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$(t\text{-Bu})_2PN{=}P(i\text{-BuNCH}_2CH_2)_3N$: New Efficient Ligand for Palladium-Catalyzed C−N Couplings of Aryl and Heteroaryl Bromides and Chlorides and for Vinyl Bromides at Room Temperature

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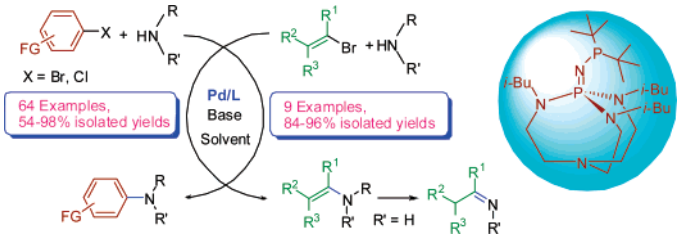

By employing $Pd(OAc)_2$, Cs_2CO_3, or NaOH, and the new ligand $(t\text{-Bu})_2PN{=}P(i\text{-BuNCH}_2CH_2)_3N$ (**3a**), an electronically diverse array of aryl bromides and chlorides possessing base-sensitive substituents (nitro, ester, and keto) provide coupling products with bulky aryl amines in good to excellent yields. Aryl halides possessing other functional groups including cyano, amino, trifluoromethyl, and phenol, coupled with equal ease, producing highly functionalized amines in good to excellent yields. Moreover, an aryl chloro group can be preserved in the presence of a bromo substituent under our reaction conditions. BOC-protected amines also participated efficiently. Heterocyclic bromides and chlorides underwent clean couplings with amines in excellent yields. An important strength of our protocol is the use of lower palladium loadings than those reported earlier, without compromising yields. The air-stable palladium complex (η^3-cinnamyl)PdCl·(**3a**) (**5**) was also employed successfully in C−N coupling reactions while the crotyl analogue was less efficacious. The **3a**/$Pd(OAc)_2$ catalyst system promotes, for the first time, efficient coupling of vinyl bromides with a variety of amines to produce imines and enamines at *room temperature*.

Introduction

C(aryl)−N bond formation is one of the most powerful routes to the synthesis of arylamines, compounds that have a diverse range of potential applications.[1a−o,2] Cross-coupling of amines with aryl halides (or halide equivalents such as tosylates and triflates) using palladium catalysis is the preferred methodology because of its advantages over approaches such as nucleophilic aromatic substitution,[1p] Ullmann coupling,[3] reductive amination,[1h] and nitration followed by reduction.[1h] These advantages include better functional group tolerance, a single-step procedure, commercial availability of starting materials, and relatively mild reaction conditions. In recent years substantial progress has been made on copper-catalyzed Ullmann couplings by several groups,[3] thus opening the possibility for protocols competitive with palladium-catalyzed C−N bond-forming aminations. It should be noted, however, that most of the Ullmann coupling methods employ aryl iodides or bromides as coupling partners, with aryl chlorides resulting in relatively poor yields.[3l,3n]

Palladium-catalyzed cross-coupling of aryl halides and amines for the generation of arylamines was first studied by Migita[4] and was subsequently developed by Buchwald and Hartwig.[1a−o,5] The pioneering work of these investigators led to remarkable advances in our understanding of fundamental aspects of these reactions.[1a−o] Recently, Buchwald−Hartwig (BH) amination was successfully extended to the synthesis of structurally varied enamines, imines, sulfoximes, indoles, and enamides which have long been known as valuable synthetic intermediates in organic synthesis.[1m] 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.

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First generation catalyst systems included monodentate phosphines [e.g., P(*o*-tol)$_3$][5c,6] while chelating bidentate phosphines such as 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)[7a−d] or 1,1′-bis(diphenylphosphino)ferrocene (DPPF)[7e] comprise second generation catalyst systems that greatly improved the scope of amination reactions.

Third generation soft ligands [e.g., P(*t*-Bu)$_3$,[8] *o*-(biphenyl)P(*t*-Bu)$_2$,[9] and N-heterocyclic carbenes][10] are very active and general for aminations because such bulky ligands promote metal−ligand dissociation in the oxidative addition of aryl halides to Pd(0).[11] A generally important aspect of efficient coupling reactions is the proper choice of ligand for stabilizing catalytically active Pd(0) complexes. As has been recently observed by Lloyd-Jones, "Often unpredictably, the choice of ligand in Pd-catalyzed reactions can make surprisingly little difference or can open up new avenues".[12a] This factor is particularly important with less reactive aryl bromide and chloride substrates. Additional examples of ligands that have been advanced in recent years for Pd-catalyzed C−N bond formation include 2-dicyclohexylphosphanyl-1-trityl-1*H*-imidazole,[13a] pyrazole-based phosphines,[13b] [2-di(*tert*-butyl)phosphinoethyl]-*N*-methylaniline,[13c] di(*tert*-butyl)neopentylphosphine (DTBNpP),[13d] 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phospha-adamantane,[13e] chlorophosphine $(CH_2)_2(NCMe_3)_2PCl$,[13f] clickphos,[13g] 1-(2-norbornyl)-2,2,6,6-tetramethylphosphorinane,[13h] di(1-adamantyl)-*n*-butylphosphine,[13i] dicyclohexyl-2-(*N*-arylindolyl)phosphine,[13j] *N*-aryl-2-(di-*tert*-butylphosphino)-imidazoles,[13k] the 9-ethylfluorenyldicyclohexyl phosphonium

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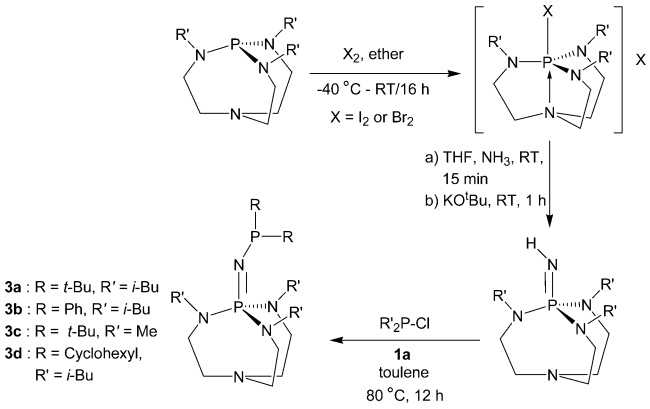
salt ($EtFluPCy_2 \cdot HBF_4$),[13l] and Cp^*PCy_2.[13m] The potential of palladium-catalyzed BH amination under microwave conditions has also been examined.[14] Although Ni(0)/N-heterocyclic carbene and Ni(0)/phosphine systems are also known to catalyze C−N cross-coupling reactions,[15] palladium remains the metal of choice because of its greater efficiency[1a−o] which is strongly determined by the ancillary ligand employed.[1a−o,15e,16]

SCHEME 1. Synthesis of 3a−d[30]



Sigma-donor ligands such as phosphines are capable of appropriately tuning the steric and electronic properties of the metal while minimizing palladium precipitation.[17] The enhanced catalytic activity of this generation of ligands, used in combination with Pd(II) or Pd(0), has been attributed to the formation of highly active monoligated [PdL] species.[18] Because most of the current cross-coupling methodologies have one or more limitations (e.g., high catalyst loadings, poor substrate generality, and harsher conditions), the pivotal nature of the ligand[11,12,19] makes it desirable to seek improved ligands for economic and environmental reasons.

In recent years our explorations of the chemistry of proazaphosphatranes of type **1**, first synthesized in our laboratories, have shown them to be potent catalysts, promoters, and strong nonionic stoichiometric bases that facilitate a variety of useful organic transformations.[20] Thus, commercially available **1a** is a highly active ligand in Suzuki,[21] α-arylation,[22] Stille,[23] and Buchwald−Hartwig amination reactions of aryl bromides and

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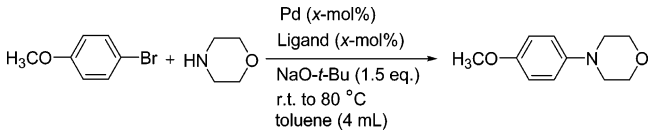
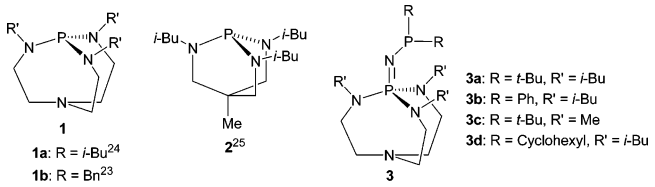
TABLE 1. Screening Reactions[a]



entry	palladium source	mol (%)	ligand	mol (%)	time (h)	temp (°C)	yield (%)[b]
1	$Pd(OAc)_2$	2.0	**3a**	4.0	1.0	23	96
2[c]	$Pd_2(dba)_3$	2.0	**3a**	4.0	1.0	23	97
3	$Pd_2(dba)_3$	2.0	**3a**	2.0	1.0	23	97
4	$Pd_2(dba)_3$	1.0	**3a**	1.0	1.0	23	96
5	$Pd(OAc)_2$	1.0	**3a**	1.0	24	23	55
6	$Pd(OAc)_2$	1.0	**3a**	2.0	0.5	23	58
7	$Pd(OAc)_2$	0.50	**3a**	1.0	0.5	80	96
8	$Pd(OAc)_2$	0.50	**3a**	0.50	0.5	80	97
9	$Pd(OAc)_2$	0.25	**3a**	0.50	0.5	80	97[d]
10	$Pd(OAc)_2$	0.25	**3a**	0.25	2.0	80	65
11	$Pd(OAc)_2$	0.10	**3a**	0.10	20	80	12
12	$Pd(OAc)_2$	0.25	**3b**	0.50	16	80	13
13	$Pd(OAc)_2$	0.25	**3c**	0.50	1.5	80	42
14	$Pd(OAc)_2$	0.25	**3d**	0.50	4.0	80	55

[a] Reaction conditions: *p*-bromoanisole (3 mmol), morpholine (3.6 mmol), sodium *tert*-butoxide (4.5 mmol, 432 mg). [b] Isolated yields (average of two runs). [c] dba = dibenzylideneacetone. [d] Reported yield of 68% using 5 mol % Pd, 10 mol % $ClP(t\text{-}BuNCH_2)_2$, see ref 13f; 95% using 1 mol % Pd and 1 mol % of $[(\mu\text{-}PPh_2CH_2PPh_2)Co_2(CO)_4][\mu,\eta\text{-}PhCCP(t\text{-}Bu)_2]$, see ref 26b; and 78% using 2 mol % Pd and 4 mol % 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride, see ref 10b.

chlorides.[24] Later, we developed ligand **2** and investigated its efficacy in amination reactions.[25] However, these protocols, and others as well,[26] require 1−2 mol % of palladium and 1−4 mol % ligand in the case of bromides,[24,25] 2−5 mol % Pd and 2−10 mol % of ligand for chlorides,[24a,26g] and/or the need for elevated temperatures ranging from 100 to 140 °C.[13c,27] There are relatively few protocols that employ palladium loadings below 2% for BH aminations of selected aryl chlorides, and reaction temperatures can vary considerably.[13j,2j,10a] For example, Hartwig et al. recently reported[12v] that 0.001−2 mol % palladium loading was effective with (*R*)-(−)-di-*tert*-butyl-{1-[(*S*)-2-(dicyclohexylphosphanyl)ferrocenyl]ethyl}phosphine for the amination of aryl and heteroaryl chlorides at temperatures ranging from 25 to 100 °C. With the use of Cu(I) catalysts, a temperature of 160 °C and a relatively complicated catalyst synthesis of the ligand were required.[28a] Moreover, the Ullmann approach is generally effective only for aryl bromides and iodides.[3a,28b−c] Recently, Ackermann et al. reported the use of phosphine oxides as ligands for amination reactions.[13f,29a] However, high Pd (5 mol %) and ligand (10 mol %) loadings and a temperature of 105 °C were necessary.[13f,29a]



