Ammonia Arylation

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A P,N-Ligand for Palladium-Catalyzed Ammonia Arylation: Coupling of Deactivated Aryl Chlorides, Chemoselective Arylations, and Room Temperature Reactions**

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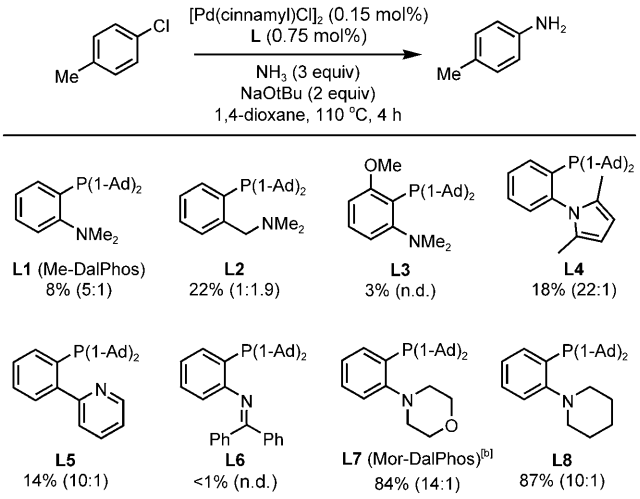
Ammonia is an abundant and inexpensive nitrogen source that represents an ideal reagent for amine synthesis. Despite its tremendous potential to provide more direct and economical routes to nitrogen-containing molecules, the use of ammonia in transition-metal-catalyzed reactions has only very recently begun to be realized.[1] The copper- or palladium-catalyzed cross-coupling of aryl halides and amines is a well-established and important method for the synthesis of arylamines in both academic and industrial settings,[2] and recent advances in catalyst design have enabled the use of ammonia as a coupling partner to generate primary arylamines.[3–7] Despite the success of these initial reports, a number of serious limitations regarding the scope and utility of metal-catalyzed cross-couplings of aryl halides and ammonia still exist and must be addressed before this method can be considered a viable alternative to more traditional aniline syntheses. In the case of copper, high loadings of metal and ligand are typically required (10–50 mol%) and less reactive but more economically attractive aryl chlorides,[8] or more readily accessible pseudohalides derived from phenols, are poor reaction partners.[3] Limitations regarding the palladium-catalyzed cross-coupling of ammonia[4–7] include the coupling of electron-rich, sterically unbiased aryl chlorides as well as the selective coupling of ammonia in the presence of additional amine functionality (chemoselectivity).[9] In addition, currently known systems require catalyst loading of 0.5–5 mol% of palladium as well as elevated temperatures (70–120 °C) to maintain reasonable activity for even simple aryl chloride substrates. The slow rate of oxidative addition of electron-rich aryl chlorides, combined with a lower tendency for such species lacking *ortho*-substitution to undergo reductive elimination[10] from the requisite [L_nPd(Ar)amido] species, can provide a rationale for the difficulties posed by such reaction partners and the elevated reaction temperatures required for catalyst turnover. Herein, we report the preparation of a suitably designed P,N-ligand that addresses several of the above-described challenges in ammonia cross-coupling, including highly chemoselective transformations and the first report of aryl chloride and aryl tosylate coupling with ammonia at room temperature.

Recently, we initiated a research program employing P,N-ligands as alternatives to more traditional archetypes in C–N coupling reactions. We envisioned that easily prepared and tunable ligands of this type might provide a useful middle ground in Buchwald–Hartwig aminations between strongly chelating bisphosphanes[2a] and biarylmonophosphanes[2b] that feature only weak secondary metal–ligand interactions. We have found **L1** (Me-DalPhos) to be a broadly useful ligand for the palladium-catalyzed cross-coupling of aryl chlorides and amines (including ammonia); however, modestly electron-rich substrates lacking *ortho*-substitution gave very poor results, requiring harsh reaction conditions and giving undesired diarylamines as the major product.[11,12a] Indeed, within the field of palladium-catalyzed cross-coupling of ammonia, only the Josiphos/[Pd{P(*o*-tol)$_3$}$_2$] system developed by the Hartwig group has been reported to effect reactions of this type (4-chlorotoluene, 55% yield; 1 mol% of Pd at 100 °C; TOF = 5.5 h^{-1}).[7] With the aim of addressing some of the outstanding issues in ammonia arylation catalysis, a series of air-stable phenylene-bridged P,N-ligands featuring the bulky di(1-adamantyl)phosphino (P(1-Ad)$_2$) fragment were synthesized (**L2**–**L8**; Scheme 1). Although attempts to cross-couple 4-chlorotoluene under the challenging test conditions (0.3 mol% of Pd, 3 equiv of NH_3; 4 h) afforded poor



