl chloride (if a liquid, 1.0 mmol), amine (if a liquid, 1.2 mmol), and toluene (3 mL) were then successively added by syringe. The reaction mixture was heated at 100 °C until the starting material had been completely consumed as judged by TLC (24 h). The mixture was cooled to room temperature, adsorbed onto silica gel, and then purified by column chromatography (hexanes/ethyl acetate as eluent).

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General Procedure for the $Pd_2(dba)_3$/3-Catalyzed Amination Reactions of Aryl Chlorides with NaOH as the Base (Table 9). An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd_2(dba)_3$ (1 mol %) and NaOH (1.4 mmol) in air. Amine (1.2 mmol) and aryl chloride (1.0 mmol) were also added at this time if they were solids. The flask was capped with a rubber septum, evacuated, and then flushed with argon. This cycle was repeated three times. Ligand **3** (4 mol %) was then added via syringe from a stock solution (2 mM in toluene). Aryl chloride (if a liquid, 1.0 mmol), amine (if a liquid, 1.2 mmol), and toluene (3 mL) were then successively added by syringe. The reaction mixture was then heated at 100 °C until the starting material had been completely consumed as judged by TLC (40 h). The mixture was subsequently cooled to room temperature, adsorbed onto silica gel, and then purified by column chromatography (hexanes/ethyl acetate as eluent).

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Supporting Information Available: Experimental details, references for known compounds, and copies of ^1H and ^{13}C NMR spectra for all the compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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