Very recently we focused our efforts on synthesizing ligands of type **3** which feature a bulky imino-proazaphosphatrane substituent capable of imparting enhanced electron richness to the $^tBu_2P$ phosphorus via electron donation from its three planar "equatorial" ^{i}BuN nitrogens and from potential transannulation

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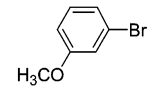
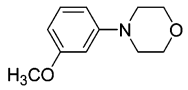
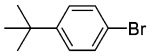
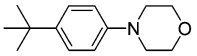
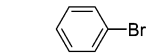
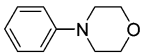
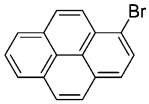
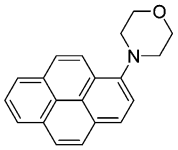
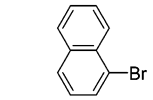
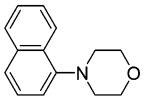
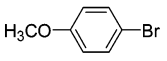
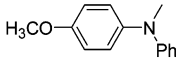
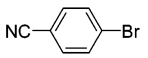
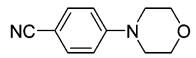
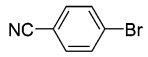
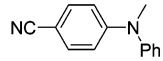
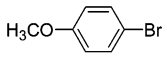
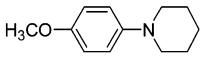
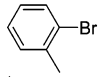
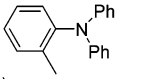
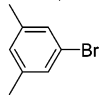
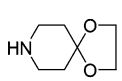
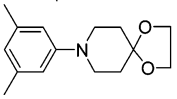
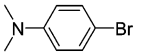
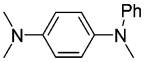
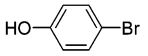
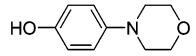
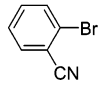
TABLE 2. Pd/3a-Catalyzed Aminations of Aryl Bromides[a]

entry	aryl bromide	amine	time (h)	product	yield (%)[b]	lowest, highest lit. yield
1			0.5		98	80,[c] 96[d]
2			0.5		98	81,[e] 99[f]
3			0.5		96	82,[g] 94[h]
4			1		97	–
5			1		85	–
6			2		94	89,[i] 100[j]
7			12		84	74[k]
8[l]			12		90	36,[m] 99[j]
9			2		89	67,[n] 98[o]
10			12		95	44,[p] 99[d]
11			0.5		95	–
12			8		92	89[j]
13[q]			24		95	80,[r] 83[s]
14[t]			24		83	–

[a] Reaction conditions: aryl bromide (3 mmol), amine (3.6 mmol), sodium *tert*-butoxide (4.5 mmol, 432 mg), $Pd(OAc)_2$ (0.25 mol % unless otherwise stated), **3a** (0.5 mol % unless otherwise stated), toluene (4 mL), 0.5−24 h at 80 °C. [b] Isolated yields (average of two runs). [c] Using 1 mol % Pd, 1 mol % of ligand, $[(\mu\text{-}PPh_2CH_2PPh_2)Co_2(CO)_4][\mu,\eta\text{-}PhCCP(t\text{-}Bu)_2]$, see ref 26b. [d] Using 1 mol % Pd, 2 mol % $Ph_5FcP(t\text{-}Bu)_2$, see ref 32a. [e] Using 5 mol % Pd, 6 mol % 2-dicyclohexylphosphanyl-1-trityl-1*H*-imidazole, see ref 13a. [f] Using 0.5 mol % Pd, 1.5 mol % of 5-(di-*tert*-butylphosphino)-1′,3′,5′-triphenyl-1′*H*-[1,4′]bipyrazole, see ref 13b. [g] Using 2 mol % Pd, 3 mol % 3,5-dimethyl-1-(2r-diphenylphosphino)phenylpyrazole, see ref 33a. [h] Using 1 mol % Pd, 1 mol % of $[(\mu\text{-}PPh_2CH_2PPh_2)Co_2(CO)_4][\mu,\eta\text{-}PhCCP(t\text{-}Bu)_2]$, see ref 26b. [i] Using 0.5 mol % Pd, 0.5 mol % di(*tert*-butyl)neopentylphosphine (DTBNpP), see ref 13d. [j] Using 1 mol % Pd, 0.8 mol % $P(t\text{-}Bu)_3$, see ref 33b. [k] Using 3 mol % Pd, 4.5 mol % 2-biphenyl)dicyclohexylphosphine, see ref 33c. [l] Using 0.5 mol % $Pd_2(dba)_3$ and 1.0 mol % **3a** with 2 mmol aryl bromide. [m] Using 1 mol % Pd, 1.1 mol % $PhN(Me)CH_2CH_2P(t\text{-}Bu)_2$, see ref 13c. [n] Using 0.5 mol % Pd, 1 mol % **2**, see ref 25. [o] Using 4 mol % Pd, 4 mol % 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phospha-adamantane, see ref 13e. [p] Using 1.0 mol % Pd, 1.0 mol % DTBNpP, see ref 13d. [q] Using 1 mol % $Pd_2(dba)_3$, 4 mol % of **3a**, and $LiN(SiMe_3)_2$ was used in place of sodium *tert*-butoxide. [r] Using 2.0 mol % Pd, 2.4 mol % 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl, see ref 26n. [s] Using 2.0 mol % Pd, 4 mol % **1a**, see ref 24c. [t] Using 1.0 mol % $Pd(OAc)_2$, 2 mol % **3a** at 120 °C.

of its basal planar nitrogen.[30] Herein we report the use of **3a** as an effective ligand for palladium-catalyzed Buchwald−Hartwig aminations of aryl and heteroaryl bromides and chlorides with primary arylamines, an alkylamine, and a dialkylamine. Aryl bromides with bulky ortho subsituents could be coupled with primary arylamines and dibutylamine. From the corresponding $[(\eta^3\text{-allyl})PdCl]_2$ (**4**) complex, the (η^3-cinnamyl)PdCl(**3a**) (**5**) and its (η^3-crotyl) analogue (**6**) were synthesized, structurally characterized by X-ray diffraction, and employed for the amination of several aryl bromides and chlorides. Finally, we describe the use of **3a** for the synthesis of imines and enamines by the Pd-catalyzed, room-temperature amination of vinyl

(30) (a) Kingston, J. V.; Ellern, A.; Verkade, J. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4960−4963. (b) For the synthesis of **3a** and **3b**, see Kingston, J. V.; Verkade, J. G. *J. Org. Chem.* **2007**, *72*, 2816−2822 while that of **3c** and **3d** is reported here.

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

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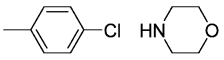
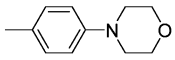
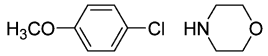
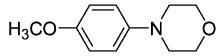
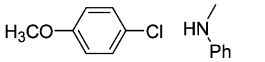
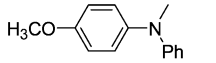
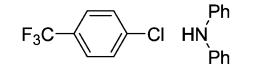
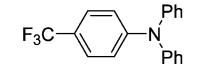
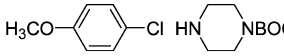
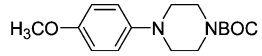
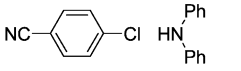
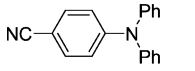
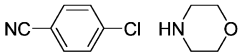
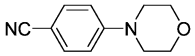
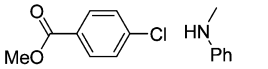
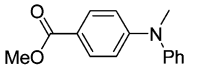
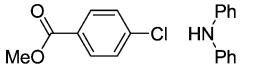
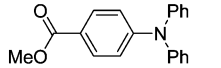
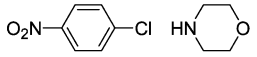
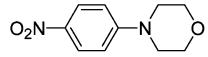
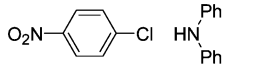
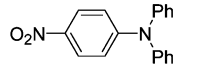
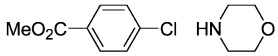
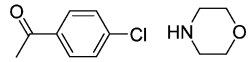
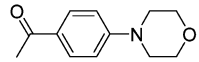
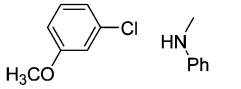
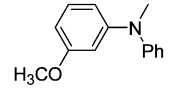
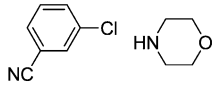
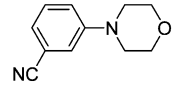
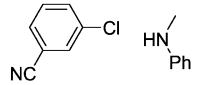
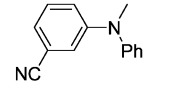
1			1		97	75,[d] 97[e]
2			24		49[c]	
3			1		94	63,[f] 95[g] 80[h]
4			1		94	91,[i] 93[j]
5			1		95	59,[d] 99[k]
6			1		94	99[k]
7			14		90 94[l]	92,[k] 96[g]
8			18		91	75,[j] 75,[m] 96[n]
9[o]			48		90	85,[p] 98[q]
10[o]			24		71	97[s]
11[r]			20		80	
12[t]			16		94	58,[g] 99[u]
13[t]			18		93	90,[u] 98[s]
14[r]			24		80	90,[v] 98[w]
15[t]			20		90 48[x]	84,[s] 95[u]
16			1		97	86,[k] 95[y]
17[z]			22		89	80[aa]
18[z]			26		85	–

[a] Reaction conditions: aryl chloride (3 mmol), amine (3.6 mmol), sodium *tert*-butoxide (4.5 mmol, 432 mg), $Pd(OAc)_2$ (0.5 mol % except where noted otherwise), **3a** (1 mol %), toluene (4 mL), 1−48 h, 80 °C. [b] Isolated yields (average of two runs). [c] Using $Pd(OAc)_2$ (0.25 mol %), **3a** (0.5 mol %). [d] Reported yield using 5 mol % Pd and 10 mol % of $ClP(t\text{-}BuNCH_2)_2$, see ref 13f. [e] Using 0.5 mol % Pd, 1.0 mol % ClickPhos, see ref 13 g. [f] Using 5 mol % Pd, 10 mol % $ClP(t\text{-}BuNCH_2)_2$, see ref 13f. [g] Using 1 mol % Pd, 2.0 mol % $Ph_5FcP(t\text{-}Bu)_2$, see ref 32a. [h] Reported yield using 2 mol % of Pd with NHC ligand at 50 °C, see ref 10d. [i] Using 2 mol % Pd, 2 mol % 1-(2-norbornyl)-2,2,6,6-tetramethylphosphorinane, see ref 13h. [j] Using 0.5 mol % Pd, 1.0 mol % ligand di(1-adamantyl)-n-butylphosphine, see ref 13i. [k] Using 1 mol % Pd, 2 mol % ligand **1a**, see ref 24d. [l] Reported yield using 8 mol % of Pd and 8 mol % of **1a**, see ref 24a. [m] Using 1.0 mol % Pd, 2.0 mol % dicyclohexyl-2-(*N*-arylindolyl)phosphine, see ref 13j. [n] Using 5.0 mol % Pd, 7.5 mol % 1-(*N*,*N*-dimethylamino)-1′-(dicyclohexylphosphino)biphenyl, see ref 34. [o] Cs_2CO_3 was used as the base in place of NaO*t*Bu. [p] Using 4.0 mol % Pd, 8.0 mol % ligand **2**, see ref 25. [q] Using 3.0 mol % Pd, 4.5 mol % ligand 2-dicyclohexylphosphino-2′-methoxy-1,1′-binaphthyl, see ref 12q. [r] K_3PO_4 (2.0 equiv) was used as the base in place of NaO*t*Bu. [s] Using 1 mol % $Pd[P(t\text{-}Bu)_3]_2$ see ref 18d. [t] $Pd_2(dba)_3$ and NaOH were employed in place of $Pd(OAc)_2$ and sodium *tert*-butoxide. [u] Using 2.0 mol % Pd, 4.0 mol % **1a**, see ref 24d. [v] Using 2.0 mol % Pd, 4.0 mol % (*o*-biphenyl)PCy_2 see ref 26l. [w] Using 4.0 mol % Pd, 8.0 mol % **2**, see ref 25. [x] Reported yield using 1 mol % Pd with NHC ligand at 100 °C, see ref 10c. [y] Using 4 mol % Pd, 8 mol % **1a**, see ref 24d. [z] Using 1.0 mol % $Pd(OAc)_2$, 2 mol % **3a** at 120 °C. [aa] Using 1.0 mol % palladacycle, see ref 9a.

bromides with, respectively, primary amines or secondary arylamines and morpholine.

