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Application of a New Bicyclic Triaminophosphine Ligand in Pd-Catalyzed Buchwald−Hartwig Amination Reactions of Aryl Chlorides, Bromides, and Iodides

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The new bicyclic triaminophosphine ligand P(*i*-BuNCH$_2$)$_3$CMe (**3**) has been synthesized in three steps from commercially available materials and its efficacy in palladium-catalyzed reactions of aryl halides with an array of amines has been demonstrated. Electron-poor, electron-neutral, and electron-rich aryl bromides, chlorides, and iodides participated in the process. The reactions encompassed aromatic amines (primary or secondary) and secondary amines (cyclic or acyclic). It has also been shown that the weak base Cs_2CO_3 can be employed with ligand **3**, allowing a variety of functionalized substrates (e.g., those containing esters and nitro groups) to be utilized in our amination protocols. This ligand provides a remarkably general, efficient, and mild palladium catalyst for aryl iodide amination. Although **3** is slightly air and moisture sensitive, easy procedures can be adopted that avoid the need of a glovebox. Comparisons of the efficacy of **3** in these reactions with that of the proazaphosphatrane P(*i*-BuNCH$_2$CH$_2$)$_3$N (**2**) reveal that in addition to the opportunity for transannulation in **2** (but not in **3**), other significant stereoelectronic contrasts exist between these two ligands which help account for differences in the activities of the Pd/**2** and Pd/**3** catalytic systems.

Introduction

The synthesis of arylamines from amines and aryl halides (or halide equivalents such as tosylates and triflates) using palladium methodology is of considerable importance in the literature,[1] primarily because arylamines possess a diverse range of potential applications in the pharmaceutical,[2] dye,[3] agricultural,[4] and polymer[5] industries. Arylamines have also been demonstrated to be useful as ligands for transition metals.[6]

The palladium-catalyzed process for the synthesis of arylamines has several advantages over commonly employed approaches such as nucleophilic aromatic substitution, Ullmann coupling,[7] reductive amination, and nitration followed by reduction. Advantages include better functional group compatibility, a one-step reaction, ready availability of starting materials from a myriad of commercial sources, and relatively mild reaction conditions. Palladium-catalyzed cross-coupling of aryl halides and amines to generate arylamines was first studied by Migita[8] and was subsequently developed by Buchwald and Hartwig.[1] The pioneering work of these investigators led to remarkable advances in our understanding of fundamental aspects of these reactions.[9] One such aspect is the proper choice of ligand that can stabilize catalytically active Pd(0) complexes. Lloyd-Jones recently noted, "Often unpredictably, the choice of ligand in Pd-catalyzed reactions can make surprisingly little difference or can open up new avenues".[10]

The variety of effective ligands that have been introduced for Pd-catalyzed amination reactions can be classified in terms of the three generations over which they have evolved. First generation catalyst systems included monodentate phosphines [e.g., P(*o*-tol)$_3$][11] while chelating

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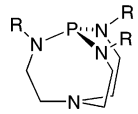
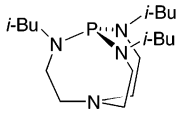
bidentate phosphines such as BINAP[12] or DPPF[13] comprise second generation catalyst systems that greatly improved the scope of amination reactions. Further improvements came with the advent of electron-rich sterically hindered third generation phosphines such as P(*t*-Bu)$_3$[14] and *o*-(biphenyl)P(*t*-Bu)$_2$.[15] Nonphosphine ligands, such as *N*-heterocyclic carbenes (saturated as well as unsaturated), can also be considered to belong to this generation.[16] Third generation catalysts permitted the use of otherwise notoriously unreactive but cheaper aryl chlorides as substrates in amination reactions.

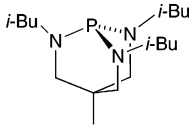
In recent years our explorations of the chemistry of proazaphosphatranes of type **1**, first synthesized in our laboratories, have shown them to be exceedingly potent catalysts, promoters, and strong nonionic stoichiometric bases that facilitate a variety of useful organic transformations.[17] More recently, we discovered that commercially available **2** is a highly active ligand in Suzuki[18] and Buchwald−Hartwig amination reactions of aryl halides, including those of aryl chlorides.[19,20]



