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Development of nonproprietary phosphine ligands for the Pd-catalyzed amination reaction

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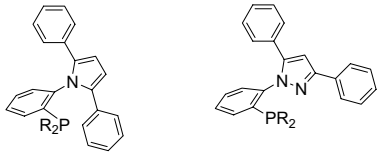
Abstract—A new family of pyrazole and bi-pyrazole phosphine ligands are reported that perform efficiently in the Pd-catalyzed amination reaction. Of the ligands screened, ligand **1** emerged as the most compatible for couplings involving both primary and secondary amines with typical yields of 84–99%.

Over the past decade, a considerable effort has been focused on the development of new ligands for expanding the applications of Pd-catalyzed reactions.[1] In the pharmaceutical industry, we have frequently relied on Pd-catalyzed processes for carrying out key bond formations.[2] Our industry has been particularly attracted to recent innovations of Pd-catalyzed amination reactions, since many potential drug candidates possess functionality easily accessed through this methodology.[3] A number of research groups in both academia and industry have pursued the development of ligands for the Pd-catalyzed amination reaction.[4] However, the majority of this work has been patented, which has encumbered our freedom to operate in this area.[5] A few years ago Pfizer initiated a program to develop phosphine ligands of comparable efficiency to those already recognized as optimally designed for the Pd-catalyzed amination reaction. We previously reported a series of biaryl ligands (Fig. 1; **2**–**5**) that are easily prepared,[6] but these ligands do not possess the general scope or exceptional catalytic activity of Buchwald's most efficient biaryl ligands.[7] Herein we describe a phosphine ligand (**1**) of modular design that has the breadth of substrate scope and catalytic activity to meet the majority of our needs. We note that the work described in this publication and our earlier communications[6] has not been patented and are, therefore, in the public domain so that all parties have free access to this technology.



2 R = *t*-Bu
3 R = Cyclohexyl

4 R = *t*-Bu
5 R = *i*-Pr

Figure 1. Previously prepared arylpyrrole and arylpyrazole phosphine ligands.

From our prior work, ligands **2**, **3**, **4**, and **5** were shown to perform adequately in the amination reaction, although ligand **4** appeared to be the most general of this set of ligands. It is readily prepared from the parent triphenylpyrazole by introducing the di-*tert*-butylphosphine via a directed lithiation.[8] Within this family of ligands we identified **2** as a ligand that performs very efficiently with primary amines, a difficult class of substrates for which even ligand **4** was not ideal.[9] We suspect that the excellent activity of this ligand is due to the two ortho substituents on the biaryl system, which block potential palladation of the arene and create a severe steric environment to promote reductive elimination.[10] Another advantage of ligand **2** (and **3**) is that the pyrrole nitrogen cannot complex to the Pd as readily as the pyrazole nitrogen in ligands **4** and **5**. We suspect that the less reliable activity of ligands **4** and **5** is due to nitrogen chelation, which ultimately makes these ligands incompatible with weak bases and other reaction conditions. Despite some clear advantages to the design of ligand **2**, we elected not to continue further studies with

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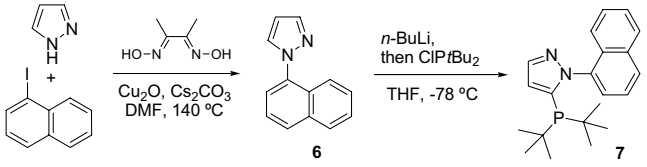
this particular ligand (**2**) due to the difficulty that we encountered in its preparation (a problematic lithiation/trapping with di-*tert*-butylchlorophosphine). Instead, we moved on to a design (**7**) that would avoid binding of the Pd to the heterocyclic nitrogens by introduction of the phosphine on the pyrazole of the biaryl system via a facile directed lithiation.

We began by preparing a series of ligands similar to **7**, which possess a pyrazole appended to an arene (Scheme 1).[11] Related ligands, using heterocycles other than pyrazole in the biaryl system, have been prepared by Degussa and are highly efficient in the Pd-catalyzed amination reaction.[12] For our series, pyrazole serves as an ideal handle for introducing the phosphine via directed lithiation. Of these ligands, **7** is fairly general in scope (Table 1) but for certain substrates reduction side products predominate. The reactions were conducted with 0.0025 equiv $Pd_2(dba)_3$, 0.015 equiv **7** and 2 equiv KOH or 1.25 equiv NaO*t*Bu in 1.0 M *tert*-amyl alcohol as solvent. KOH and NaO*t*Bu are interchangeable as bases and we observed that KOH outperforms NaO*t*Bu in some cases.