Results and Discussion

Recently we reported the synthesis of ligands **3a** and **3b** in good yields,[30b] and the synthesis of ligands **3c** and **3d** are reported herein (Scheme 1). Among these candidate ligands, **3a** and **3d** (synthesized in 88 and 80% yields, respectively) have been the most effective to date in cross-coupling reactions. The aforementioned yields are comparable or better than the overall yields reported with $P(t\text{-}Bu)_3$ (88%[15e,31a]) and $Ph_5FcP(t\text{-}Bu)_2$ (40−65%)[32a] both of which are commonly used for C−N coupling reactions.

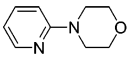
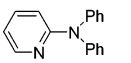
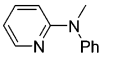
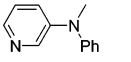
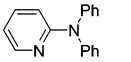
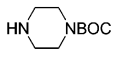
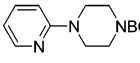
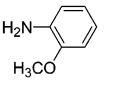
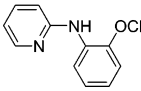
Optimization of Coupling Conditions. The cross-coupling of 4-bromoanisole with morpholine was conducted as a model reaction for screening purposes, and the results are summarized in Table 1. Initially, room-temperature reactions were performed using $Pd(OAc)_2$ or $Pd_2(dba)_3$ with **3a** (entries 1−6). Nearly quantitative yields of the coupling product were achieved with 2−4 mol % of Pd (entries 1−4), but moderate yields were obtained at 1 mol % of Pd (entries 5 and 6). While 1 mol % of both Pd and ligand (entry 4) was reasonably efficient at room temperature, the Pd and **3a** concentrations can be substantially reduced (entries 7−10) to 0.25 and 0.5 mol %, respectively (entry 9), by operating at 80 °C. Not unexpectedly, the less sterically bulky analogous ligands **3b**−**d** gave poorer product yields (entries 12−14, respectively).

Amination of Aryl Bromides Using the Pd/3a Catalyst System. Using the conditions in entry 9 of Table 1, the scope of our methodology was explored for a variety of aryl bromides (Table 2) at 80 °C, including examples possessing deactivating or activating functionalities. By contrast, biphenyl- or ferrocenyl-based alkylphosphine catalysts or P(*t*-Bu)$_3$ generally require 100 °C for the amination of functionalized aryl bromides over 4−39 h,[32,26l] although in some cases reactions can be carried out at room temperature using 0.05−5 mol % of palladium.[32,26l,34] Several structurally diverse aryl bromides including heteroaryl and polynuclear aromatics (entries 4 and 5) were also smoothly aminated, and most of these reactions were completed in less than 4 h. Although the use of the conventional base, NaO*t*Bu, was found to be ineffective for phenolic compounds, this limitation can be overcome by using $LiN(SiMe_3)_2$.[26o,26n,24c] This change resulted in an excellent yield of coupled product (Table 2, entry 13). An electron-withdrawing substituent on the ortho position in the aryl bromide substrate also resulted in a good isolated yield using the present catalytic system (Table 2, entry 14).

Using the conditions in entry 9 in Table 1, **3a** pre-exposed to air for 24 h gave a 93% isolated yield of product (average of 4 runs) in 1 h. By contrast, P(*t*-Bu)$_3$, a highly effective ligand for a wide variety of Pd-catalyzed cross-coupling reactions[31b] including aminations, is destroyed in air within 2 h.[9b] It has been reported by Fu that the air sensitivity problem of P(*t*-Bu)$_3$ can be overcome by the use of its HBF_4 salt,[31d] although this does require an additional salt-forming step and additional base in the coupling reaction for phosphine deprotonation.

Amination of Aryl Chlorides Using the Pd/3a Catalyst System. Next, we applied our protocol to the amination of aryl chlorides (Table 3) which, though less reactive, are more desirable substrates than their bromide and iodide counterparts in terms of cost and availability.[19b,24a] Here, 0.5 mol % Pd loading was needed, while 0.25 mol % of Pd catalyst required longer reactions times to provide only a moderate yield (entry 2). Interestingly, electron-poor and electron-rich aryl chlorides afforded generally excellent yields of the desired coupled product. For substrates containing base-sensitive groups (entries 9−15, Table 3), NaO-t-Bu was found to be an inappropriate base. However, this limitation was overcome in entries 9−11 and 14 wherein weaker bases such as Cs_2CO_3 and K_3PO_4 were found to work well for the ester functionality. Finely ground NaOH in combination with $Pd_2(dba)_3$ allowed efficient coupling of 4-nitrochlorobenzene with morpholine and diphenylamine (entries 12 and 13). Interestingly, a phase-transfer catalyst was not required as was the case when NaOH and KOH were used as bases in amination reactions carried out with $Pd[P(t\text{-}Bu)_3]_2$.[18d] The ketone functionality is also well tolerated in our protocol using NaOH as the base (entry 15) with no α-arylated product formed in detectable amounts, in contrast to what is often the case in cross-couplings.[18d] The presence of an electron-withdrawing substituent on the meta position of an aryl chloride substrate causes C−N bond forming reactions to proceed with difficulty.[9a] Using the present protocol, good yields of coupled products (Table 3, entries 17 and 18) were isolated.

TABLE 4. Pd/3a-Catalyzed Aminations of Heteroaryls[a]

entry	ArX	amine	time (h)	product	yield (%)[b]	lit. yield lowest, highest
1[c]			24		95	70,[d] 93[e]
2			24		99	87[g]
3[f]			12		95	
4			11		99	98[h]
5			16		83	80,[h] 98[j]
					89[i]	
6			12		96	99[k]
7			8		98	92,[k] 98[l]
8[m]			22		91	–

[a] Reaction conditions: heteroaryl chloride (3 mmol), amine (3.6 mmol), sodium *tert*-butoxide (4.5 mmol, 432 mg), $Pd(OAc)_2$ (0.5 mol % unless otherwise stated), **3a** (1.0 mol %), toluene (4 mL), 80 °C. [b] Isolated yields (average of two runs). [c] 0.25 mol % of $Pd(OAc)_2$ and 1.0 mol % **3a** was used. [d] Using 2 mol % $Pd[(o\text{-}tolyl)_3P]_2Cl_2$, 90−100 °C, see ref 36. [e] Using 0.5 mol % Pd, 1 mol % **2**, see ref 25. [f] Ligand **3a** (0.5 mol %) in the presence of $Pd_2(dba)_3$ (0.25 mol %) instead of $Pd(OAc)_2$. [g] Using 4.0 mol % Pd, 8.0 mol % **2**, see ref 25. [h] Using 1 mol % Pd, 2 mol % **1a**, see ref 24d. [i] Reported yield using 4 mol % Pd and 8 mol % **1a**, see ref 24a. [j] Using 0.5 mol % Pd, 1 mol % 2-(di-*tert*-butylphosphino)-*N*-(1-naphthyl)-1*H*-benzimidazole, see ref 13k. [k] Using 1.0 mol % Pd, 1.0 mol % **1a**, see ref 24d. [l] Using 1.0 mol % Pd, 2.0 mol % di(1-adamantyl)-*n*-butylphosphine, see ref 13i. [m] Using 1.0 mol % $Pd_2(dba)_3$, and 2 mol % **3a**.

Amination of Heteroaryl Bromides and Chlorides Using the Pd/3a Catalyst System. The *N*-arylpiperazine moiety is embedded in several pharmacologically interesting targets, such as ligands of serotonin (5-HT)-receptors, antifungals, antivirals, antibacterials, and cholesterol ester transfer protein inhibitors.[24d,25] The efficient synthesis of such a moiety using a low Pd loading is shown in Table 3, entry 6, and a related example is given in Table 4, entry 7. The additional reactions of bromo and chloropyridines in Table 4 also proceeded without difficulty using the $Pd(OAc)_2$/**3a** or $Pd_2(dba)_3$/**3a** catalyst system, giving

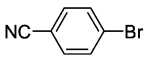
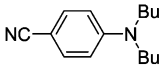
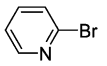
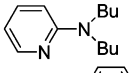
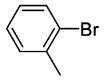
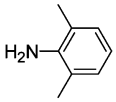
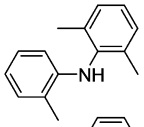
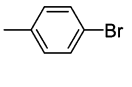
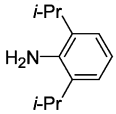
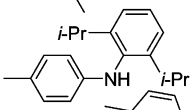
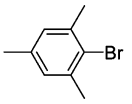
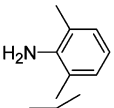
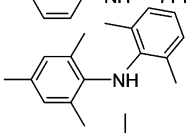
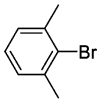
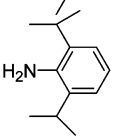
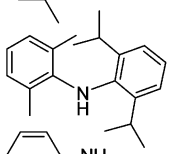
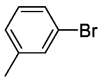
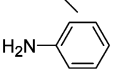
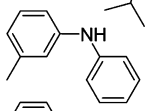
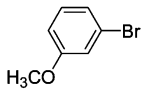
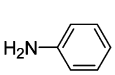
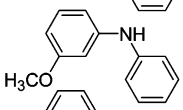
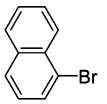
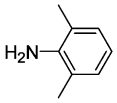
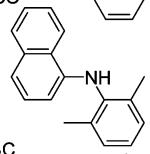
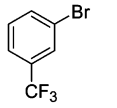
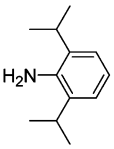
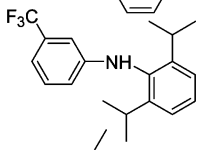
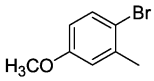
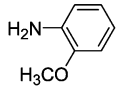
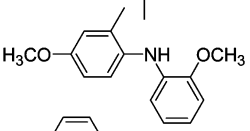
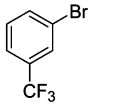
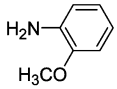
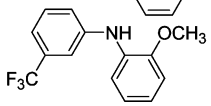
(31) (a) Rampf, F.; Militzer, H.-C. (Bayer AG, DE) Eur. Pat. Appl. EP1354886, 2003; *Chem. Abstr.* **2003**, *139*, 307893. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211. (c) For the stability of variety of phosphines toward oxygen, see Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096−5101. (d) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295−4298.