Scheme 1. Ligand screening for the palladium-catalyzed cross-coupling of ammonia and 4-chlorotoluene.[a] [a] Conversions and $ArNH_2$/Ar_2NH ratio (indicated in parenthesis) determined by GC analysis. [b] 99% conversion (15:1) after 16 hours. n.d. = not determined.

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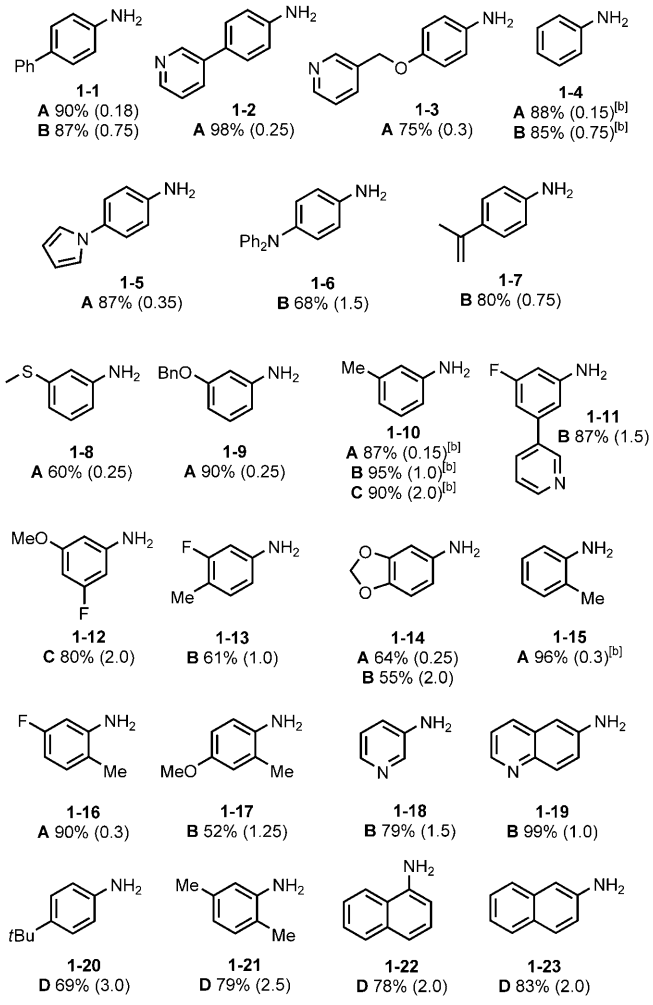
results for most of the ligands, the variant featuring an *ortho*-morpholino group (**L7**; Mor-DalPhos)[12a] gave exceptional results; at 110 °C, 84 % conversion was achieved after 4 hours (TOF = 70 h^{-1}), with an excellent mono- to diarylation ratio (14:1). Whereas the piperidine-derived ligand **L8** performed similarly well and exhibited only a modest decrease in selectivity, a variant of **L7** in which the $P(1\text{-Ad})_2$ group was replaced by PCy_2 was ineffective, only affording small amounts of diarylated product (approx. 10 %). Reactions conducted at 65 °C with **L7** were also successful when 1.5 mol % Pd was employed (98 % at 20 h; 23:1).[12b]