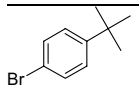
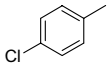
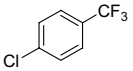
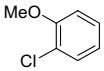
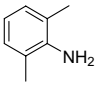
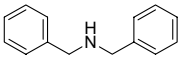
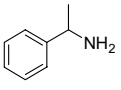
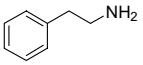
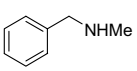


Scheme 1. Synthesis of pyrazole phosphine ligand **7**.

The preparation of **7** requires only two steps, but the synthesis requires a high temperature cross-coupling that is difficult to drive to completion and provides product **6** as an oil, which does not allow for a clean up prior to the lithiation. Because this process looked to be challenging to scale up, we decided to pursue the design of a ligand that would still have a related biaryl architecture but would avoid this assembly strategy. Our key design considerations were blocking the biaryl's ortho positions to palladation and utilizing a readily assembled crystalline core amenable to directed lithiation. The ligand we identified, which met these criteria, was **1**.

We were attracted to triphenyl-bi-pyrazole (**10**) derived ligands based on our past experience with this type of crystalline core (ligands **4** and **5**). With triaryl-bi-pyrazole-type ligands, we were able to accomplish facile lithiation on the less substituted pyrazole, which simplified their synthesis, and were able to avoid the issue of N–Pd coordination that plagues ligands **4** and **5** during coupling reactions. The preparation of **1** requires 4 steps, and is shown in Scheme 2. Each step is amenable to scale up, all raw materials are commodities, and the modular synthesis allows for modification of the substituents to probe structure–activity relationships within this family of ligands. The first step of the synthesis involves bromination of dibenzoylmethane.[13] On scale we elected to use pyridinium tribromide rather than bromine, due to the ease of handling the solid brominating reagent. The reaction is carried out in acetonitrile and upon completion, the product is crystallized from solution prior to quenching the reaction with sodium bisul-

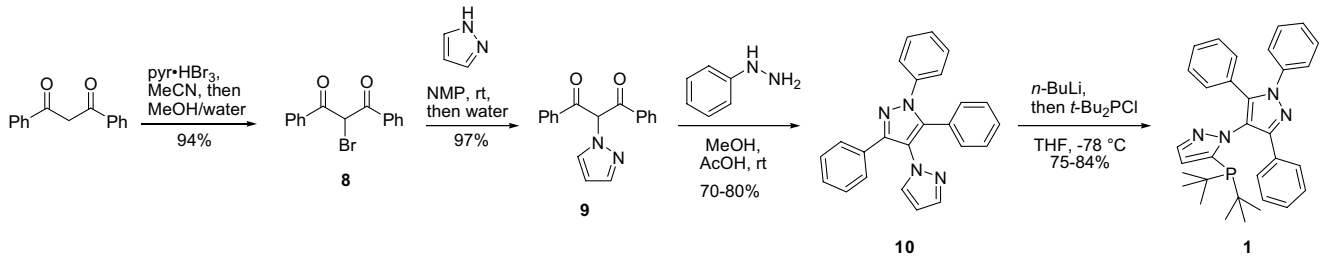
Table 1. Aryl amination reactions of primary and secondary amines with aryl halides catalyzed by $Pd_2(dba)_3$ with phosphine ligands **1** and **7**[a]

Amine	Ligand	Aryl halide (%)			
					
	**1**	99	99	97	99
	7	96	99	85	93
	**1**	99	94	93	99
	**1**	86	88	60	<5
	7	96	98	95	<5
	**1**	95	98	95	99
	7	99	80	99	96
	**1**	84	79	93	95
	7	90	79	40	87[b]
	**1**	96	98	87	93
	7	94	88	96	94
	**1**	95	99	92	98

Yields represent isolated, purified product.

[a] Conditions: 1.25 equiv amine, 1 equiv aryl halide, 0.0025 equiv $Pd_2(dba)_3$, 0.015 equiv ligand, 2 equiv KOH or 1.25 equiv NaO*t*Bu in *t*-amyl alcohol/water as solvent at 90 °C.

[b] Used 2% Pd.