(32) (a) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553−5556. (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580.

(33) (a) Mukherjee, A.; Sarkar, A. *ARKIVOC* **2003**, *9*, 87−95. (b) Guino, M.; Hii, K. K. *Tetrahedron Lett.* **2005**, *46*, 6911−6913. (c) Zhang, X-X.; Harris, M. C.; Sadighi, J. P.; Buchwald, S. L. *Can. J. Chem.* **2001**, *79*, 1799−1805.

(34) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723.

TABLE 5. Pd/3a-Catalyzed Aminations of Aryl Bromides with Primary and Acyclic Secondary Amines[a]

entry	aryl bromide	amine	time (h)	product	yield (%)[b]	lit. yield lowest, highest
1[c]			1		62	94[d]
2			24		96	84,[f] 88[g]
3[e]			14		97	
4			12		98	–
5			0.5		98	47[h]
6			4		98	96,[i] 99[j]
7[k]			5		96	90,[l] 91[m]
8[n]			12		93	90[o]
9[n]			12		71	96[j]
10[e]			20		86	–
11[e]			24		97	–
12[e]			14		97	–
13[e]			14		98	–

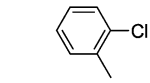
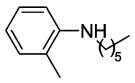
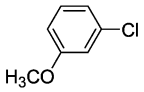
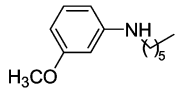
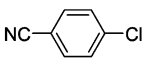
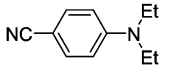
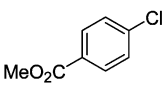
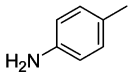
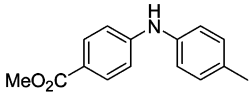
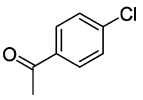
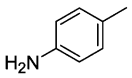
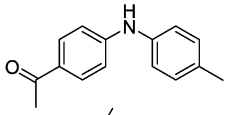
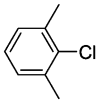
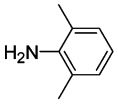
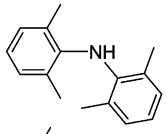
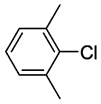
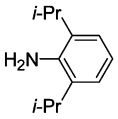
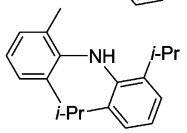
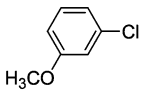
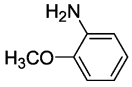
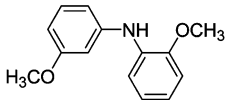
[a] Reaction conditions: aryl bromide (3 mmol), amine (3.6 mmol), sodium *tert*-butoxide (4.5 mmol, 432 mg), $Pd(OAc)_2$ (0.25 mol % unless otherwise stated), **3a** (0.5 mol %, unless otherwise stated), toluene (4 mL), 0.5−24 h, 80 °C. [b] Isolated yields (average of two runs). [c] Using 0.5 mol % $Pd_2(dba)_3$ and 1.0 mol % **3a**. [d] Using 1.0 mol % Pd, 2.0 mol % $Ph_5FcP(t\text{-}Bu)_2$, see ref 32a. [e] Using 0.5 mol % $Pd(OAc)_2$ and 1.0 mol % **3a**. [f] Using 2.0 mol % Pd, 4.0 mol % **2**, see ref 25. [g] Using 3.0 mol % Pd, 4.5 mol % (*rac*)-[2-(diphenylphosphino) ferrocenyl] ethyl methyl ether, see ref 38. [h] Using 1.0 mol % Pd, 1.0 mol % (DTBNpP·HBF_4), see ref 13d. [i] Using 0.5 mol % Pd, 1.0 mol % **2**, see ref 25. [j] Using 2 mol % Pd, 4 mol % **1a**, see ref 24b. [k] Using 0.25 mol % $Pd_2(dba)_3$ and 0.5 mol % **3a**. [l] Using 5 mol % Pd, 7.5 mol % (DPEPhos), see ref 37. [m] Using 5 mol % Pd, 7.5 mol % (DPEPhos), see ref 33c. [n] Using 0.2 mol % $Pd_2(dba)_3$ and 0.4 mol % **3a**. [o] Using 1.0 mol % Pd, 1.0 mol % $P(t\text{-}Bu)_3$, see ref 39.

generally excellent product yields. In most instances, monodentate phosphine ligands are considered unsuitable for use with this class of substrates because pyridines can compete with such ligands for palladium to form catalytically inactive *trans*-bis(pyridine)palladium species,[35] although electron-rich ligands can inhibit such side reactions.[24a,12b] It appears that the extraordinary electron-richness and steric bulk of ligand **3a** inhibits this side reaction.[30b] The result in entry 5 of Table 4 is noteworthy in that the use of ligand **1a** required 4 and 8 mol % of Pd and **1a**, respectively.[24a] Our present protocol was also considerably more successful for the formation of the highly functionalized heteroaryl amine in entry 7 of Table 4 than that in which 1 mol % of Pd and 2 mol % of ligand **1a** was employed at 100 °C.[24d] Similarly, 2-bromopyridine coupled very efficiently with morpholine and diphenyl amine (Table 4, entries 1, 2) in contrast to the necessity for 0.5 and 4 mol % of Pd(0) and **2**, respectively.[25]

(35) Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030−3039.

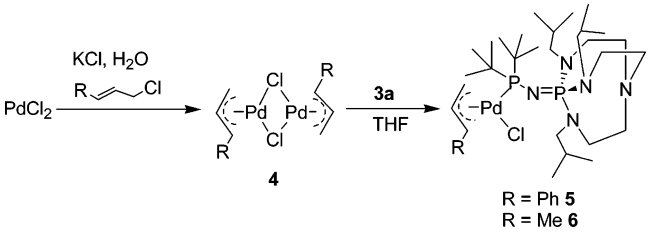
(36) Basu, B.; Jha, S.; Mridha, N. K.; Bhuiyan, Md. M. H. *Tetrahedron Lett.* **2002**, *43*, 7967−7969.

TABLE 6. Scope of Pd/3a-Catalyzed Amination of Aryl Chlorides with Primary and Acyclic Secondary Amines[a]

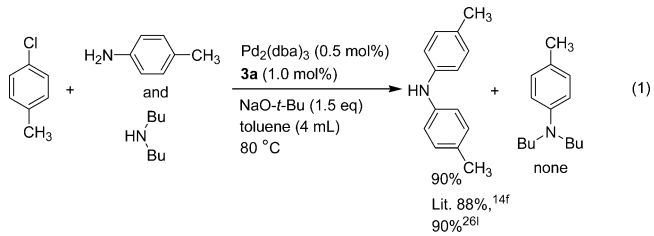
entry	aryl chloride	amine	time (h)	product	yield (%)[b]	lit. yield lowest, highest
1[c]			18		62	92,[d] 95[e]
2[f]			4		55	43,[g] 95[h]
3[f]			8		59	56[g]
4[i]			36		93	–
5[j]			24		87	95[k]
6[l]			16		98	87,[m] 95[n]
7[o]			14		98	70,[m] 91[p]
8[q]			18		95	–

[a] Reaction conditions: aryl chloride (3 mmol), amine (3.6 mmol), sodium *tert*-butoxide (4.5 mmol, 432 mg), $Pd(OAc)_2$ (*x* mol %, see footnotes), **3a** (*x* mol %, see footnotes), toluene (4 mL), 4−36 h, 80 °C. [b] Isolated yields (average of two runs). [c] Using 1.5 mol % $Pd(OAc)_2$, 3.0 mol % **3a**. [d] Using 1.0 mol % Pd, 2.0 mol % $Ph_5FcP(t\text{-}Bu)_2$, 70 °C, see ref 32a. [e] Using 1.0 mol % $Pd[P(t\text{-}Bu)_3]_2$, see ref 18d. [f] Using 2.5 mol % $Pd(OAc)_2$, 5.0 mol % **3a**. [g] Using 5 mol % Pd, 10 mol % **1a**, see ref 24a. [h] Using 1.0 mol % Pd, 2.0 mol % $Ph_5FcP(t\text{-}Bu)_2$, 100 °C, see ref 32a. [i] Using $Pd_2(dba)_3$ (0.5 mol %) instead of $Pd(OAc)_2$, **3a** (1.0 mol %), Cs_2CO_3 (4.5 mmol, 1.466 g) in place of sodium *tert*-butoxide. [j] Using 0.5 mol % $Pd_2(dba)_3$, 1.0 mol % **3a**, NaOH (4.5 mmol, 180 mg) in place of sodium *tert*-butoxide. [k] Using 1 mol % Pd, 2 mol % (2-biphenyl)dicyclohexylphosphine, see ref 26l. [l] Reaction with 0.1 mol % $Pd_2(dba)_3$ and 0.2 mol % **3a** was carried out at 100 °C. [m] Using 0.5 mol % Pd, 1.0 mol % di(1-adamantyl)-*n*-butylphosphine, ref 26i. [n] Using 1.0 mol % Pd, 2.0 mol % **1a**, 120 °C, ref 24d. [o] Using 0.25 mol % $Pd_2(dba)_3$, 0.5 mol % **3a**. [P] Using 5 mol % Pd, 10 mol % $ClP[2,6\text{-}(i\text{Pr})_2C_6H_3NCH_2]_2$, see ref 29a. [q] Using 1.0 mol % $Pd_2(dba)_3$ and 2.0 mol % **3a**.

SCHEME 2. Synthesis of (3a)Pd(R-allyl)Cl Complexes 5 and 6



Aminations with primary anilines lacking an ortho substituent usually demand 2−5 mol % of Pd and are carried out at 80 or 100 °C.[24d,26g] Pleasingly, our present protocol with 4-chlorotoluene and *p*-toluidine proceeded to completion at 80 °C with a loading of only 1 mol % of Pd, affording the desired product in 90% yield (eq 1), and it does so selectively in the presence of a secondary amine as has also been observed for other ligands.[12f,12w] This yield was quite comparable with that achieved with Buchwald's[26l] method using 0.5 mol % of Pd and 1.0 mol % of (2-biphenyl)di-*tert*-butylphosphine, or with the approach of Maes et al.[14f] using 1 mol % Pd and 2.0 mol % of 2-(dicyclohexylphosphanyl)biphenyl under mocrowave conditions at 200 °C.