1



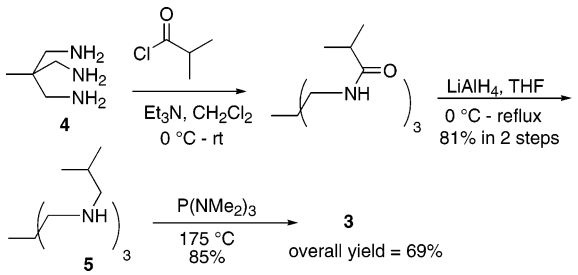
2



3

We believed that the unusually high activity of **2** in Suzuki and Buchwald−Hartwig amination reactions was due primarily to (a) the electron-donating capability of the three planar PN$_3$ nitrogens, (b) a desirable degree of bulk provided by the isobutyl groups, and (c) potential transannulation from the bridgehead nitrogen's lone pair to phosphorus.[18] Thus in contrast, acyclic triaminophosphines [e.g., P(NMe$_2$)$_3$ or P(N*i*-Bu$_2$)$_3$] were shown to be very ineffective ligands in amination reactions partly because the phosphorus in these triaminophosphines is not sufficiently electron-rich owing to a departure of the conformation of these molecules from a C_{3v} arrangement of the P(NC$_2$)$_3$ moiety in which the unhybridized lone pair orbital on each nitrogen lies tangential to a circle whose plane is perpendicular to and contains the 3-fold axis at its center.[21,22]

SCHEME 1



In view of the efficiency of ligand **2** in Buchwald−Hartwig amination reactions,[19,20] its bicyclic nature prompted us to speculate whether ligand **3** could also be employed in these transformations, since the two ligands are structurally quite similar. The three PN nitrogens in proazaphosphatranes such as **2** have virtually planar geometries and those in **3** can be assumed to have the same property. Because **3** is a liquid (see below) that did not crystallize well at low temperature, the determination of its molecular structure by X-ray means was precluded. Such a study reported by us for the oxide analogue OP(MeNCH$_2$)$_3$CMe revealed nearly perfect C_{3v} symmetry with a sum of the angles around the nitrogens of 357°.[23] As in this derivative of **3**, the three PN nitrogens in **3** are also capable of providing electron density to the phosphorus, thereby electronically enriching the Pd(0)L$_n$ complex for oxidative addition with aryl halides. In addition, the bulky isobutyl groups in **3** would facilitate reductive elimination. Importantly, however, ligand **3** (unlike **2**) lacks the possibility for basicity enhancement through transannulation. Thus utilization of **3** as a ligand could potentially provide insight regarding the importance of transannulation in the activity of **2**. In this article, we describe the synthesis of the new ligand **3**, which though structurally similar to **2**, has quite different stereoelectronic properties. Here we also present the utility of **3** in Pd-catalyzed Buchwald−Hartwig amination reactions of aryl chlorides, bromides, and iodides and we provide a rationale for differences in the activity of the Pd/**3** and Pd/**2** systems.

Results and Discussion

Synthesis of Ligand 3. This ligand was synthesized from triamine **4** as summarized in Scheme 1. Although commercially available,[24] **4** can be easily prepared in three high-yield steps from cheaper and commercially available 1,1,1-tris(hydroxymethyl)ethane.[25] Treatment

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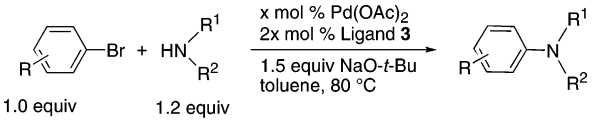
SCHEME 2

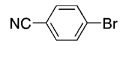
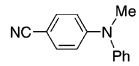
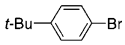
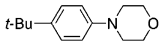
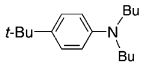
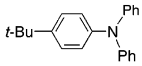
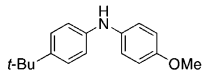
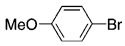
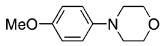
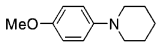
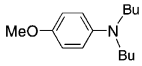
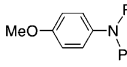
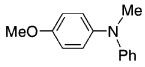
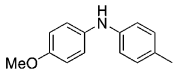
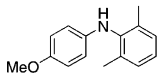
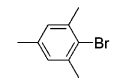
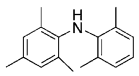
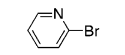
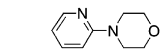
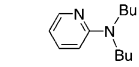
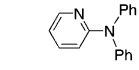
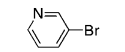
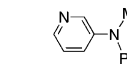


of triamine **4** with isobutyryl chloride followed by $LiAlH_4$ reduction resulted in the formation of triisobutyl-substituted amine **5** in 81% yield in two steps. Ring closure of **5** to **3** was achieved by heating the former in the presence of $P(NMe_2)_3$ at 175 °C for 48 h to afford **3** as a colorless liquid in 85% yield and in 69% overall yield from **4**. Ligand **3** was unambiguously characterized by ^1H, ^{13}C, and ^{31}P NMR spectroscopy as well as elemental analysis (see Experimental Section). Remarkably, ^{31}P NMR spectroscopic monitoring of **3**, kept in the air for 40 h, revealed that about 90% of **3** remained unchanged. Interestingly, P(*t*-Bu)$_3$, a highly effective ligand for a wide variety of Pd-catalyzed cross-coupling reactions,[26] including amination reactions, has been shown to be destroyed in air within 2 h.[15b] Although **3** showed a high degree of air and moisture stability, we recommend that it be stored under argon.

