CHEMISTRY
A EUROPEAN JOURNAL

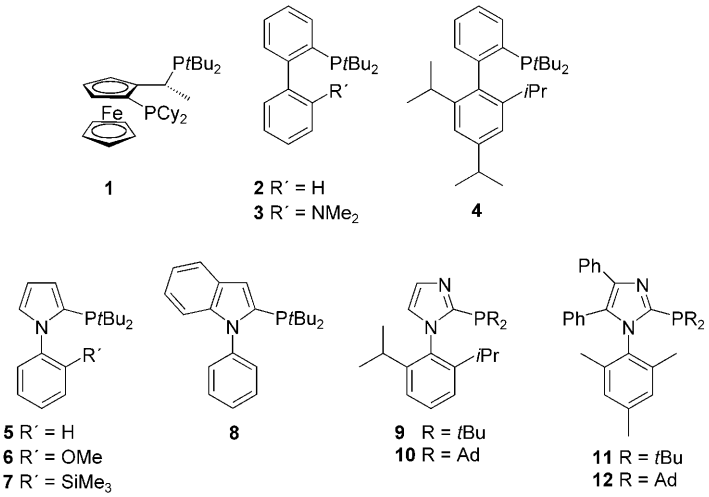
DOI: 10.1002/chem.200802678

A General Palladium-Catalyzed Amination of Aryl Halides with Ammonia

Thomas Schulz, Christian Torborg, Stephan Enthaler, Benjamin Schäffner, Andreas Dumrath, Anke Spannenberg, Helfried Neumann, Armin Börner, and Matthias Beller*[a]

Anilines are important intermediates in the manufacture of agrochemicals, dyes, pharmaceuticals, and other industrial products.[1] Hence, there is a continuing interest in easier and more cost-efficient preparations.[2] In the past decade transition-metal-catalyzed C–N bond-forming reactions have emerged as a potent tool for the production of aryl amines. Due to the seminal contributions of the groups of Buchwald and Hartwig, palladium-catalyzed C–N cross-coupling reactions of aryl halides with various *N*-nucleophiles have become one of the most valuable organic transformations.[3] Despite the impressive results in the production of secondary and tertiary amines,[4] relatively little work has been done on the amination of aryl halides to produce primary aryl amines. Problems encountered with the direct utilization of ammonia are: 1) the displacement of the ligand bound to the Pd center by ammonia leading to a catalytically non-reactive complex,[5] 2) the tendency of complexes bearing an amido group to form stable bridging structures,[6] and 3) the increased activity of a resulting primary aniline compared to ammonia leading to diaryl amines. To avoid these problems synthetic equivalents of ammonia have been employed including allyl,[7] benzyl,[8] and silyl amines,[9] imines,[10] and amides.[11] Unfortunately, the corresponding coupling products have to be cleaved after the reaction, which leads to unwanted side products.[12] Hence, the use of ammonia as an *N*-nucleophile is still by far the most desired approach[13] because of its inherent atom economy, and the low cost and availability of ammonia.[14]

In 2006, Hartwig and Shen[15] published the first selective palladium-catalyzed monoarylation of ammonia employing the bulky Josiphos bisphosphine **1** as ancillary ligand (Scheme 1). Simple alkyl-substituted aryl iodides, bromides, and even chlorides were converted successfully to the corresponding anilines in good yields. In addition, the isolation of the first organopalladium complex with a terminal NH_2-functionalized ligand and its reductive elimination of aryl amine were reported. Afterwards, Buchwald and Surry[16] published a Pd-catalyzed synthesis of anilines with ammonia using monophosphines **2**–**4**. Here, a mixture of $[Pd_2(dba)_3]$ (dba = *trans*,*trans*-dibenzylideneacetone) and dialkylphosphinobiphenyl ligand **3** gave the highest selectivity in the formation of anilines from the corresponding aryl bromides of all applied ligands. Although being quite efficient in the conversion of the substrates tested, both Hartwig and Buchwald[17] have not reported the conversion of more challenging substrates such as aminoaryl halides, halostyrenes, halopyridines, and functionalized aryl chlorides. Hence, there is still interest for more general procedures in the Pd-catalyzed monoarylation of ammonia.