(1)

Amination of Sterically Bulky Aryl Bromides with Primary Arylamines and Dibutylamine Using the Pd/3a Catalyst System. With 1.5−2.5 mol % of $Pd(OAc)_2$, couplings of more recalcitrant primary and acyclic secondary amines were accomplished, providing the corresponding substituted anilines in excellent yields (Table 5), while the reaction between 4-bromobenzonitrile and dibutylamine gave a moderate product

yield (entry 1). Steric hindrance on either or both coupling partners was very well tolerated. Particularly noteworthy is the 98% product yield achieved in entry 6 in which both coupling partners are severely sterically encumbered. Efficient coupling was observed in the case of 2,6-diisopropylaniline with 4-bromotoluene using 0.25 and 0.5 mol % of **3a**/Pd (entry 5, Table 5) which contrasts with the considerably lower yields reported in a literature protocol using higher Pd (1 mol %) and ligand (1 mol % DTBNpP) loadings.[13d] With DPEphos {bis[2-(diphenylphosphino)phenyl] ether}, *rac*-BINAP, or DPPF as the ligand, the reaction involving 2-bromo-*m*-xylene and 2,6-diisopropylaniline required a catalyst loading of 5 mol % Pd and a reaction temperature of 120 °C.[37] Impressively, the use of Pd/**3a** efficiently promotes this coupling with only 0.25 mol % Pd and 0.5 mol % ligand at 80 °C (Table 5, entry 7). As can be seen from Table 5, several diverse aromatic secondary and tertiary amines were synthesized with the present protocol.

Amination of Aryl Chlorides with Primary Arylamines, a Primary Alkylamine, and a Secondary Dialkylamine Using the Pd/3a Catalyst System. Reactions of aryl chlorides with hexyl- and diethylamine using 1.5−2.5 mol % of Pd and 2.5−5 mol % of **3a** gave modest product yields (Table 6, entries 1−3) although these yields are better than those we reported earlier with a Pd and **1a** loadings of 5 and 10 mol %, respectively.[24a] For substrates bearing ester or keto functional groups, the use of Cs_2CO_3 or NaOH, respectively, in place of NaO-*t*-Bu as a base leads to the most efficient and mild catalytic protocols that have to our knowledge been reported to date for arylaminations of aryl chlorides (entries 4 and 5 of Table 6). The near-quantitative product yield in the reaction of the sterically hindered coupling reactants in entry 6 in the presence of only 0.1 mol % of Pd and 0.2 mol % of **3a** at 100 °C is perhaps not entirely surprising since formation of a highly hindered aryl amidopalladium intermediate of the type ArNPd(L)Ar′ is expected. Here the product-forming reductive elimination step should be facile in the presence of a bulky ligand such as **3a** owing to release of strain from the highly coordinated palladium metal center.[24d] 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 PCy_3 (96%)[26i] or $DMAPPAd_2$ [di(1-adamantyl)-3-(*N*,*N*-dimethylamino)propyl phosphine] (96%)[26i] reveals ligand activities comparable to ours for this reaction. However, catalyst systems based on $PhPCy_2$ (90%), P(*t*-Bu)$_3$ (77%), (*o*-biphenyl)PCy_2 (42%), and $BuPCy_2$ (78%) as ligands at the same Pd loadings were inferior.[26i] The highly bulky arylamine in entry 7 of Table 6 is also a challenging reaction,[29a] but it too proceeds in excellent yield using the Pd/**3a** system at a very low Pd and ligand loading. A meta-substituted aryl chloride couples afficiently with an ortho-substituted amine (entry 8 of Table 6) under our conditions.

Amination of Aryl Chlorides and Bromides Using Complex 5. The efficacy of bulky electron-rich phosphines such as trialkylphosphines[40] and biarylphosphines[41] in Pd-catalyzed couplings has been attributed to the formation of monoligated [PdL] species.[42] Examples of well-defined isolable complexes of this type are rare,[9a,10a] and tertiary phosphines are often used as free ligands in a 2:1 ratio with Pd(II) or Pd(0) sources.[9a,10a] Here we report a straightforward and convenient synthesis of air- and moisture-stable complexes of the type Pd(R-allyl)Cl-(**3a**) [R = cinnamyl (**5**) and crotyl (**6**)] which we have evaluated in C−N coupling reactions.

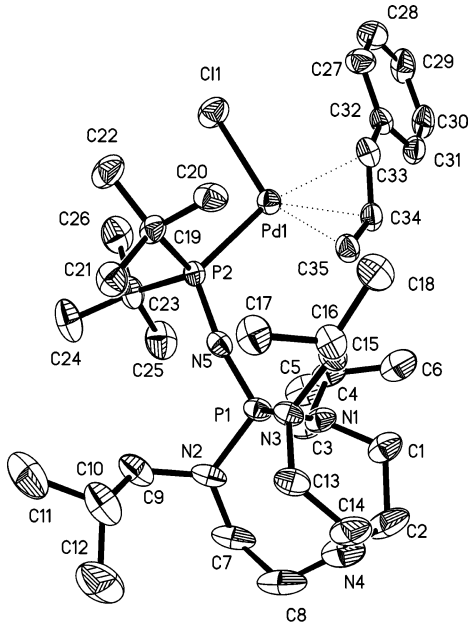


FIGURE 1. Molecular structure of palladium phosphine complex **5** depicted with 50% probability thermal ellipsoids. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å): Pd−C(33) 2.374(4); Pd−C(34) 2.190(4); Pd−C(35) 2.062(4); Pd−P(2) 2.3154(12), and Pd−Cl(1) 2.3959(13).

Reaction of the $[Pd(R\text{-allyl})Cl]_2$ dimers prepared by literature means[43] (R-allyl = cinnamyl and crotyl) with **3a** in dry THF (see Scheme 2) allowed isolation of complexes **5** and **6**, respectively, in excellent yields (99% and 97%, respectively). Single crystals of **5** and **6** suitable for X-ray diffraction were obtained by cooling a concentrated solution of **5** or **6** in CH_2Cl_2/hexanes for 2 days in a refrigerator. As observed with (NHC)Pd(R-allyl)Cl complexes,[10a] the carbon trans to the chlorine atom [C(35) in Figure 1and C(27) in Figure 2] is considerably closer to the palladium center [Pd−C(35), 2.062(4) Å; Pd−C(27), 2.077(4) Å] than the carbon trans to the ligand **3a**, namely, C(33) in Figure 1 and C(29) in Figure 2 [Pd−C(33), 2.374(4) Å; Pd−C(29), 2.298(3) Å]. It is interesting to note that the Pd−C(33) in **5** and Pd−C(29) bonds in **6** are considerably longer than the corresponding bond distances in the corresponding (NHC)Pd(R-allyl)Cl complexes[10a] [Pd−$C_{(trans)}$, 2.284(9) for R-allyl = cinnamyl); 2.209(16) for R-allyl = crotyl]. This significant elongation of the Pd−C distance in **5** and **6** may well enhance reductive elimination of allyl halide

(37) Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1998**, *39*, 5327−5330.
(38) Marcoux, J. F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568−1569.
(39) Yu, M.; Wang, M.; Chen, X.; Hong, B.; Zhang, X.; Cheng, C. *J. Chem. Res.* **2005**, 558−560.
(40) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861−2873. See also: refs 12j, 13d, 18a−d, and 16b.
(41) (a) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369−4378. (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550−9561. (c) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978−13980. See also: refs 9b and 12f.
(42) For a concise overview on monoligated palladium species, see: Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366−374.
(43) (a) Palenik, R. C.; Palenik, G. J. *Synth. React. Inorg. Met.-Org. Chem.* **1992**, *22*, 1395−1399. (b) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033−2046.

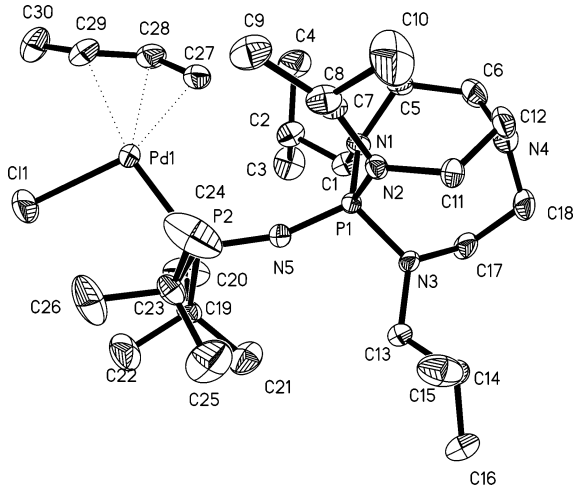


FIGURE 2. Molecular structure of palladium phosphine complex **6** depicted with 50% probability thermal ellipsoids. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å): Pd−C(29) 2.298(3); Pd−C(28) 2.170(3); Pd−C(27) 2.077(4); Pd−P(2) 2.3285(8), and Pd−Cl(1) 2.3760(11).

leading to the formation of catalytically active [(L)Pd(0)] species. Favorable steric protection of the Pd center in **5** could arise from the presence of the two bulky *tert*-butyl groups on the phosphorus of **3a** bonded to the metal. Interestingly, the palladium center was coordinated only by the tertiary phosphine with no obvious tendency to interact with the imino nitrogen on **3a**. The results of the use of complex **5** for several coupling reactions of aryl halides with amines are presented in Table 7.

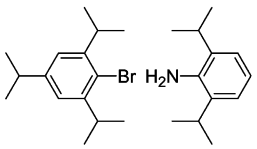
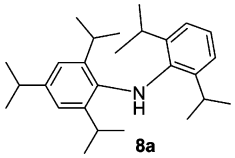
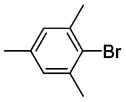
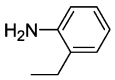
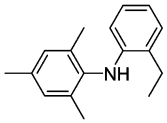
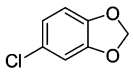
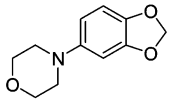
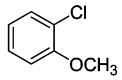
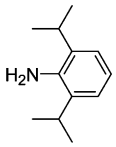
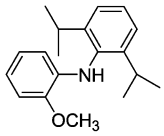
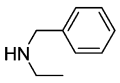
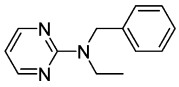
As seen in Table 7, the new palladium allyl complex **5** showed excellent activity for the amination of a variety of amines and aryl halides. Initially we tested **5** in the cross-coupling of sterically bulky coupling partners which resulted in excellent isolated product yields in entry 1. In an effort to clarify the influence of L and the R-allyl moiety on the reactivity of these complexes, a series of experiments were conducted and the results are also summarized in Table 7. A 1:2 molar ratio of $Pd(OAc)_2$ to **3a** gave an impressive yield of product (95%, entry 2) and a 1:1 molar ratio of $Pd(OAc)_2$ to **3a** gave a somewhat diminishcd yield (88%, entry 3). However, the same pair of experiments with $PdCl_2$ and **3a** gave an 85 and a 77% product yield (entries 4 and 5, respectively). Thus, in the absence of the ancillary cinnamyl moiety in complex **5**, 2 equiv of the phosphine become necessary to achieve high yields whether the Pd source is the acetate or the chloride. It has been postulated in the literature that (NHC)Pd(R-allyl)Cl complexes undergo nucleophilic attack at the allyl moiety by the base (KOtBu) or participate in a chloride/alkoxide σ-metathesis, followed by reductive elimination, liberating in both cases a catalytically active [L-Pd(0)] species and cinnamyl *tert*-butyl ether[10a] as in Scheme 3. As was observed in the case of (NHC)Pd(R-allyl)Cl complexes,[10a] the effect of the R group in the catalytic activity of complexes **5** and **6** is quite significant. Thus the crotyl complex **6** possessing the smaller methyl group resulted in an 87% isolated yield (entry 6) compared with 98% for the cinnamyl analogue (entry 1, Table 7). A comparison of the bond distances around the metal center in complexes **5** and **6** supports this observation. Thus the Pd−C bond trans to ligand **3a** in structures of **5** and **6** is considerably longer than other Pd−C distances in the complex, and this distance is longer than in **5** than in **6**. These results are in accord with the notion that the cinnamyl moiety plays a crucial role in a possibly rate-limiting reductive elimination step that generates the (L)-Pd^0 species.[10a] This is further supported by our observation that in the presence of 20 equiv of cinnamyl chloride, only a 35% yield of product was obtained (entry 7 of Table 7). However, if cinnamyl *tert*-butyl ether is formed in these reactions, as has been postulated as a possibility,[10a] its concentration is too low to be detected by GC-MS spectroscopy. This was demonstrated with the product mixture of a reaction involving 1-bromo-2,4,6-isopropylbenzene (0.03 mmol) and morpholine (0.05 mmol), complex **5** (0.03 mmol), and NaO*t*Bu (1.5 equiv with respect to aryl bromide) in toluene at 80 °C for 24 h. Under these same reaction conditions in the absence of the coupling partners, no cinnamyl *tert*-butyl ether could be detected by GC-MS. The noticeable reduction in yield in entry 7 of Table 7 may also be due the possibility of a competing oxidative addition reaction that reduces the availability of the **3a**-Pd(0) species (see Scheme 3). It is also interesting to note that when cinnamyl chloride is added in stoichiometric amounts to **3a** and 0.5 $Pd_2(dba)_3$ or $Pd(OAc)_2$ in a 1:1:1 ratio, product yields were somewhat diminished (Table 7, entries 8 and 9, respectively) from those achieved with the pure complex **5**. These results suggest that *in situ* generation of complex **5** and/or of a similarly active complex can be accomplished fairly efficiently. Under similar conditions, however, palladium chloride gave only a poor product yield (Table 8, entry 10) perhaps owing to the presence of extra chloride which could be expected to supress chloride dissociation from the palladium. The present protocol involving monoligated palladium complex **5** appears to be quite general and efficient for BH-amination reactions, resulting in good to excellent yields of coupled products (Table 7, entries 11−13). It is interesting to note that the heterocyclic aryl chloride in Table 7, entry 14 coupled with *N*-ethylbenzylamine efficiently under the same reaction conditions.