Catalytic Activity of 3 in Aryl Bromide Amination Reactions. Our initial test of the efficacy of **3** in Pd-catalyzed amination reactions involved aryl bromides with NaO-*t*-Bu as the base. We were intrigued to discover that conditions developed for the amination reactions that employed **2** as the ligand[27] also worked for ligand **3**. The general reaction conditions for the coupling reaction are described in Scheme 2 and results are provided in Table 1.

For the majority of substrates, 0.5 mol % of Pd was sufficient to achieve high yields of arylamines, and most of these reactions were completed in less than 20 h. No attempts were made to optimize reaction times. Electron-poor, electron-neutral, and electron-rich aryl bromides, including bromopyridines, were readily aminated with the Pd(OAc)$_2$/**3** catalyst system. Primary anilines with ortho substituents and secondary anilines were efficiently coupled at 80 °C. As was the case with the Pd(OAc)$_2$/**2** catalyst system, amination reactions of highly sterically hindered substrates with Pd(OAc)$_2$/**3** also proceeded exceedingly well (entry 13, Table 1).[19] Hydrodehalogenation side products were detectable in most cases by TLC. The Pd(OAc)$_2$/**3** catalyst system was also effective for the arylation of cyclic secondary amines (entries 2, 6, 7, and 14, Table 1). Di-*n*-butylamine (a member of a normally difficult class of substrates) was also cleanly coupled, giving the desired product in very good to acceptable yields. For this class of amines, 2 mol % of Pd was needed (entries 3, 8, and 15, Table 1). This result contrasts that observed when ligand **2** was employed, namely, that reactions of acyclic secondary amines proceeded in only moderate yields (57−70%) and required 5 mol % of Pd.[19] Unfortunately, long-chain (*n*-hexylamine) or branched primary aliphatic amines (cyclohexylamine) did not react cleanly under our conditions.

TABLE 1. Pd/3-Catayzed Amination of Aryl and Heteroaryl Bromides[a]

Entry	Bromide	Amine	mol % Pd	Product	Yield (%)[b]
1			0.5		96
2			0.5		93
3		Bu_2NH	2		95
4		Ph_2NH	1		94[c]
5			2		78[c]
6			1		92
7			0.5		67
8		Bu_2NH	2		73
9		Ph_2NH	2		95[c]
10			0.5		92
11			2		77[c]
12			2		93
13			0.5		96
14			0.5		93
15		Bu_2NH	2		88
16		Ph_2NH	4		87[c,d]
17			5		84[d]

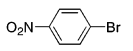
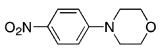
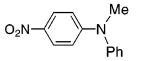
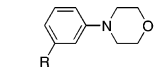
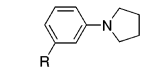
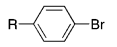
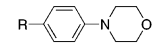
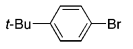
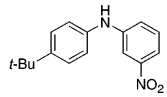
[a] Conditions: 1.0 equiv of aryl bromide, 1.2 equiv of amine, 1.5 equiv of NaO-*t*-Bu, cat. Pd(OAc)$_2$, cat. ligand **3** (2 L/Pd), 3 mL of toluene, 80 °C, 15−20 h. Reaction times have not been optimized. [b] Isolated yields. [c] Reaction was performed at 100 °C. [d] $Pd_2(dba)_3$ used in place of Pd(OAc)$_2$.

Although primary anilines without an ortho substituent reacted poorly with the **3**/Pd catalyst system at 80 °C, a reaction temperature of 100 °C allowed efficient coupling of this class of anilines. For example, the reaction of 4-bromoanisole with *p*-toluidine proceeded to completion with 2 mol % of Pd(OAc)$_2$ and 4 mol % of **3** at

(26) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

(27) Reactions were also performed with the trimethyl and triisopropyl analogues of ligand **2**. For the reaction shown in Table 1, entry 6, the trimethyl analogue provided less than 20% yield whereas triisopropyl analogue yielded 62% of the coupled product with 2 mol % of Pd in both cases.

TABLE 2. $Pd(OAc)_2$/3-Catalyzed Amination of Functionalized Aryl Bromides[a]

Entry	Bromide	Amide	Product	Yield (%)[b]
1				95
2				97
3				92[c]
4				42[c]
5				85[c]
6				61[d]

[a] Conditions: 1.0 equiv of aryl bromide, 1.2 equiv of amine, 1.5 equiv of Cs_2CO_3, 1.0 mol % of $Pd(OAc)_2$, 2.0 mol % of ligand **3** (2 L/Pd), 3 mL of toluene, 80 °C, 15−20 h. Reaction times have not been optimized. [b] Isolated yields. [c] R = CO_2Me. [d] Reaction was performed at 100 °C.