Having defined a catalyst system and reaction conditions for the cross-coupling of ammonia to a deactivated, sterically unbiased aryl chloride, we sought to explore the scope of reactivity (Scheme 2). Aryl chloride substrates possessing electron-donating groups at the *para*- or *meta*-positions were easily cross-coupled at 110 °C or 65 °C, including examples containing N-, O-, F- or S-heteroatoms. Catalyst loadings for the coupling of these challenging substrates remained low at 110 °C (0.3–0.6 mol % of Pd) and reasonable at 65 °C (1.5–4 mol % of Pd). Included in the numerous examples in Scheme 2 is the 3-fluoro-5-pyridyl-functionalized aniline **1-11**, a key intermediate in the synthesis of a potential antidepressant/anxiolytic agent.[13] This ammonia cross-coupling method (65 °C, 3 mol % of Pd, 87 % yield) offers a viable alternative to the reported nitro-reduction protocol mediated by a stoichiometric amount of $SnCl_2$.[13] 2-Substituted aryl chlorides were also suitable reaction partners, as were some heteroaromatic aryl chlorides.[14] In addition, reactions conducted at temperatures as low as 50 °C still gave excellent results (Scheme 2, **1-10** and **1-12**).

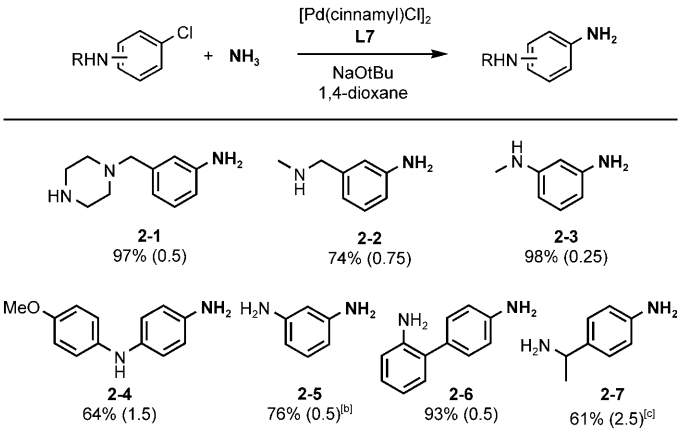
Easily prepared and inexpensive aryl tosylates are also suitable partners for ammonia cross-coupling when employing $[Pd(cinnamyl)Cl]_2$ and **L7** (Scheme 2, **1-20**–**1-23**);[15] reactions were conducted under exceptionally mild conditions (room temperature) with good yields for both unhindered substrates and 2-substituted aryl tosylates.[16]

Chemoselectivity in C–N coupling reactions employing ammonia remains a significant and unaddressed challenge.[17] Given the apparently high affinity for ammonia when conducting coupling reactions employing **L7** with $[Pd(cinnamyl)Cl]_2$, we attempted such transformations with aminoaryl chlorides containing NH functionalities (Scheme 3). Reactions of aminoaryl chlorides featuring secondary aryl/alkyl-, diaryl- or dialkylamines each afforded good to excellent yields (64–98 %) of the isolated ammonia-derived arylation product. Even more impressive was the ability of **L7** and $[Pd(cinnamyl)Cl]_2$ to selectively couple ammonia in the presence of both primary aryl- and alkylamines (Scheme 3, **2-5**–**2-7**).[18]

Given the unique activity of **L7** compared to more established bisphosphane[4,7] or biarylphosphane[5,6] ligands in the cross-coupling of ammonia, we attempted to gain insight regarding the nature of the metal–ligand interactions under conditions relevant to catalysis. Treatment of $[Pd(cinnamyl)Cl]_2$ and 2 equivalents of **L7** with NaO*t*Bu in



Scheme 2. Scope of ammonia cross-coupling to aryl chlorides and tosylates.[a] Reagents and conditions: [a] ArCl/NH_3/NaO*t*Bu = 1:3–4:2, [Pd]/**L7** = 1:2, [ArCl] = 0.10–0.05 M, (2–48 h; see the Supporting Information). Yields are of isolated material, mol % $[Pd(cinnamyl)Cl]_2$ indicated in parentheses. **A**: *T* = 110 °C. **B**: *T* = 65 °C. **C**: *T* = 50 °C. **D**: From the corresponding ArOTs at room temperature with [Pd]/**L7** = 1:1.5. [b] Yields were determined by GC analysis. Bn = benzyl.