We successfully sythesized the dicyclohexyl analogue of ligand **3a**, namely, **3d** in 80% overall yield (see Experimental Section). In evaluating the effectiveness of **3d** in a C−N coupling reaction involving bulky reaction partners (Scheme 4), we found that this ligand allowed an excellent yield of product, albeit somewhat less than that with **3a (**Table 7, entry 1). Though **3d** showed less activity than **3a** in screening studies (Table 1, entry 14), the high activity of **3d** in Scheme 4 over that in Table 1, entry 14, may arise from the higher loading of palladium and ligand used in the reaction shown in Scheme 4. It is interesting that almost exactly the same product yields were obtained for the coupling partners in Scheme 4 using **3d** were obtained for the same coupling partners when **3a** was employed under the same conditions (Table 7, entry 2).

Buchwald−Hartwig Amination of Vinyl Bromides and Chlorides Using the Pd/3a Catalyst System. Recently, we reported the synthesis of enamines and imines[1m,44] with a variety of vinyl bromides using $Pd_2(dba)_3$/**1a** (0.25 mol % of Pd and 0.5 mol % of **1a**) at 80 °C, and with vinyl chlorides at 115 °C using 2.5 mol % of Pd and 5 mol % of **1a**.[24e] In the present work, the $Pd_2(dba)_3$/**3a** catalyst system, in combination with NaO-*t*-Bu as the base, allowed vinyl bromides to couple successfully with a variety of amines *at room temperature* employing only 0.25 mol % of $Pd_2(dba)_3$ and 0.5 mol % of **3a**

(44) For an interesting feature articles on Pd-catalyzed amination of alkenyl halides for the synthesis of enamines and imines, see, Barluenga, J.; Valdés, C. *Chem. Commun.* **2005**, 4891−4901 also see ref 1m.

TABLE 7. Palladium Cinnamyl Phosphine Complex 5-Catalyzed Amination of Aryl Halides[a]

entry	aryl halide	amine	time (h)	product	yield (%)[b]
1			4	 **8a**	98
2[c]			4	**8a**	95
3[d]			4	**8a**	88
4[e]			17	**8a**	77
5[f]			17	**8a**	85
6[g]			4	**8a**	87
7[h]			4	**8a**	35
8[i]			4	**8a**	90
9[j]			4	**8a**	93
10[k]			4	**8a**	49
11			16		98
12			16		86
13			18		84 (81)[l]
14			14		95

[a] Reaction conditions: aryl halide (3 mmol), amine (3.6 mmol), sodium *tert*-butoxide (4.5 mmol, 432 mg), **5** (1 mol %, unless otherwise stated), toluene (4 mL), 80 °C. [b] Isolated yields (average of two runs). [c] 1.0 mol % $Pd(OAc)_2$ and 2.0 mol % **3a** was used. [d] 1.0 mol % $Pd(OAc)_2$ and 1.0 mol % **3a** was employed. [e] 1.0 mol % $PdCl_2$ and 1.0 mol % **3a** was employed. Reaction time was not optimized. [f] 1.0 mol % $PdCl_2$ and 2.0 mol % **3a** was employed. Reaction time was not optimized. [g] Using 1.0 mol % complex **6**. [h] Using 1.0 mol % complex **5** in the presence of 20 equiv (with respect to **5**) of cinnamyl chloride. [i] Using 0.5 mol % $Pd_2(dba)_3$, 1.0 mol % of **3a**, 1 mol % of cinnamyl chloride [j] Using 1.0 mol % $Pd(OAc)_2$, 1.0 mol % of **3a** and 1 mol % of cinnamyl chloride. [k] Using 1.0 mol % $PdCl_2$, 1.0 mol % of **3a**, and 1 mol % of cinnamyl chloride. [l] Using 0.5 mol % Pd, 1.0 mol % of di(1-adamantyl)-*n*-butylphosphine at 120 °C, ref 26i.

(Table 8). To the best of our knowledge, these conditions constitute a distinct improvement over those in previously reported methods, all of which operate at 80 °C or above for the cross-coupling of vinyl bromides.[24e,45,46] Impressively, vinyl chlorides were coupled at 80 °C using only 0.5% of $Pd_2(dba)_3$ (Table 8, entries 10, 11) which represents a 2- to 5-fold lower catalyst loading than that employed in previous protocols conducted from 90 to 110 °C.[24e,45] The present methodology uses low catalyst loading (0.5 mol % of Pd and 0.5 mol % of ligand **3a**) which is at least 2-fold (and in some cases 6-fold) less than that used at 80 °C in the Pd/BINAP catalyst system reported by others.[45a,b] For example, the reactions shown in entries 1, 3, and 9 of Table 8 when performed with the Pd/BINAP catalyst system required 3 mol % of Pd and 6 mol % of BINAP.[45a,b]

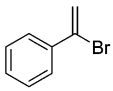
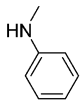
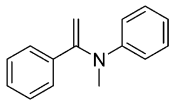
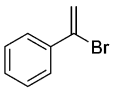
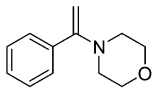
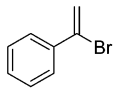
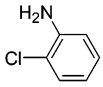
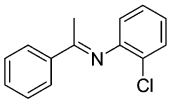
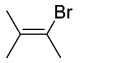
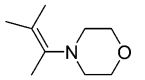
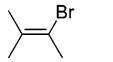
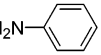
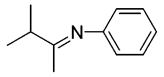
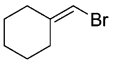
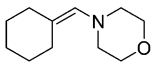
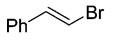
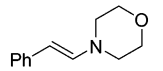
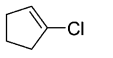
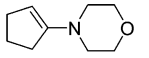
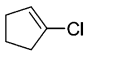
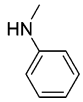
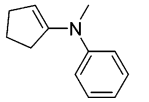
Conclusions

In summary, the new ligand **3a**, which was synthesized in good yield,[30] 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. The use of Cs_2CO_3 or NaOH in the presence of Pd/**3a** permits aryl chlorides and bromides with base-sensitive functional groups to be aminated efficiently. An important strength of our protocol is

(45) (a) Barluenga, J.; Fernández, M. A.; Aznar, F.; Valdés, C. *Chem. Commun.* **2002**, 2362−2363. (b) Barluenga, J.; Fernández, M. A.; Aznar, F.; Valdés, C. *Chem. Eur. J.* **2004**, *10*, 494−507. (c) Barluenga, J.; Fernandez, M. A.; Aznar, F.; Valdes, C. *Chem. Eur. J.* **2005**, *11*, 2276−2283. (d) Barluenga, J.; Aznar, F.; Moriel, P.; Valdés, C. *Adv. Synth. Catal.* **2004**, *346*, 1697−1701.

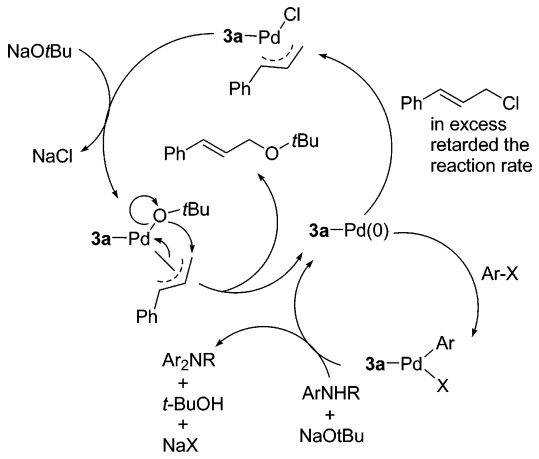
(46) Barluenga, J.; Fernández, M. A.; Aznar, F.; Valdés, C. *Chem. Commun.* **2004**, 1400−1401.

TABLE 8. Synthesis of Enamines and Imines from Vinyl Halides Using the $Pd_2(dba)_3$/3a Catalyst System[a]

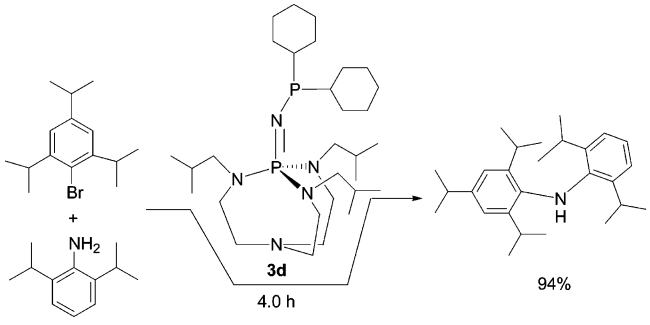
entry	vinyl halide	amine	time (h)	product	yield (%)[b]	lit. yield (%)
1[c]			2		95	65[d]
2			24		93	98[e]
3[c]			2		96	74[f]
4			14		93	96[g]
5[f]			18		88	90[i]
						100[j]
6			8		84	79[d]
7			6		91	–
8[h]			14		93	–
9			15		94	73[d]
						98[i]
10[h]			20		90	90[k]
11[h]			24		84	95[k]

[a] Reaction conditions: vinyl halide (3.0 mmol, otherwise stated in the Supporting Information), amine (3.6 mmol, otherwise stated in the Supporting Information), $Pd_2(dba)_3$ (0.25 mol %), **3a** (0.5 mol %), NaO*t*Bu (4.2 mmol, 404 mg), toluene (4 mL), 2−24 h, room temperature except where indicated. [b] Isolated yields (average of two runs). [c] Reaction was carried out at 80 °C using 0.1 mol % $Pd_2(dba)_3$, 0.2 mol % **3a**. [d] Using 1 mol % Pd, 3.0 mol % BINAP at 90 °C, see ref 45a. [e] Using 3 mol % Pd, 6 mol % BINAP, 90 °C, see ref 45b. [f] Using 1 mol % Pd, 3 mol % BINAP, 80 °C, see ref 45a. [g] Using 2 mol % Pd, 3 mol % BINAP, 90 °C, see ref 45b. [h] Reaction was carried out at 80 °C using 0.5 mol % $Pd_2(dba)_3$, 1.0 mol % **3a**. [i] Using 0.5 mol % Pd, 0.5 mol % ligand, **1a**, see ref 24e. [j] Using 4 mol % Pd, 8 mol % DavePhos, reported as 100% conversion, see ref 45c. [k] Using 5 mol % Pd, 5 mol % ligand **1a** at 115 °C, see ref 24e.