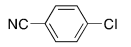
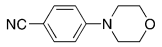
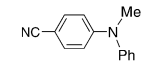
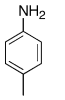
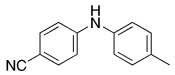
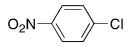
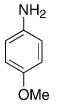
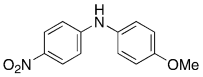
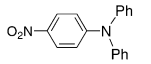
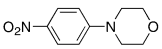
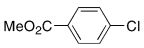
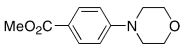
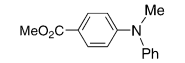
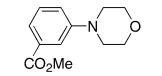
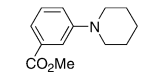
100 °C, affording the desired product in 77% yield (entry 11, Table 1). Similarly, 4-*tert*-butylbromobenzene coupled with *p*-anisidine to give a 78% yield of product (entry 5, Table 1).

Although the above protocol is reasonably useful, it involves the use of NaO-*t*-Bu as the base, thus rendering the conditions ineffective for aryl halides containing base-sensitive functional groups. After surveying a range of bases, we were pleased to find that the weaker base Cs_2CO_3 could also be employed in the presence of the Pd/**3** catalyst system, and examples of amination reactions demonstrating the use of this base are reported in Table 2. In most cases these reactions proceeded successfully at 80 °C with 1 mol % of $Pd(OAc)_2$ and 2 mol % of **3**. It is worth noting that by contrast, alkylphosphine catalysts [biphenyl- or ferrocenyl-based, or P(*t*-Bu)$_3$] generally require heating to 100 °C for the amination of functionalized aryl bromides.[14a,15b,28]

Catalytic Activity of 3 in Aryl Chloride Amination Reactions. The utilization of aryl chlorides in Pd-catalyzed cross-coupling reactions is important from a commercial as well as an academic standpoint. Consequently, a significant proportion of recent papers on amination reactions have focused on the use of aryl chlorides as substrates. The results of our investigations of such couplings using the Pd/**3** catalyst system are summarized in Table 3. We found that a higher catalyst loading (4 mol % of Pd) and a reaction temperature of 110 °C were needed to drive the reactions to completion. In a control experiment, the reaction of activated 4-chloronitrobenzene with morpholine in toluene at 110 °C gave no desired product in the presence of Cs_2CO_3. A similar

(28) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

TABLE 3. Pd/3-Catalyzed Amination of Aryl Chlorides[a]

Entry	Chloride	Amine	Product	Yield (%)[b]
1				91[d]
2				93[c]
3				97[c]
4				97[c]
5		Ph_2NH		92[c]
6				97[c]
7				98[c,d]
8				85[c]
9				77[c]
10				70[c]
11				92[c]
12				77[c]
13				70
14				52
15				55
16				64[c]
17				69[c]
18				87[c]
19				85[d]
20				84[d]

[a] Conditions: 1.0 equiv of aryl chloride, 1.2 equiv of amine, 1.5 equiv of NaO-*t*-Bu, 2.0 mol % of $Pd_2(dba)_3$, 8.0 mol % of ligand **3** (2 L/Pd), 3 mL of toluene, 110 °C, 24 h. Reaction times have not been optimized. [b] Isolated yields. [c] Cs_2CO_3 used in place of NaO-*t*-Bu. [d] $Pd(OAc)_2$ used in place of $Pd_2(dba)_3$.

experiment conducted with 4 mol % of $Pd(OAc)_2$ without any added ligand resulted in the formation of only a trace amount of product after 36 h. Among the solvents tested (toluene, THF, dioxane, and DME) toluene was found to be the most effective. Either $Pd(OAc)_2$ or $Pd_2(dba)_3$ can be used as the palladium(0) precursor. As expected, the best yields were obtained with aryl chlorides possessing electron-withdrawing groups, but electron-neutral and electron-rich aryl chlorides provided good to moderate yields of desired product. Cyclic secondary amines, secondary anilines, primary anilines, and diphenylamine participated well in our amination process. In contrast to aryl chloride aminations involving ligand **3**, those with ligand **2** can be performed at a lower temperature (80 °C) providing good to excellent yields with electronically diverse systems.[20]

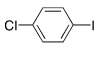
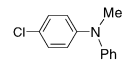
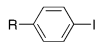
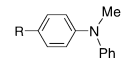
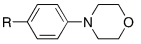
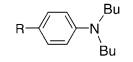
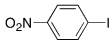
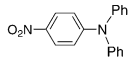
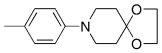
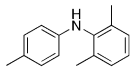
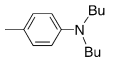
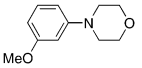
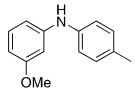
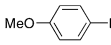
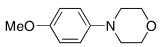
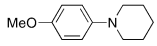
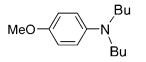
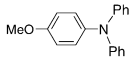
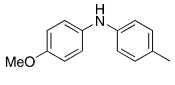
Catalytic Activity of 3 in Aryl Iodide Amination Reactions. Although more reactive, aryl iodides usually provide lower yields than their bromide counterparts in such reactions. Catalyst systems that have been described in the literature involve toxic additives such as 18-crown-6,[29] higher catalyst loading (up to 5 mol %),[13] lack of generality,[16b] and the use of the strong base (NaO-*t*-Bu).