Scheme 3. Chemoselective ammonia cross-coupling.[a] Reagents and conditions: [a] AminoarylCl/NH_3/NaO*t*Bu = 1:3–4:2, [Pd]/**L7** = 1:2, 110 °C, [ArCl] = 0.10–0.05 M. Yields are of isolated material, mol % $[Pd(cinnamyl)Cl]_2$ indicated in brackets. [b] Isolated as an 8:1 mixture of mono- and diarylation product in 96 % combined yield. [c] At 65 °C.

chlorobenzene at room temperature resulted in the quantitative formation (as evident by ^{31}P NMR spectroscopy) of a new species after 3 hours (Figure 1). Solution NMR spectros-

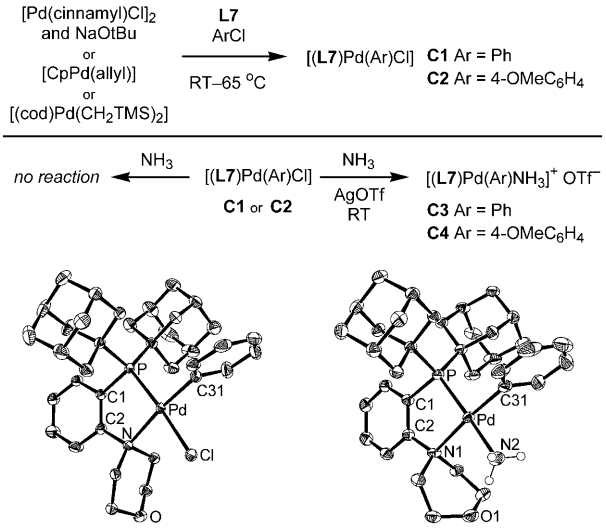
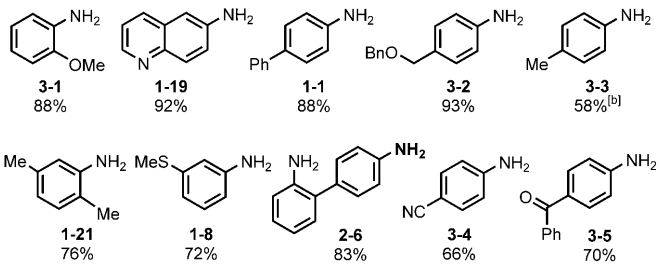


Figure 1. Reagents and conditions: **C1**: Route 1: [CpPd(allyl)] and **L7** in PhCl/THF (1:1), 65 °C, 12 h, 93%. Route 2: [(cod)Pd($CH_2TMS)_2$] and **L7** in PhCl, 40 min., RT, 99%. **C2**: [CpPd(allyl)] and **L7** in 4-chloroanisole/THF (1:1), 12 h, 65 °C, 79%. **C3** or **C4**: NH_3 (3 equiv), AgOTf (1.1 equiv), 30 min., RT (**C3** 90%; **C4** 84%). ORTEP diagrams of **C1** (left) and **C3** (right) shown with thermal ellipsoids at 50%; in **C3** some H atoms and OTf^- are omitted for clarity. cod = cycloocta-1,5-diene, Cp = cyclopentadienyl, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, TMS = trimethylsilyl.

copy and X-ray crystallographic studies confirmed the identity of this species as being the square planar Pd^{II} complex **C1**, in which **L7** is coordinated in a κ^2-*P,N* fashion with Cl *trans* to P.[19–21] Complex **C1** was also prepared successfully from alternative Pd sources in excellent yield ([CpPd(allyl)], 93%; [(cod)Pd($CH_2TMS)_2$], 99%). The analogous 4-anisolyl derivative **C2** was prepared in a similar manner and displays solution and solid state characteristics analogous to **C1**. Interestingly, no reaction was observed (as evident by ^{31}P NMR spectroscopy) upon exposure of **C1** to ammonia (2–10 equiv), thus suggesting that the N-donor arm of **L7** is not readily displaced from Pd during catalysis when employing ammonia as a substrate. In an effort to examine the reactivity of ammine ligated **L7** Pd^{II} species, the cationic ammonia adducts **C3** and **C4** were prepared in a high yield of isolated product by addition of AgOTf to either **C1** or **C2** in the presence of NH_3 (Figure 1). Treatment of **C3** with $NaN(TMS)_2$ at room temperature promoted the rapid reductive elimination of aniline from the unobserved intermediate [(**L7**)Pd(Ph)NH_2], which in turn regenerated **C1** as the major species (as evident by ^{31}P NMR spectroscopy) in the presence of chlorobenzene.