SCHEME 3. Possible Pathway for the Activation of Palladium Complex 5.



SCHEME 4. Test Reaction Using 3d as a Ligand[a]



[a] Reaction conditions: aryl halide (3 mmol), amine (3.6 mmol), sodium *tert*-butoxide (4.5 mmol, 432 mg), palladium acetate (1 mol %), **3d** (2 mol %), toluene (4 mL), 80 °C. Isolated yield (average of two runs).

the lower palladium loadings it permits compared with those reported earlier, without compromising yields. In comparing the use of our ligand in these aminations with the wide variety of phosphine ligands used in the literature for the same purpose, we determined that out of the 23 literature methods found, the present protocol employs a lower palladium loading than in 17 of those methods, a loading equivalent to that employed in 4 of them, and a higher loading than is reported for only 2 literature protocols. Moreover, compared with the 51 highest literature yields found for products obtained with a variety of

phosphines under a range of reaction conditions (see Tables 1−8), our methodology afforded higher yields for 7 products, comparable yields for 33, and lower yields for 11. We have also described the facile synthesis, structural characteristics, and the catalytic behavior of monoligated phosphine palladium complexes **5** and **6**. The Pd/**3a** catalyst system facilitates efficient coupling of vinyl bromides with a variety of amines to produce imines and enamines *at room temperature* for the first time. Explorations of the potential applications of the new class of bulky electron-rich ligands/catalysts exemplified by phosphines of type **3** (as well as di- and tri-iminophosphorane homologues) and their corresponding allyl complexes of type **5** in synthetically useful cross-coupling reactions are underway.

Experimental Section

$Pd(OAc)_2$- or $Pd_2(dba)_3$/3-Catalyzed Amination of Aryl and Vinyl Halides: 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 Tables 1−8, Scheme 4, and eq 1), ligand **3** (x mol %, see Tables 1−8, and Scheme 4, and eq 1) and base (*x* mmol, see Tables 1−8, Scheme 4, and eq 1). Amine (3.6 mmol) and aryl chloride (3.0 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. Aryl chloride (if a liquid, 3.0 mmol), amine (if a liquid, 3.6 mmol), and solvent (4 mL) were then successively added by syringe. The reaction mixture was heated at 80 °C (unless otherwise stated) until the starting material was completely consumed as judged by TLC. The mixture was cooled to room temperature, adsorbed onto silica gel after washing with ethyl acetate (3 × 15 mL), and then purified by column chromatography (hexanes/ethyl acetate as eluent; details are given in the Supporting Information). The purification method for enamines and imines can be found in the individual procedures in the Supporting Information. The palladium cinnamyl and crotyl complexes **5** and **6** were synthesized according to literature procedures.[43,10a]

Palladium Complex-Catalyzed BH Amination of Aryl Halides: General Procedure. An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with complex **5** or **6** (22.83 or 20.94 mg, respectively, 1 mol %) and sodium *tert*-butoxide (432 mg, 4.5 mmol). The flask was capped with a rubber septum, and then aryl halide (3.0 mmol), amine (3.6 mmol), and solvent (4 mL) were successively added by syringe. The reaction mixture was heated at 80 °C until the starting aryl halide was completely consumed as judged by TLC. The mixture was cooled to room temperature, adsorbed onto silica gel after washing with ethyl acetate (3 × 15 mL), and then purified by column chromatography (hexanes/ethyl acetate as eluent; details are given in the Supporting Information).

***N*-Pyrenylmorpholine (Table 2, entry 4).** General procedure was followed using 1-bromopyrene (0.843 g, 3.0 mmol), morpholine (0.312 mL, 3.6 mmol), NaO-*t*-Bu (432 mg, 4.5 mmol), $Pd(OAc)_2$ (1.68 mg, 0.0075 mmol), **3a** (7.52 mg, 0.015 mmol), and toluene (4 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 8% ethyl acetate/hexanes) to afford 839 mg (97%) of the desired product as a pale yellow greenish solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.46 (d, 1H, J = 9.2 Hz), 7.94−8.17 (m, 7H), 7.73 (d, 1H, J = 8.2 Hz), 4.08 (t, 4H, J = 4.5 Hz), 3.24 (t, 4H, J = 4.5 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 147.5, 131.8, 131.6, 127.9, 127.6, 127.1, 126.3, 126.3, 126.2, 125.7, 125.5, 125.1, 125.0, 124.9, 123.1, 117.1, 67.8, 54.1 ppm; HRMS *m*/*z* Calcd for $C_{20}H_{17}NO$: 287.13101. Found: 287.13134.

***N*-(3,5-Dimethylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane (Table 2, entry 11).** The general procedure was followed using 5-bromo-*m*-xylene (0.407 mL, 3.0 mmol), 1,4-dioxa-8-azaspiro[4.5]decane (0.461 mL, 3.6 mmol), NaO-*t*-Bu (432 mg, 4.5 mmol), $Pd(OAc)_2$ (1.68 mg, 0.0075 mmol), **3a** (7.52 mg, 0.015 mmol), and toluene (4 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 8% ethyl acetate/hexanes) to afford 704 mg (95%) of the desired product as a white crystalline solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.59 (s, 2H), 6.51 (s, 1H), 3.99 (s, 4H), 3.30 (t, 4H, J = 5.7 Hz), 2.27 (s, 6H, J = 4.5 Hz), 1.84 (t, 4H, J = 5.7 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 151.5, 138.8, 121.7, 115.0, 107.5, 64.6, 48.2, 35.0, 22.0 ppm; HRMS *m*/*z* Calcd for $C_{15}H_{21}NO_2$: 247.15723. Found: 247.15764.

2-(Methylanilino)-benzonitrile[47] (Table 2, entry 14). The general procedure was followed using 2-bromobenzonitrile (0.546 g, 3.0 mmol), *N*-methylaniline (0.391 mL, 3.6 mmol), NaO-*t*-Bu (432 mg, 4.5 mmol), $Pd(OAc)_2$ (6.73 mg, 0.03 mmol), **3a** (30.10 mg, 0.060 mmol), and toluene (4 mL) at 120 °C. The reaction mixture was purified by column chromatography on silica gel (eluent: 1% ethyl acetate/hexanes) to afford 517 mg (83%) of the desired product as a pale yellow oil. The ^{1}H NMR spectrum was in accordance with those described in the literature. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 152.7, 148.7, 134.8, 134.2, 129.5, 126.0, 124.3, 121.3, 118.3, 117.9, 109.5, 41.1 ppm; Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 79.67; H, 5.71; N, 13.40.

***N*-Methyl-*N*-(3-cyanophenyl)aniline (Table 3, entry 18).** The general procedure was followed using 3-chlorobenzonitrile (0.412 mg, 3.0 mmol), *N*-methylaniline (0.391 mL, 3.6 mmol), NaO-*t*-Bu (432 mg, 4.5 mmol), $Pd(OAc)_2$ (6.73 mg, 0.03 mmol), **3a** (30.10 mg, 0.06 mmol), and toluene (4 mL) at 120 °C. The reaction mixture was purified by column chromatography on silica gel (eluent: 1% ethyl acetate/hexanes) to afford 534 mg (89%) of the desired product as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 (t, 2H, J = 5.7 Hz), 7.25 (t, 1H, J = 5.7 Hz), 7.14−7.20 (m, 3H), 7.02−7.06 (m, 3H), 3.32 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 149.6, 147.7, 130.2, 130.0, 125.2, 125.1, 122.1, 120.3, 119.7, 118.9, 113.0, 40.4 ppm; HRMS *m*/*z* Calcd for $C_{14}H_{12}N_2$: 208.10005. Found: 208.10034.

2-(*o*-Methoxyanilino)pyridine (Table 4, entry 8). The general procedure was followed using 2-chloropyridine (0.283 mL, 3.0 mmol), *o*-anisidine (0.405 mL, 3.6 mmol), NaO-*t*-Bu (432 mg, 4.5 mmol), $Pd_2(dba)_3$ (27.57 mg, 0.03 mmol), **3a** (30.10 mg, 0.06 mmol), and toluene (4 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 546 mg (98%) of the desired product as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.25 (m, 1H), 8.07 (m, 1H), 7.49 (m, 1H), 6.84−7.00 (m, 5H), 6.73 (s, 1H), 3.88 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 155.8, 148.8, 148.4, 137.6, 130.5, 121.7, 121.1, 118.4, 115.2, 110.5, 109.8, 55.9 ppm; HRMS *m*/*z* Calcd for $C_{12}H_{12}N_2O$: 200.09496. Found: 200.09532.

2,6-Diisopropyl-*N*-(3-trifluoromethylphenyl)aniline (Table 5, entry 11). The general procedure was followed using 3-bromobenzotrifluoride (0.419 mL, 3.0 mmol), 2,6-diisopropylaniline (0.679 mL, 3.6 mmol), NaO-*t*-Bu (432 mg, 4.5 mmol), $Pd(OAc)_2$ (3.36 mg, 0.015 mmol), **3a** (15.05 mg, 0.03 mmol), and toluene (4 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 2% ethyl acetate/hexanes) to afford 936 mg (97%) of the desired product as a colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33−7.35 (m, 1H), 7.21−7.27 (m, 3H), 6.96 (d, 1H, J = 8.0 Hz), 6.73 (s, 1H), 6.61 (d, 1H, J = 8.0 Hz), 3.17 (hept, 1H), 1.16 (d, 12H, J = 4.0 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 148.6, 147.8, 134.2, 129.9, 128.1, 124.4, 115.9, 114.4, 114.3, 109.4, 28.5, 24.1 ppm; HRMS *m*/*z* Calcd for $C_{19}H_{22}F_3N$: 321.17043. Found: 321.17090.

(4-Methoxy-2-methylphenyl) (2-methoxyphenyl)amine (Table 5, entry 12). The general procedure was followed using 4-bromo-3-methylanisole (0.423 mL, 3.0 mmol), *o*-anisidine (0.405 mL, 3.6 mmol), NaO-*t*-Bu (432 mg, 4.5 mmol), $Pd(OAc)_2$ (3.36 mg, 0.015 mmol), **3a** (15.05 mg, 0.03 mmol), and toluene (4 mL). The reaction mixture was purified by column chromatography on silica gel

(47) Calestani, G.; Leardini, R.; McNab, H.; Nanni, D.; Zanardi, G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1813−1824.