Scheme 2. Preparation of bi-pyrazole phosphine ligand **1**.

fite.[14] The brominated diketone (**8**) is then alkylated with pyrazole in NMP at ambient temperature.[15] Once the alkylation is complete, water is added to ensure complete crystallization of the product, which is directly isolated from the reaction mixture. The second pyrazole ring is formed by condensation of **9** with phenylhydrazine in methanol and acetic acid.[16] In the absence of acetic acid a substantial amount of retro-aldol products are formed rather than the desired condensation product. As the condensation progresses under our optimized reaction conditions, the product crystallizes from solution. To maximize the recovery of the product, diisopropyl ether is added to the reaction mixture prior to filtration of crystalline **10**. To complete the synthesis, bi-pyrazole **10** is lithiated with *n*-BuLi at −78 °C in THF over 1.5 h.[17] During lithiation, the lithiated pyrazole crystallizes from solution as a white suspension. The anion is trapped with di-*tert*-butylchlorophosphine after gradual warming to ambient temperature to afford **1** as a crystalline solid.[18]

When screening ligand **1**, we immediately recognized that we had developed a robust catalyst with a relatively broad substrate scope (Table 1) that included arylchlorides.[19] We had initially screened primary amines, which tend to be the most problematic since they are more susceptible to β-hydride elimination, and they tend to form bis(amine)-Pd complexes, which impede catalysis.[20] With our past ligands (including **7**), the combination of phenethylamine and chlorobenzotrifluoride resulted in low yields due to substantial reduction side products. With the current ligand (**1**), this issue with reduction side products is diminished, as realized by the 93% yield. Most of the model substrates coupled efficiently using potassium hydroxide (2 equiv) as the base in *tert*-amyl alcohol (1.0 M) and water (0.04 M) as solvent at 90 °C, at the loading of 0.25 mol % $Pd_2(dba)_3$ with 1.5 mol % **1**.[21] Typically, the couplings are complete within 30 min for couplings involving 2,6-dimethylaniline or morpholine, while couplings utilizing primary amines are allowed to heat for 2–5 h before reaching completion. Of the substrates screened, only some reactions with dibenzylamine led to low yields. Virtually no product is formed in the coupling between dibenzylamine and chloroanisole,[22] and a very modest yield is realized when dibenzylamine is coupled with chlorobenzotrifluoride. Other substrate combinations with issues include couplings with bromonitrobenzene, which result in no conversion, most likely due to electron transfer to the Pd, and couplings with 2-chloropyridine, which result in incomplete conversions with all amines at low catalyst loading.[23] Coupling reactions with benzophenone imine are unreliable due to the variable levels of ammonia present in the starting imine that inhibit the Pd catalyst; however, benzophenone hydrazone was found to be an ideal substrate when coupled with 4-bromo-*tert*-butylbenzene (97% isolated yield). Regarding the Pd source, we found that $Pd_2(dba)_3$ is more reliable than $Pd(OAc)_2$, especially with primary amines.[24] A minimal amount of water is added to the reactions to help dissolve the base (KOH) and the salt by-products. Adding more water does slow down the reaction rate but does not ultimately limit the extent of conversion that is achieved.

We intend to continue to explore the reaction scope of ligand **1** to identify in which cross-coupling applications it is most efficient, and we hope to identify a more reliable ligand for heterocyclic substrates (most notably 2-chloropyridine). We are considering bidentate ligands as a viable alternative for use with the heterocyclic substrates, especially in light of prior reports suggesting that BINAP[25] or Xantphos[26] can be highly effective with chloropyridines.[27] Overall, the modular design of ligand **1** should enable facile preparation of derivatives to probe other members of this family of ligands and optimize our design to specific substrate classes.