Recently, Buchwald's group has reported an efficient procedure for the coupling of aryl iodides with amines using biphenyl-based phosphine ligands and Xantphos, a chelating bisphosphine.[30] Although their procedure was effective when NaO-*t*-Bu was the base, reactions involving Cs_2CO_3 had several disadvantages. First, higher temperatures were required to achieve good yields (100 or 120 °C). Second, cosolvents (Et_3N or *t*-BuOH) were needed for rate enhancements. Third, secondary acyclic amines and diarylamines were problematic. The single case of a reaction involving an acyclic secondary amine that was described utilized electronically favored 4-iodobenzophenone as a substrate and that reaction required 5 mol % of Pd loading. Since the appearance of that report, we described a Pd catalyst system utilizing ligand **2** for the amination of aryl iodides,[19] which though attractive, utilized the strong base (NaO-*t*-Bu) that limits substrate scope. Thus a catalyst system that can achieve a higher degree of versatility for aryl iodide aminations would be desirable.

By an extension of our amination experiments that gave promising results with aryl bromides and chlorides, we found that the $Pd(OAc)_2$/**3** catalyst system, in combination with Cs_2CO_3 as the base, allowed a variety of aryl iodides to couple successfully with amines at 80 °C (20−40 °C lower than the literature reports).

Exceptions to this approach were reactions in which a primary aniline lacking an ortho substituent was used as a coupling partner. For unfunctionalized substrates, NaO-*t*-Bu was also able to function as the base. For activated aryl iodides, and for one example of a deactivated aryl iodide, 0.5 mol % of Pd led to excellent yields of diarylamines (entries 1, 2, 3, and 11, Table 4). The use of 2 mol % of Pd allowed the reaction of unactivated and deactivated aryl iodides to occur in good yields (entries 6, 7, 11, and 12, Table 4). As observed with aryl bromides, reactions of aryl iodides with primary anilines lacking an ortho substituent required the use of a somewhat higher reaction temperature (entries 10 and 15, Table 4). Reactions of an acyclic secondary amine with aryl iodides also occurred at 80 °C (entries 4, 8, and 13, Table 4). Reactions of diphenylamine also proceeded smoothly at 100 °C with the Pd/**3** catalyst system when Cs_2CO_3 was employed (entries 5 and 14, Table 4). As with aryl bromides, reactions of aryl iodides with primary aliphatic amines gave poor results when Cs_2CO_3 or NaO-*t*-Bu was employed as the base. Notwithstanding this limitation, it appears that the Pd/**3** catalyst system utilizing Cs_2CO_3 as the base is the most efficient, general, and mild catalytic combination reported to date for the amination of aryl iodides.

TABLE 4. $Pd(OAc)_2$/3-Catalyzed Amination of Aryl Iodides[a]

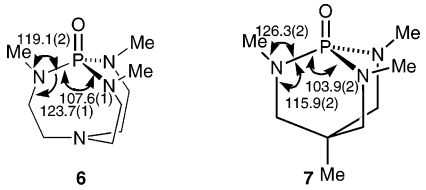
Entry	Iodide	Amine	mol % Pd	Product	Yield (%)[b]
1			0.5		96
2			0.5		93[c]
3			0.5		93[c]
4		Bu_2NH	2		90[c]
5		Ph_2NH	1		80[d]
6			2		77
7			2		97
8		Bu_2NH	2		80
9			0.5		83
10			2		75[d]
11			0.5		96
12			2		77
13		Bu_2NH	5		60
14		Ph_2NH	4		83[d]
15			2		71[d]

[a] Conditions: 1.0 equiv of aryl iodide, 1.2 equiv of amine, 1.5 equiv of Cs_2CO_3, cat. $Pd(OAc)_2$, cat. ligand **3** (2 L/Pd) 3 mL of toluene, 80 °C, 15−20 h. Reaction times have not been optimized. [b] Isolated yields. [c] R = CO_2Et. [d] Reaction was performed at 100 °C.

(29) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066.
(30) Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560.