(eluent: 2% ethyl acetate/hexanes) to afford 709 mg (97%) of the desired product as a colorless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.21 (m, 1H), 6.77−6.90 (m, 5H), 6.67 (d, 1H, J = 7.2 Hz), 5.74 (s, 1H), 3.94 (s, 3H), 3.83 (s, 3H), 2.27 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 156.45, 147.24, 136.29, 134.62, 133.52, 125.61, 121.23, 118.03, 116.50, 112.38, 112.00, 110.23, 55.87, 55.74, 18.55 ppm; HRMS *m*/*z* Calcd for $C_{15}H_{17}NO_2$: 243.12593. Found: 243.12625.

***N*-(3-Trifluoromethylphenyl)-*o*-anisidine (Table 5, entry 13).** The general procedure was followed using 3-bromobenzotrifluoride (0.419 mL, 3.0 mmol), *o*-anisidine (0.405 mL, 3.6 mmol), NaO-*t*-Bu (432 mg, 4.5 mmol), $Pd(OAc)_2$ (3.36 mg, 0.015 mmol), **3a** (15.05 mg, 0.03 mmol), and toluene (4 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 2% ethyl acetate/hexanes) to afford 786 mg (98%) of the desired product as a colorless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29−7.38 (m, 4H), 7.18 (d, 2H, J = 7.5 Hz), 6.95−6.99 (m, 3H), 6.29 (s, 1H), 3.92 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 149.2, 143.9, 132.2, 131.7, 130.0, 125.8, 123.1, 121.6, 121.1, 120.6, 117.3, 117.2, 116.3, 114.1, 114.1, 111.0, 55.9 ppm; HRMS *m*/*z* Calcd for $C_{14}H_{12}NO$: 267.08710. Found: 267.08758.

***N*-(4-Methoxycarbonylphenyl)-*N*-(4-methylphenyl)-amine[48] (Table 6, entry 4).** The general procedure was followed using methyl 4-chlorobenzoate (0.511 g, 3.0 mmol), *p*-toluidine (0.386 mg, 3.6 mmol), Cs_2CO_3 (1.466 g, 4.5 mmol), $Pd_2(dba)_3$ (13.73 mg, 0.015 mmol), **3a** (15.05 mg, 0.03 mmol), and toluene (4 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 471 mg (93%) of the desired product as a pale yellow solid. The ^{1}H NMR spectrum is in accordance with that described in the literature. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 167.3, 149.1, 138.3, 133.4, 131.7, 130.3, 121.6, 120.6, 114.7, 52.0, 21.1 ppm; HRMS *m*/*z* Calcd for $C_{15}H_{15}NO_2$: 241.11028. Found: 241.11066.

2,3′-Dimethoxydiphenylamine (Table 6, entry 8). The general procedure was followed using 3-chloroanisole (0.367 mL, 3.0 mmol), *o*-anisidine (0.405 mL, 3.6 mmol), NaO-*t*-Bu (432 mg, 4.5 mmol), $Pd_2(dba)_3$ (27.47 mg, 0.03 mmol), **3a** (30.10 mg, 0.06 mmol), and toluene (4 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 2% ethyl acetate/hexanes) to afford 786 mg (98%) of the desired product as a colorless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37 (m, 1H), 7.21 (m, 1H), 6.91 (m, 3H), 6.76 (m, 2H), 6.52 (m, 1H), 6.19 (s, 1H), 3.90 (s, 3H), 3.81 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 160.9, 148.7, 144.4, 132.9, 130.3, 121.1, 120.4, 115.6, 111.7, 110.8, 106.6, 104.2, 55.9, 55.48 ppm; HRMS *m*/*z* Calcd for $C_{14}H_{15}NO_2$: 229.11028. Found: 229.11059.

***N*-(2,4,6-Triisopropylphenyl)-*N*-(2,6-diisopropylphenyl)-amine (Table 7, entry 1).** The general procedure was followed using 2,4,6-triisopropylbromobenzene (0.694 mL, 3.0 mmol), 2,6-diisopropylaniline (0.678 mL, 3.6 mmol), NaO-*t*-Bu (432 mg, 4.5 mmol), Pd-complex-**5** (22.82 mg, 0.03 mmol), and toluene (4 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: hexanes) to afford 1.11 g (98%) of the desired product as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.06−7.25 (m, 4H), 4.90 (bs, 1H), 3.14−3.30 (m, 4H), 2.29−3.01 (sept, 1H), 1.51 (d, 6H, J = 6.9 Hz), 1.22−1.32 (m, 24H) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 143.9, 142.1, 414.3, 140.2, 138.4, 124.2, 122.3, 121.9, 34.3, 28.2, 28.2, 28.1, 27.9, 24.6, 24.0, 23.9 ppm; HRMS *m*/*z* Calcd for $C_{27}H_{41}N$: 379.32390. Found: 379.32452.

Product in Table 7, Entry 12. The general procedure followed using 5-chloro-1,3-benzodioxole (0.350 mL, 3.0 mmol), morpholine (0.312 mL, 3.6 mmol), NaO-*t*-Bu (432 mg, 4.5 mmol), Pd-complex-**5** (22.82 mg, 0.03 mmol), and toluene (4 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 8% ethyl acetate/hexanes) to afford 0.539 g (86%) of the desired product as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.72 (d, 1H, J = 8.4 Hz), 6.54 (d, 1H, J = 2.4 Hz), 6.33 (*dd*, 1H, $^3J_{H-H}$ = 8.4 Hz, $^4J_{H-H}$ = 2.4 Hz), 5.88 (s, 2H), 3.82 (m, 4H), 3.01 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 148.5, 147.6, 414.9, 108.8, 108.4, 101.2, 99.8, 67.2, 51.2 ppm; HRMS *m*/*z* Calcd for $C_{11}H_{13}NO_3$: 207.08954. Found: 207.08980.

Product in Table 7, Entry 14. The general procedure was followed using 2-chloropyrimidine (0.343 mL, 3.0 mmol), *N*-ethylbenzylamine (0.527 mL, 3.6 mmol), NaO-*t*-Bu (432 mg, 4.5 mmol), Pd-complex-**5** (22.82 mg, 0.03 mmol), and toluene (4 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 2% ethyl acetate/hexanes) to afford 0.609 g (95%) of the desired product as a syrupy liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.33 (m, 2H), 7.27 (m, 5H), 6.45 (m, 1H), 4.92 (s, 2H), 3.67 (m, 2H), 1.19 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.9, 158.1, 139.2, 128.7, 127.5, 127.2, 109.6, 49.9, 41.9, 12.6 ppm; HRMS *m*/*z* Calcd for $C_{13}H_{15}N_3$: 213.12660. Found: 213.12686.

Synthesis of (3a)Pd(cinnamyl)Cl (5). To a stirred solution of **4** (0.30 g, 0.6 mmol) in dry THF was added **3a** (0.60 g, 1.2 mmol) at room temperature. The reaction mixture was stirred for 3 h, and then the volatiles were removed, leaving **5** as a bright yellow solid (0.89 g, 99%). ^{31}P NMR (161.8 MHz, C_6D_6, 25 °C): δ = 94.73 (d, $^2J_{P-P}$ = 8.4 Hz) and 13.0 ppm (br). ^{1}H NMR (400 MHz, C_6D_6, 25 °C): δ = 0.89 (d, 18H), 1.27 (d, 18H), 1.95 (sep, 3H), 2.60−3.40 (br m, 18H), 5.08 (dd, 1H), 5.69 (m, 1H), 7.20 (m, 3H) and 7.35 ppm (d, 2H). ^{13}C NMR (100.6 MHz, C_6D_6 25 °C): 137.1, 128.3, 127.3, 126.8, 108.9, 102.3, 102.0, 67.8, 55.0, 50.4, 48.4, 41.0, 30.1, 27.9, 25.5, 21.7. Anal. Calcd for $C_{35}H_{66}ClN_5P_2Pd$: C, 55.26; H, 8.74; N, 9.21; P, 8.14. Found: C, 56.01; H, 8.72; N, 9.28; P, 7.8.

Synthesis of (3a)Pd(crotyl)Cl (6). To a stirred solution of $[Pd(crotyl)Cl]_2$ (0.16 g, 0.41 mmol) in dry THF was added **3a** (0.41 g, 0.82 mmol) at room temperature. The reaction mixture was stirred for 3 h, and then the volatiles were removed under reduced pressure, leaving **2** as a bright yellow solid (0.55 g, 97%). ^{31}P NMR (161.8 MHz, C_6D_6, 25 °C): δ = 93.09 (s) and 13.23 ppm (br, d). ^{1}H NMR (400 MHz, C_6D_6, 25 °C): δ = 0.95 (d, 18 H), 1.31 (d, 18 H), 1.65 (m, 3H), 2.01 (m, 3H), and 2.60−3.50 ppm (br, 20H). ^{13}C NMR (100.6 MHz, C_6D_6 25 °C): δ = 17.6, 21.9, 28.3, 30.3, 48.7, 50.9, 55.5, 102.1, and 114.0 ppm. Anal. Calcd for $C_{30}H_{65}ClN_5P_2Pd$: C, 51.50; H, 9.36; N, 10.01. Found: C, 51.00; H, 8.80; N, 10.03.

Synthesis of 3d. To a stirred solution of $HN{=}P(i\text{-}BuNCH_2CH_2)_3N)$[30] (0.50 g, 1.40 mmol) in dry toluene (15 mL) at room temperature was added proazaphosphatrane **1a** (0.48 g, 1.40 mmol) followed by Cy_2PCl (0.39 g, 1.40 mmol). The reaction mixture was then heated at 80 °C for 12 h. Evaporation of the solvent and other volatiles under reduced pressure left a colorless sticky solid residue which was extracted into dry diethyl ether (30 mL) leaving the hydrochloride salt of **1a** $[HP[(i\text{-}BuNCH_2CH_2)_3N]Cl]$ behind. Volatiles were removed under reduced pressure, which provided a sticky solid residue. Addition of about 2 mL of dry acetonitrile quickly resulted in the formation of a white solid **3d** that was filtered and dried under reduced pressure (0.68 g, 88%). ^{31}P NMR (161.8 MHz, C_6D_6, 25 °C): δ = 61.05 (d, $^2J_{P-P}$ = 66.8 Hz) and 18.57 ppm (d, $^2J_{P-P}$ = 66.8 Hz); ^{1}H NMR (400 MHz, C_6D_6, 25 °C): δ = 1.05 (d, 18 H), 1.44 (m, 11 H), 1.68−1.85 (*m*, 4H), 1.90−2.10 (m, 4H), 2.23 (m, 7H), 2.48 (t, 6H) and 2.72 ppm (br, 11H); ^{13}C NMR (100.6 MHz, C_6D_6 25 °C): δ = 55.2, 55.2, 55.1, 55.1, 50.3, 49.2, 49.2, 41.8, 41.7, 41.6, 41.5, 30.5, 30.3, 29.5, 29.3, 29.2, 29.1, 29.1, 29.6, 29.0, 28.8, 28.7, 28.0, 21.4 ppm. HRMS *m*/*z* Calcd for $C_{30}H_{61}N_5P_2$: 553.4402. Found: 553.44114.

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Supporting Information Available: Complete experimental details, references to the known compounds, copies of ^{1}H and ^{13}C NMR spectra for all coupling products, and the preparation of **3c**. Details of the X-ray data collection, structure solution, and structure refinement; tables of crystal data, atomic coordinates, bond distances, and bond angles for compound **5** and **6** and their cif files. This material is available free of charge via the Internet at http://pubs.acs.org.

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