References and notes

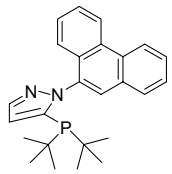
1. (a) *Metal-Catalyzed Cross-Coupling Reactions*; 2nd ed.; de Meijere, A., Diederich, F., Eds., Wiley-VCH: Weinheim, Germany, 2004; (b) Tsuji, J. In *Palladium Reagents and Catalysts, Innovations in Organic Synthesis*; John Wiley and Sons: New York, 1996.
2. (a) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366; (b) Herrmann, W. A.; Ofele, K.; von Preysing, D.; Schneider, S. K. *J. Organomet. Chem.* **2003**, *687*, 229; (c) Yasuda, N. *J. Organomet. Chem* **2002**, *653*, 279.
3. Lednicer, D. In *Strategies for Organic Drug Synthesis and Design*; Wiley: New York, 1998.
4. Reviews on catalyst development for the amination reaction in industry and academia: (a) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599; (b) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley-Interscience: New York, 2002; Vol. I, p 1051; (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.
5. Some groups with patents in this area include: MIT (Buchwald), Yale (Hartwig), Univ. New Orleans (Steve Nolan), Tosoh, Symyx, Degussa, and Takasago.
6. (a) Singer, R. A.; Tom, N. J.; Frost, H. N.; Simon, W. M. *Tetrahedron Lett.* **2004**, *45*, 4715; (b) Singer, R. A.; Caron,

S.; McDermott, R. E.; Arpin, P.; Do, N. M. *Synthesis* **2003**, 1727.