Employing **C1** as a precatalyst for ammonia arylation led to striking results: good to excellent conversions were observed for a number of aryl chloride substrates at room temperature (Scheme 4).[22] These conditions are considerably milder than the best conditions currently reported for such



Scheme 4. Room temperature cross-coupling of aryl chlorides and ammonia.[a] Reagents and conditions: [a] 5 mol% of **C1**, ArCl/NH_3/NaO*t*Bu = 1:3:2, [ArCl] = 0.10–0.06 M, at room temperature (1–24 h; see the Supporting Information). Yields are of isolated material. [b] Conversions were determined by GC analysis.

reactions. While the use of 5 mol% of **C1** enabled the rapid conversion of *ortho*-substituted or electron-poor aryl chlorides (> 95% conversion after 1–2 h), such substrate characteristics were not prerequisites for achieving high conversions and yields at room temperature. Even though a full understanding of the properties of **C1** that engender enhanced reactivity under mild conditions is currently lacking, [(**L7**)Pd(Ar)Cl] species, such as **C1,** may represent the active catalyst in cross-coupling reactions that employ [Pd(cinnamyl)Cl]$_2$/**L7** precatalyst mixtures. The direct use of **C1** may serve to by-pass undesirable side-reactions that may occur during catalyst activation steps.

In conclusion, we have developed an air-stable P,N-ligand (**L7**; Mor-DalPhos) that advances the scope and utility of palladium-catalyzed ammonia cross-coupling reactions. A variety of aryl chloride and aryl tosylate substrates can be coupled efficiently, most notably electron-rich species lacking *ortho*-substitution under a range of conditions. The unique preference for ammonia coupling when using Pd/**L7** mixtures can be exploited in unprecedented chemoselective arylations, and for the first time, the room temperature palladium-catalyzed cross-coupling of ammonia has been achieved. Our efforts to advance our understanding of the unprecedented catalytic performance of Pd/**L7**, and to further utilize such catalysts in challenging cross-coupling applications, will be the subject of future reports.

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[1] Selected recent examples: a) M. J. Pouy, L. M. Stanley, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, *131*, 11312; b) T. Nagano, S. Kobayashi, *J. Am. Chem. Soc.* **2009**, *131*, 4200; c) H. Rao, H. Fu, Y. Jiang, Y. Zhao, *Angew. Chem.* **2009**, *121*, 1134; *Angew. Chem. Int. Ed.* **2009**, *48*, 1114; d) C. Zhou, F. Chen, D. Yang, X. Jia, L. Zhang, J. Cheng, *Chem. Lett.* **2009**, *38*, 708; e) C. Gunanathan, D. Milstein, *Angew. Chem.* **2008**, *120*, 8789; *Angew. Chem. Int. Ed.* **2008**, *47*, 8661; f) V. Lavallo, G. D. Frey, B. Donnadieu, M.

Soleilhavoup, G. Bertrand, *Angew. Chem.* **2008**, *120*, 5302; *Angew. Chem. Int. Ed.* **2008**, *47*, 5224.

[2] For reviews, see: Pd: a) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534; b) D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 6438; *Angew. Chem. Int. Ed.* **2008**, *47*, 6338; c) S. L. Buchwald, C. Mauger, G. Mignani, U. Scholz, *Adv. Synth. Catal.* **2006**, *348*, 23; d) A. R. Muci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, *219*, 131; e) J. F. Hartwig in *Modern Arene Chemistry* (Ed.: D. Astruc), Wiley-VCH, Weinheim, **2002**, p. 107; Cu: f) F. Monnier, M. Taillefer, *Angew. Chem.* **2009**, *121*, 7088; *Angew. Chem. Int. Ed.* **2009**, *48*, 6954.

[3] a) H. Xu, C. Wolf, *Chem. Commun.* **2009**, 3035; b) L. Jiang, X. Lu, H. Zhang, Y. Jiang, D. Ma, *J. Org. Chem.* **2009**, *74*, 4542; c) D. Wang, Q. Cai, K. Ding, *Adv. Synth. Catal.* **2009**, *351*, 1722; d) Z. Guo, J. Guo, Y. Song, L. Wang, G. Zou, *Appl. Organomet. Chem.* **2009**, *23*, 150; e) N. Xia, M. Taillefer, *Angew. Chem.* **2009**, *121*, 343; *Angew. Chem. Int. Ed.* **2009**, *48*, 337; f) J. Kim, S. Chang, *Chem. Commun.* **2008**, 3052; g) M. K. Elmkaddem, C. Fischmeister, C. M. Thomas, J.-L. Renaud, *Chem. Commun.* **2010**, *46*, 925.