Scheme 1. Active phosphine ligands for selective Pd-catalyzed amination of aryl halides.

It is important to note that besides palladium, the amination of aryl halides with ammonia is possible under copper

[a] T. Schulz, C. Torborg, Dr. S. Enthaler, B. Schäffner, A. Dumrath, A. Spannenberg, Dr. H. Neumann, Prof. Dr. A. Börner, Prof. Dr. M. Beller
Leibniz-Institut für Katalyse e.V. an der Universität Rostock
Albert-Einstein-Strasse 29a, 18059 Rostock (Germany)
Fax: (+49) 381-1281-5000
E-mail: matthias.beller@catalysis.de

catalysis. However, these procedures are limited to aryl iodides[18] and some bromides.[19] To date, efficient Cu-catalyzed coupling protocols of ammonia with aryl chlorides are not known.[20]

We have been interested in the development of new ancillary ligands for Pd-catalyzed coupling reactions for some time. Examples include di-1-adamantylphosphines (cata*CX*ium A),[21] carbene ligands,[22] and 2-phosphino-*N*-arylindoles and -pyrroles (cata*CX*ium P).[23] The latter ligands can be easily prepared by a two-step lithiation–phosphorylation method from the corresponding heterocycles. Such a modular synthesis is important in the fine chemical and pharmaceutical industry, since fine-tuning catalysts in cross-coupling reactions is often required. Recently, our group reported an efficient approach for the synthesis of novel bulky, electron-rich imidazole-based monophosphines[24] and their successful application in the Pd-catalyzed hydroxylation of aryl halides. Here, we report for the first time that 2-phosphino-*N*-arylpyrroles **5** and **7**, 2-phosphino-*N*-arylindole **8** , and dialkyl-2-(*N*-arylimidazolyl)phosphines **11** and **12** work well in the selective Pd-catalyzed amination of aryl halides to the corresponding aniline derivatives (Scheme 1).

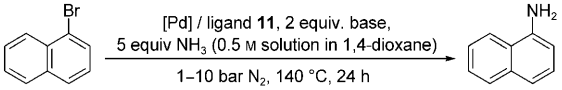
After some exploratory testing a catalyst derived from $[Pd(CH_3CN)_2Cl_2]$ and ligand **11** showed good activity in the amination of 1-bromonaphthalene with NaO*t*Bu and a 0.5 M solution of ammonia in 1,4-dioxane at 140 °C under a nitrogen atmosphere of 5 bar (Table 1). To determine the optimal reaction conditions different parameters such as palladium source, base, and nitrogen pressure were then screened. The use of NaO*t*Bu gave the best results in the model reaction, whereas all other tested bases including different inorganic phosphates, carbonates, and hydroxides remained ineffective. Interestingly, KO*t*Bu showed much worse results in C–N bond formation than NaO*t*Bu although the starting material was fully converted with both bases. Except for palladium on charcoal, the palladium source had no significant influence on the reaction; good to excellent yields (79–95 %) were achieved under all the reaction conditions studied. Increasing the pressure up to 10 bar gave slightly improved yield compared to 1 bar and 5 bar, respectively.

In comparison to the amination protocol adopted by Hartwig and Shen,[15] the preparation of a pre-catalyst system formed from the corresponding palladium source and phosphine and handling in a dry box under inert atmosphere are not required. The novel palladium/monophosphine catalyst system is formed in situ from the air- and moisture-stable *N*-aryl-2-(dialkylphosphino)imidazoles and the palladium source.