7. X-Phos and related biaryl ligands have been shown to possess excellent catalytic efficiency in the Pd-catalyzed amination reaction, see: (a) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653; (b) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978.
8. For directed lithiations on pyrazoles, see: Micetich, R. G.; Baker, V.; Spevak, P.; Hall, T. W.; Bains, B. K. *Heterocycles* **1985**, *23*, 943.
9. Ligand **4** failed to operate effectively with many primary amines, especially when attempting couplings with electron rich aryl halides.
10. For rationale on the biaryl design of phosphine ligands, see (a) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871; (b) Kocovsky, P. et al. *J. Am. Chem. Soc.* **1999**, *121*, 7714.
11. Ligand **7** was prepared in two steps by a cross-coupling between pyrazole and iodonaphthalene using literature conditions (Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Eur. J. Org. Chem.* **2004**, 695), followed by a directed lithiation. A solution of 2.5 M *n*-BuLi in hexanes (7.6 mL, 1.2 equiv) was added to a solution of 1-pyrazolylnaphthalene (3.08 g, 15.9 mmol, 1 equiv) in THF (32 mL) at −78 °C. The solution was stirred at −78 °C for 1.5 h and then di-*tert*-butylchlorophosphine (3.6 mL, 1.2 equiv) was added. The reaction mixture was allowed to warm to rt and stir for an additional hour. Then the reaction was worked up with MTBE (61 mL) and water (37 mL). The organic layer was washed with brine (25 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo to a volume of ~20 mL. Heptane (50 mL) and diisopropyl ether (24 mL) were added sequentially to the concentrate. This solution was further concentrated to a volume of about 20 mL and crystals formed. The crystals were stirred for 3 h at 0 °C and filtered to isolate **7** as a light tan solid (2.65 g, 50%). Mp 125–126 °C; ^{1}H NMR ($CDCl_3$): δ 7.95 (d, $J = 7.9$ Hz, 1 H), 7.88 (d, $J = 7.7$ Hz, 1H), 7.87 (d, $J = 2.1$ Hz, 1H), 7.55–7.45 (m, 3H), 7.38 (dt, $J = 8.3$, 0.83 Hz, 1H), 7.16 (t, $J = 8.3$ Hz, 1H), 6.88 (t, $J = 2.1$ Hz, 1H), 1.19 (br s, 9H), 1.06 (br s, 9H); ^{13}C NMR ($CDCl_3$): $\delta = 142.0$ (d, $J = 26$ Hz), 139.8, 137.8, 134.3, 131.6, 129.7, 128.1, 127.1 (d, $J = 3.8$ Hz), 126.9, 126.6, 124.7, 124.0, 113.2 (d, $J = 4.5$ Hz), 32.1 (d, $J = 19$ Hz), 30.6 (d, $J = 14.3$ Hz); Anal. Calcd for $C_{21}H_{27}N_2P$: C, 74.53; H, 8.04; N, 8.28. Found: C, 74.43; H, 8.11; N, 8.18.
12. Beller and Degussa prepared ligands related to **7** based on a heterocyclic-biaryl design, see: (a) Zapf, A. et al. *Chem. Commun.* **2004**, 38; (b) Harkal, S.; Rataboul, F.; Zapf, A.; Fuhrmann, C.; Riermeier, T.; Monsees, A.; Beller, M. *Adv. Synth. Catal.* **2004**, *346*, 1742; (c) Rataboul, F.; Zapf, A.; Jackstell, R.; Harkal, S.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 2983.
13. Preparation of **8**: A solution of pyridinium tribromide (38.2 g, 1.3 equiv) in acetonitrile (80 mL) was added to a solution of dibenzoylmethane (20.0 g, 89.2 mmol, 1 equiv) in acetonitrile at 10–15 °C (80 mL) over 15–30 min. The reaction was allowed to stir for 30 min at 10–15 °C. The reaction was diluted with methanol (100 mL), followed by slow addition of water (200 mL) over 15 min at 10–15 °C to crystallize **8**. The reaction mixture was cooled to 0 °C and stirred for about 1 h. The yellow suspension was then treated with an aqueous solution of sodium bisulfite (5.0 g in 40 mL of water) at 0 °C to reduce excess bromine. After stirring for 15 min at 0 °C, the suspension was filtered and the filtercake was washed with a cold 1:1 mixture of methanol and water to afford **8** as a white, crystalline solid (25.3 g, 94%). Mp 87–88 °C; ^{1}H NMR ($CDCl_3$): δ 7.98 (d, $J = 7.5$ Hz, 4H), 7.59 (t, $J = 7.5$ Hz, 2H), 7.46 (t, $J = 7.5$ Hz, 4H), 6.54 (s, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 189.2$, 134.5, 134.0, 129.5, 129.2, 52.9; Anal. Calcd for $C_{15}H_{11}BrO_2$: C, 59.43; H, 3.66; N, 0.0. Found: C, 59.27; H, 3.33; N, <0.05.
14. Quenching the reaction with **8** still in solution results in some reduction of **8** to the starting material, which complicates subsequent steps.
15. Note that **9** is isolated as a mixture of keto (major) and enol (minor) forms. Preparation of **9**: Pyrazole (17.1 g, 3 equiv) was added to a solution of **8** (25.3 g, 83.5 mmol, 1 equiv) in NMP (50 mL) at rt. After stirring at rt for 48 h, the product had crystallized. Water (270 mL) was added to the reaction mixture over 15 min to completely crystallize **9**, and the slurry was stirred for another 6 h. The reaction mixture was filtered and the filtercake was washed with water. The product, **9**, was isolated as an off-white to pale yellow solid (23.7 g, 97%) as a >10:1 ratio of keto/enol forms (NMR data reported for the major keto form). Mp 135–137 °C; ^{1}H NMR ($CDCl_3$): δ 7.64 (d, $J = 2.1$ Hz, 1H), 7.41–7.36 (m, 2H), 7.27–7.23 (m, 9H), 7.18 (d, $J = 2.1$ Hz, 1H), 6.25 (t, $J = 2.1$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 187.5$, 141.2, 134.7, 134.2, 132.1, 128.5, 128.0, 108.1; Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.50; H, 4.86; N, 9.60.
16. Preparation of **10**: A solution of phenyl hydrazine (12.0 mL, 1.5 equiv) in methanol (24 mL) was added to a suspension of **9** (23.8 g, 82.0 mmol, 1 equiv) in methanol (48 mL) and acetic acid (48 mL). After 24 h the reaction mixture was diluted with diisopropyl ether (240 mL). The crystals were stirred for 24 h and then cooled to 0 °C and stirred an additional hour before filtering. The filtercake was washed twice with diisopropyl ether, and **10** was isolated as a white solid (23.6 g, 80%). Mp 168–169 °C; ^{1}H NMR ($CDCl_3$): δ 7.75 (d, $J = 2.1$ Hz, 1H), 7.44–7.11 (m, 16H), 6.33 (d, $J = 2.1$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 148.1$, 141.2, 141.1, 140.0, 133.1, 131.1, 129.5, 129.3, 129.2, 128.7, 128.6, 128.1, 127.8, 127.0, 125.5, 121.2, 112.5, 107.1; Anal. Calcd for $C_{24}H_{18}N_4$: C, 79.54; H, 5.01; N, 15.46. Found: C, 79.16; H, 4.87; N, 15.30.
17. Preparation of **1**: **10** (50.1 g, 138.3 mmol) was dissolved in THF (400 mL) and cooled to −78 °C. A solution of 2.5 M *n*-butyllithium in hexanes (66.0 mL, 166 mmol) was added and the resulting reaction mixture was stirred at −78 °C for 1.5 h. At this time, di-*tert*-butylchlorophosphine (32 mL, 166 mmol) was added. The reaction mixture was allowed to gradually warm to room temperature over 1 h and was stirred at room temperature for an additional hour. The reaction was quenched with water (300 mL) and was diluted with *tert*-butyl methyl ether (600 mL). The organic layer was separated and washed with brine (200 mL). The organic layer was then dried over anhydrous sodium sulfate and concentrated in vacuo to a total volume of about 200 mL. The solution was diluted with *tert*-butyl methyl ether (400 mL) and was concentrated to a volume of about 300 mL. Crystals began to form and the suspension was cooled to 0 °C to crystallize more material. After stirring for 2 h, the mixture was diluted with heptane (600 mL) to induce further crystallization and the slurry was stirred for 4 h before filtration. The filtercake was washed with heptane to afford **1** as a white solid (59.0 g, 84%). Mp 191–193 °C; ^{1}H NMR ($CDCl_3$): δ 7.93 (d, $J = 1.7$ Hz, 1H), 7.48–7.11 (m, 15H), 6.62 (d, $J = 1.7$ Hz, 1H), 0.69 (d, $J = 12.5$ Hz, 9H), 0.57 (d, $J = 12.5$ Hz, 9H); ^{13}C NMR ($CDCl_3$): $\delta = 150.0$, 143.5 (d, $J = 26$ Hz), 141.5, 140.4, 140.1, 132.3, 130.2, 129.0, 128.9, 128.8, 128.7, 128.5, 128.3, 127.8, 127.7, 125.8, 121.1, 113.9 (d, $J = 4.5$ Hz),