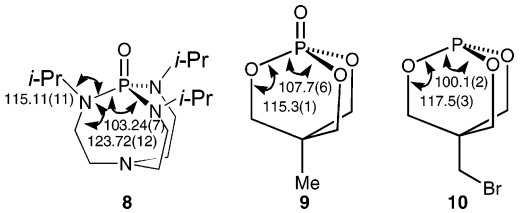
Salient Features of a Convenient Reaction Protocol. Although ligand **3** is slightly moisture and air-sensitive, easy procedures can be adopted that avoid the need for a glovebox. A stock solution of **3** was prepared in toluene, and the appropriate amount was collected with a syringe. NaO-*t*-Bu and Cs_2CO_3 were stored inside the glovebox and were moved (in small amounts) to the outside just before use. Thus, for all the reactions presented in this paper, aryl halide (if solid), amine (if solid), base, and palladium acetate were weighed in air in a Schlenk flask. The flask was then evacuated and purged with argon three times. Ligand **3** was then added via syringe and also aryl halides and amines (if liquids). It was determined that the order of addition of reagents was not important.

Stereoelectronic Comparisons of Ligands 2 and 3. The difference in reactivity between **2** and **3** in palladium-catalyzed aryl halide aminations can be attributed to the presence of interesting contrasts in their stereoelectronic properties. Because of the greater constraint in the bicyclic smaller cage framework of **3** relative to **2**, steric protection of the phosphorus in the former by the isobutyl groups may well be diminished substantially. This suggestion is supported by the PNC_{exo} bond angle of 119.1(2)° in **6**[31] and 126.3(2)° in **7**.[23] We



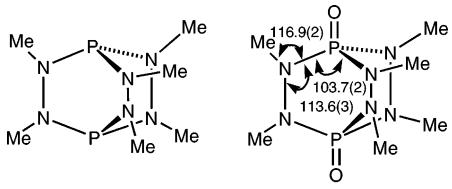
6 **7**

believe that a similar difference in PNC_{exo} bond angles exists between the trivalent phosphorus ligands **2** and **3**, although structural data are available only for **8**,[32] which is an analogue of **2**. Thus the average of the PNC_{exo} bond angles in **8** [115.11(11)°] represents a ca. 4° decrease from that in **6** owing to narrowing of the NPN bond angle in **8**, while the PNC_{cage} angle remains quite constant in both compounds. A similar decrease in PNC_{exo} angle from **7** to **3** can be expected for the same reason. Support for the suggestion that the PNC_{cage} angle remains quite constant upon oxidation (or coordination) of the phosphorus emanates from a comparison of the structural metrics of **9**[33] and **10**[34] in which opening of the OPO bond angle from **10** to **9** does not greatly affect the POC angle.



8 **9** **10**

Although the structures of **11**[35] and **12**[36] have been obtained by crystallographic means, the standard deviations for the metrics of interest in **11** are too large (3° to 4°) to make a useful comparison for our purposes. For crystallographic metric differences to be significant, we believe they should be outside 3 × esd values. As expected from the foregoing discussion, the NPN [103.7(2)°] and PNN [113.6(3)°] bond angles in **12** are similar to their counterparts in **7**.[37]



11 **12**

It thus appears that any opening of the NPN bond angle in **2** or **3** upon coordination to the palladium(II) center in the oxidative addition intermediate would result mainly in widening of the PNC_{exo} angle by perhaps comparable amounts in each ligand, thereby reducing steric hindrance to coordination. The smaller steric encumbrance of the phosphorus in **3** compared with that in **2** (stemming from the larger PNC_{exo} angle in the former) would enhance the donor capability of the phosphorus of **3**, thereby favoring the oxidative addition step. The greater constraint in **3** also confers on it a more rigid C_{3v} symmetry that maximizes electron donation from each PN_3 nitrogen lone pair to the phosphorus,[38] whereas in **2**, conformational inversion around the molecular axis between extreme C_3 conformations mitigates such electron donation. Thus in the absence of transannulation in **2**, **3** can be assumed to be the more basic ligand based on its larger PNC_{exo} angle and its conformational rigidity.

The idea that the basicity of ligand **3** is greater than that of untransannulated **2**, but less than that of transannulated **2** can be used to rationalize observed differences in the activities of these ligands in palladium-assisted aminations of aryl halides. In the case of aryl bromides and iodides, the scope of such reactions supported by the Pd/**3** system appears at first glance to be quite similar to that facilitated by the Pd/**2** system. However, the scope is actually greater for the Pd/**3** system because substrates bearing base-sensitive substituents are much better tolerated. As with aryl bromides and iodides, the Pd/**3** system is also effective in catalyzing aminations of aryl chlorides possessing base-sensitive substituents. This advantage can be rationalized on the basis of the more weakly basic nature of **3** compared with **2** if transannulation of **2** in the oxidative addition intermediate of these aryl halides (Figure 1) is occurring

(31) Tang, J.-S.; Mohan, T.; Verkade, J. G. *J. Org. Chem.* **1994**, *59*, 4931.

(32) Wroblewski, A. E.; Pinkas, J.; Verkade, J. G. *Main Group Chem.* **1995**, *1*, 69.

(33) Nimrod, D. M.; Fitzwater, D. R.; Verkade, J. G. *J. Am Chem. Soc.* **1968**, *90*, 2780.