Next, different phosphine ligands were investigated in the model amination reaction and compared with commercially available ligands (Table 2). The *N*-phenylpyrrole/indole-substituted (**5**, **7**, and **8**)[23a,b] and the more sterically demanding imidazole-based phosphines **11** and **12**[24b] resulted in the highest yields up to 82 %. The 2-methoxy-functionalized ligand **6** showed a lower yield than the trimethylsilyl-substituted one, which is explained by the different electronic properties of both ligands. Evidently, small changes in the phosphine ligand have a significant influence on the catalytically active system. The very bulky ligands **9**, **10**, **13**, and **15** confirm this conclusion and gave the monoarylated amine in moderate yields (24–56 %). Notably, the more bulky adamantyl-substituted ligands are inferior compared to *tert*-butyl- and cyclohexyl-substituted ones (**9**, **10**, **13**), whereas ligands **11** and **12** do not show this dependency. The comparison of phosphine **14** and the 4,5-diphenyl-functionalized derivative **12** demonstrates that the phenyl backbone is responsible for an increase of the yield. This can be explained by steric as well as electronic factors. The bulkiness of **11** becomes evident considering Figure 1, in which its molecular structure (determined by X-ray analysis) is depicted. The commercially available ligands cata*CX*ium A (**16**) and tri-*tert*-butylphosphine (**17**) turned out to be ineffective for this transformation.

Finally, the scope of the catalyst system $Pd(OAc)_2$/**11** was examined by reacting various aryl bromides and chlorides with ammonia (available as a 0.5 M solution in 1,4-dioxane) in the presence of NaO*t*Bu as base at 120 °C and a nitrogen atmosphere of 10 bar. In some cases the use of the "simple" ligand **5** showed similar results and in one case (Table 3, entry 22) gave much better yield. Different alkyl- and aryl-

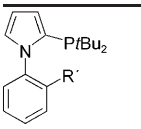
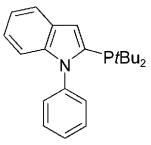
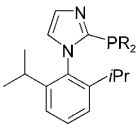
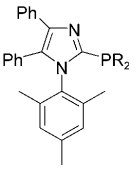
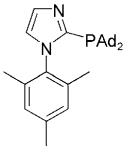
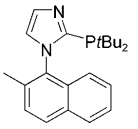
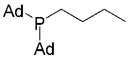
Table 1. Influence of different reaction parameters on the Pd-catalyzed amination of 1-bromonaphthalene.



	Conv. [%]	Yield [%][d]
Base[a]		
NaO*t*Bu	>99	79
NaOH	50	13
Na_3PO_4	<5	<1
Na_2CO_3	<5	<1
KO*t*Bu	>99	10
K_3PO_4	79	14
K_2CO_3	15	3
Cs_2CO_3	36	9
none	<10	<1
[Pd] source[b]		
$Pd(OAc)_2$	>99	95
$[Pd(dba)_2]$	>99	93
$[Pd(CH_3CN)_2Cl_2]$	>99	79
$PdCl_2$	>99	80
Pd/C	59	2
$p(N_2)$ [bar][c]		
1	>99	78
5	>99	79
10	>99	86

[a] 5 mol % $[Pd(CH_3CN)_2Cl_2]$, 10 mol % ligand **11**, 2 equiv base, 5 equiv NH_3 (0.5 M solution in 1,4-dioxane), 5 bar N_2, 140 °C, 24 h. [b] 5 mol % [Pd], 10 mol % ligand **11**, 2 equiv NaO*t*Bu, 5 equiv NH_3 (0.5 M solution in 1,4-dioxane), 5 bar N_2, 140 °C, 24 h. [c] 5 mol % $[Pd(CH_3CN)_2Cl_2]$, 10 mol % ligand **11**, 2 equiv NaO*t*Bu, 5 equiv NH_3 (0.5 M solution in 1,4-dioxane), 1–10 bar N_2, 140 °C, 24 h. [d] GC yields (internal standard: hexadecane).