[4] Q. Shen, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 10028.

[5] D. S. Surry, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 10354.

[6] T. Schulz, C. Torborg, S. Enthaler, B. Schäffner, A. Dumrath, A. Spannenberg, H. Neumann, A. Börner, M. Beller, *Chem. Eur. J.* **2009**, *15*, 4528.

[7] G. D. Vo, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, *131*, 11049.

[8] A. F. Littke, G. C. Fu, *Angew. Chem.* **2002**, *114*, 4350; *Angew. Chem. Int. Ed.* **2002**, *41*, 4176.

[9] For a recent review, see: N. A. Afagh, A. K. Yudin, *Angew. Chem.* **2010**, *122*, 270; *Angew. Chem. Int. Ed.* **2010**, *49*, 262.

[10] J. F. Hartwig, *Inorg. Chem.* **2007**, *46*, 1936.

[11] R. J. Lundgren, A. Sappong-Kumankumah, M. Stradiotto, *Chem. Eur. J.* **2010**, *16*, 1983.

[12] a) Ligands **L1** (Me-DalPhos) and **L7** (Mor-DalPhos) are now commercially available from Strem Chemicals; b) the use of 3 equivalents of NH_3 gave superior results compared to 2 or 5 equivalents, and the [Pd]:**L7** appeared to be less important with minimal differences observed when varying the ratio from 1.5 to 4.

[13] S. M. Bromidge et al., *J. Med. Chem.* **2000**, *43*, 1123. See the full reference in the Supporting Information.

[14] Attempts to cross-couple 2-chloropyridines or 8-chloroquinoline led to nearly exclusive diarylation.

[15] a) Room temperature C–N coupling using ArOTs has been achieved recently with alternative amine coupling partners: T. Ogata, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 13848; b) the palladium-catalyzed amination of ArOTs substrates with ammonia at 50 °C has been reported.[7]

[16] Electron-poor aryl tosylates led to significant amounts of the corresponding phenol, as did aryl triflates.

[17] For selected reports on chemoselective amine cross-coupling, see: a) X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653; b) M. R. Biscoe, T. E. Barder, S. L. Buchwald, *Angew. Chem.* **2007**, *119*, 7370; *Angew. Chem. Int. Ed.* **2007**, *46*, 7232; c) B. P. Fors, D. A. Watson, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 13552.

[18] The cross-coupling of 2-bromoaniline and ammonia has been reported.[6]

[19] The *trans* disposition of P and Cl was confirmed in solution for **C1** and **C3** on the basis of nOe experiments. The Supporting Information contains experimental procedures and characterization data for all new compounds. CCDC 763339 (**C1**·CH_2Cl_2), CCDC 763337 (**C2**·CH_2Cl_2), and CCDC 763338 (**C3**·CH_2Cl_2) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[20] For a recent example of a (κ^2-*P,N*)Pd species relevant to cross-coupling catalysis, see: A. G. Sergeev, T. Schulz, C. Torborg, A. Spannenberg, H. Neumann, M. Beller, *Angew. Chem.* **2009**, *121*, 7731; *Angew. Chem. Int. Ed.* **2009**, *48*, 7595.

[21] While Kwong and co-workers workers have developed active P,N-ligands for palladium cross-coupling reactions, structural studies suggest that these coordinate in a (κ^2-*P,C*)Pd manner: a) C. M. So, Z. Zhou, C. P. Lau, F. Y. Kwong, *Angew. Chem.* **2008**, *120*, 6502; *Angew. Chem. Int. Ed.* **2008**, *47*, 6402; b) C. M. So, C. P. Lau, F. Y. Kwong, *Angew. Chem.* **2008**, *120*, 8179; *Angew. Chem. Int. Ed.* **2008**, *47*, 8059.

[22] To the best of our knowledge, the mildest example of palladium-catalyzed cross-coupling of aryl chlorides with NH_3 was reported by Vo and Hartwig[7] (70 °C; 200 psi NH_3), employing electronically activated substrates (benzoate or cyano).