(34) Milbrath, D. S.; Springer, J. P.; Clardy, J. C.; Verkade, J. G. *J. Am. Chem. Soc.* **1976**, *98*, 5493.

(35) Vandoorne, W.; Hunt, G. W.; Perry, R. W.; Cordes, A. W. *Inorg. Chem.* **1971**, *10*, 2591.

(36) Gilje, J. W.; Seff, K. *Inorg. Chem.* **1972**, *11*, 1643.

(37) However, the PNC angle in **12** [116.9(2)°] is considerably smaller than this angle in **7**, which may be associated with the observation that the nitrogens in **12** are not planar. See ref 35.

(38) (a) Clarke, M. L.; Cole-Hamilton, D. J.; Slawin, A. M. Z.; Woollins, J. D. *Chem. Commun.* **2000**, 2065. (b) Clarke, M. L.; Cole-Hamilton, D. J.; Woollins, J. D. *J. Chem. Soc., Dalton Trans.* **2001**, 2721.

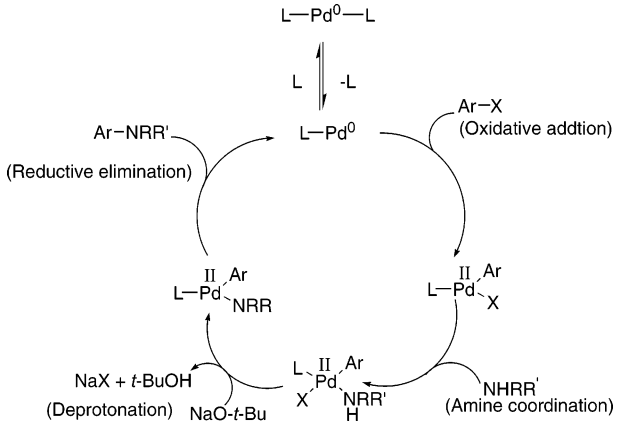


FIGURE 1. Outline of the catalytic cycle for Buchwald−Hartwig amination reactions.

to some significant degree.[39] The relatively poor σ-donor ability of **3** compared with transannulated **2** in the arylPd(II)amine(X) complex (Figure 1) allows the amine to bind more tightly when **3** is the ligand, thus rendering the N−H proton more acidic, consequently enabling a relatively weak base such as Cs_2CO_3 to function. It should be noted that attempts to isolate an oxidative addition intermediate with **3** or with **2** (or sterically less hindered analogues of the latter) have thus far failed.

The general and substantial increase in activity of the Pd/**2** system relative to the Pd/**3** system in aminations of aryl chlorides not bearing base-sensitive substituents suggests that **2** transannulates to a greater extent in the corresponding aryl chloride than in aryl bromide or aryl iodide oxidative addition intermediates, owing to the presence of a more electronegative halide on the aryl chloride oxidative addition intermediate. This intermediate is thus stabilized by enhanced phosphorus atom basicity[17] in **2** through enhanced transannulation in this ligand.

In summary, the new bicyclic triaminophosphine ligand **3**, which was synthesized in three facile steps, generates a very active and broadly useful Pd catalyst system for Buchwald−Hartwig amination reactions. Couplings of an electronically diverse array of aryl halides with amines are realized in good to excellent yields. In addition, the use of Cs_2CO_3 in the presence of ligand **3** in these reactions permits aryl chlorides, bromides, and iodides with base-sensitive functional groups to be aminated efficiently. It appears that though the basicity of **3** is greater than that of untransannulated **2** this relationship can be reversed on coordination of these ligands in their respective Pd(II) oxidative addition intermediates arising from aryl halides. Although it has been shown that significant versatility can be achieved in the amination of aryl bromides and iodides with use of the Pd/**3** catalyst system, there are limitations to our protocol for aryl chlorides. The latter substrates require higher catalyst loading and a reaction temperature of 110 °C, and primary alkylamines (normal or branched chain) do not function well as reagents. The same is true for the Pd/**2** system except that the reactions can be carried out at 80 °C.

(39) The existence of variable degrees of transannulation in adducts of proazaphosphatranes has been documented from crystallographic data. See ref 17.