32.1 (d, $J = 18$ Hz), 32.1 (d, $J = 19$ Hz), 30.0 (d, $J = 27$ Hz), 29.8 (d, $J = 27$ Hz); Anal. Calcd for $C_{32}H_{35}N_4P$: C, 75.86; H, 6.96; N, 11.06. Found: C, 75.62; H, 6.96; N, 10.86.

18. This chemistry has been conducted on Kilo Lab scale to produce 2 kg batches of **1** without incident. Please contact the corresponding author for scaleup and process safety information.
19. Roy and Hartwig have demonstrated the problematic nature of arylchlorides in cross-coupling reactions, see: Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 13944.
20. (a) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2745; (b) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 3534.
21. General procedure for Pd-catalyzed amination reactions with ligand **1**: $Pd_2(dba)_3$ (6 mg, 0.0025 equiv), 19 mg of **1** (0.015 equiv) and 322 mg of KOH 87% pellets (2 equiv) in 2.5 mL of *tert*-amyl alcohol and 0.100 mL of water were added to a flask under nitrogen. After 5–10 min of stirring the dark solution (the pellets did not dissolve until heated or unless they were stirred longer at rt), the amine (1.25 equiv) was added followed by the aryl halide (2.5 mmol, 1.00 equiv). The resulting reaction mixture typically became an orange color and was heated to 90 °C. After 5 h the reaction was complete (consumption of halide by GC). The reaction was cooled to rt and diluted with 20 mL of MTBE and 10 mL of water. The organic layer was dried over sodium sulfate and concentrated in vacuo for purification on 35 mL of silica gel using hexane/ethyl acetate. Isolated yields of the products are reported in Table 1.
22. During the course of screening ligands, we had found that the ligand shown below (related to **7**) coupled 2-chloroanisole and dibenzylamine in 50% yield with 0.5 mol % Pd. However, this ligand failed to work as effectively with other substrates.



23. Increasing the catalyst loading to 2 mol % Pd typically resulted in conversions of 80–90% for 2-chloropyridine with the model amines that we used. Ligand **7** seemed to perform slightly better than ligand **1** with 2-chloropyridine, but still required the increased catalyst loading to achieve complete conversions.
24. When using $Pd(OAc)_2$ in couplings with primary amines, in some cases almost no product formation was observed. This could be due to a greater prevalence of bis-amine Pd complexes forming in the absence of dba, ultimately leading to catalyst deactivation.
25. Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7241.
26. Yin, J.; Zhao, M. M.; Huffman, M. A.; McNamara, J. M. *Org. lett.* **2002**, *4*, 3481.
27. We already have preliminary results indicating that it is possible to lithiate **10** twice and to trap with chlorophosphines. We intend to evaluate other trapping agents that would lead to systems with heteroatoms other than phosphorus serving as a secondary contact to Pd.