Experimental Section

Synthesis of Bicyclic Ligand 3. Isobutyryl chloride (80.0 mmol) in 20 mL of dry CH_2Cl_2 was added dropwise to a mixture of tris(2-aminomethyl)ethane **4** (20.0 mmol) and triethylamine (80.0 mmol) in 40 mL of dry CH_2Cl_2 at 0 °C. The mixture was stirred at room temperature overnight. After the precipitate that formed was filtered, the filtrate was concentrated on a rotary evaporator and then diluted with water (30 mL). The product was extracted with EtOAc (3 × 100 mL) and then the organic layers were combined and dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford a slurry that was used in the next step without further purification. The slurry (18.0 mmol, as crude product) in 50 mL of dry THF was added dropwise to a solution of $LiAlH_4$ (126.0 mmol) in 200 mL of dry THF over a period of 30 min. The mixture was then refluxed for 3 days after which it was cooled to 0 °C. Fifty milliliters of a 10% KOH solution in water was then added and the mixture was again heated to reflux for 4 h. The white precipitate that had formed was filtered and washed with hot THF (3 × 100 mL) and the filtrates were then combined. THF was removed under reduced pressure and the crude product obtained was distilled under vacuum to afford **5** in 81% yield from **4** as a colorless oil (bp 78−80 °C/200 mTorr). ^{1}H NMR ($CDCl_3$) δ 0.86 (d, 21 H, J = 6.7 Hz), 1.53 (br s, 3H), 1.65 (m, 3H), 2.33 (d, 6H, J = 6.6 Hz), 2.50 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 20.9, 22.8, 28.3, 38.4, 58.6, 59.3. Anal. Calcd for $C_{17}H_{39}N_3$: C, 71.58; H, 13.68; N, 14.74. Found: C, 71.71; H, 13.30; N, 14.66.

Tris(2-isobutylaminomethyl)ethane **5** (8.8 mmol) and $P(NMe_2)_3$ (9.0 mmol) were charged to a 50-mL flask under Ar. The flask was placed in a 175 °C oil bath and the reaction mixture was stirred for 3 days at that temperature. The crude material obtained was distilled under vacuum to afford **3** in 85% yield (overall yield from **4**, 69%) as a colorless oil (bp 80−82 °C/200 mTorr). ^{1}H NMR (C_6D_6) δ 0.58 (s, 3H), 0.88 (d, 18H, J = 6.6 Hz), 1.70 (m, 3H), 2.46 (d, 6H, J = 3.1 Hz), 2.62 (m, 6H). ^{13}C NMR (C_6D_6) δ 20.4, 22.6, 27.0 (d, J = 11.0 Hz), 34.3 (d, J = 1.6 Hz), 59.8 (d, J = 4.0 Hz), 61.6 (d, J = 25.0 Hz). ^{31}P NMR (C_6D_6) δ 81.6. Anal. Calcd for $C_{17}H_{36}N_3P$: C, 65.17; H, 11.50; N, 13.42. Found: C, 64.27; H, 11.70; N, 13.64.

Pd(OAc)$_2$/3-Catalyzed Amination of Aryl and Heteroaryl Bromides (Table 1): General Procedure. An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd(OAc)_2$ (x mol %, see Table 1) and NaO-*t*-Bu (1.5 mmol). Amine (1.2 mmol) and aryl bromide (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** (2x mol %, see Table 1) was then added via syringe from a stock solution. Aryl bromide (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 the temperature indicated in Table 1 until the starting material had been completely consumed as judged by TLC (15−20 h). The mixture was then cooled to room temperature, adsorbed onto silica gel, and then purified by column chromatography (hexanes/ethyl acetate as eluent).

Pd(OAc)$_2$/3-Catalyzed Amination of Functionalized Aryl Bromides (Table 2): General Procedure. An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd(OAc)_2$ (x mol %, see Table 2) and Cs_2CO_3 (1.5 mmol). Amine (1.2 mmol) and aryl bromide (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** (2x mol %, see Table 2) was then added via syringe from a stock solution. Aryl bromide (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 a temperature indicated in Table 2 until the starting material had been completely consumed as judged by TLC (15−20 h). The mixture was cooled to room temperature, adsorbed onto silica

gel, and then purified by column chromatography using a mixture of hexanes and ethyl acetate as eluent.

$Pd(OAc)_2$- or $Pd_2(dba)_3$/3-Catalyzed Amination of Aryl Chlorides (Table 3): General Procedure. An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd(OAc)_2$ or $Pd_2(dba)_3$ (x mol %, see Table 3) and NaO-*t*-Bu (1.5 mmol) or Cs_2CO_3 (1.5 mmol). 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** (2x mol %, see Table 3) was then added via syringe from a stock solution. 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 110 °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).

$Pd(OAc)_2$/3-Catalyzed Amination of Aryl Iodides (Table 4): General Procedure. An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd(OAc)_2$ (× mol %, see Table 4) and NaO-*t*-Bu (1.5 mmol) or Cs_2CO_3 (1.5 mmol). Amine (1.2 mmol) and aryl iodide (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** (2x mol %, see Table 4) was then added via syringe from a stock solution. Aryl iodide (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 a temperature indicated in Table 4 until the starting material had been completely consumed as judged by TLC (15−20 h). The mixture was cooled to room temperature, adsorbed onto silica gel, and then purified by column chromatography (hexanes/ethyl acetate as eluent).

Acknowledgment. The authors thank the National Science Foundation for financial support in the form of a grant.

Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for all compounds, references for products in Tables 1−4, and ^{31}P NMR spectra for ligand **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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