Table 2. Ligands for Pd-catalyzed amination of 1-bromonaphthalene.[a]

Ligand		R	R′	Yield [%][b]
	**5**		H	80
	6		OMe	50
	7		$SiMe_3$	76
	**8**			80
	**9**	*t*Bu		51
	10	Ad		24
	13	Cy		56
	**11**	*t*Bu		82
	12	Ad		78
	**14**			50
	**15**			44
	**16**			2
$PtBu_3/HBF_4$	**17**			13

[a] 5 mol% $[Pd(CH_3CN)_2Cl_2]$, 10 mol% ligand, 2 equiv NaO*t*Bu, 5 equiv NH_3 (0.5 M solution in 1,4-dioxane), 5 bar N_2, 140 °C, 24 h. [b] GC yields (internal standard: hexadecane).

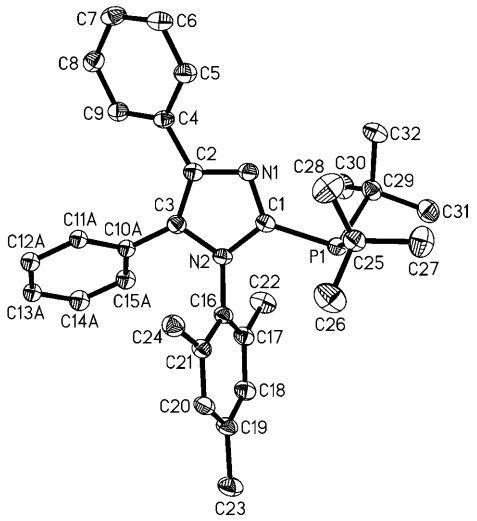
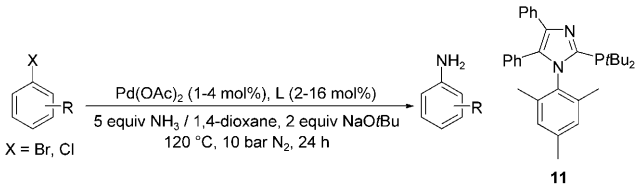
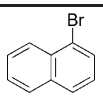
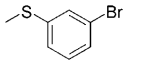
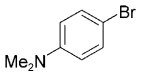
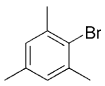
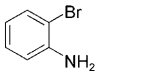
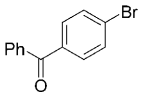
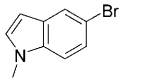
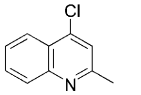
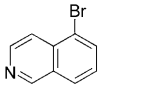
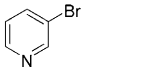
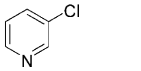
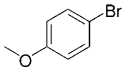
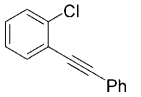


Figure 1. Molecular structure of ligand **11**. Hydrogen atoms are omitted for clarity. The thermal ellipsoids correspond to 30% probability.

Table 3. Palladium-catalyzed amination of aryl halides.[a]



Entry	Substrate	Yield [%][b]	Entry	Substrate	Yield [%][b]
1		93[c]			
2		67[d]	17		66[g]
3		93[e]			
4		90	18		70
5		95[c]			
6		95[e]	19		86[j]
7		70[f]			
8		96			
9		95[e]	20		80
10		72[f]			
11		75[g]	21		90
12		71	22		>99[k]
13		68[h]	23		70[l]
14		>99[i]	24		28[m]
15		89[i]	25		30[m]
16		68	26		53[n]

[a] 0.2 mmol aryl halide, 2 mol% $Pd(OAc)_2$, 8 mol% ligand **11**, 2 equiv NaO*t*Bu, 2.0 mL 0.5 M NH_3/1,4-dioxane, 10 bar N_2, 120 °C, 24 h. [b] GC yields (internal standard: hexadecane). [c] With ligand **5**, 96% yield. [d] Carried out in a pressure tube under an atmospheric pressure of argon. [e] 1 mol% $Pd(OAc)_2$, 4 mol% ligand **11**. [f] 1 mol% $Pd(OAc)_2$, 2 mol% ligand **11**. [g] With 16 mol% of ligand **11**. [h] Product: 2-chloroaniline. [i] Product: 2-aminoaryl halide. [j] With ligand **5**, 89% yield. [k] With ligand **5**; with ligand **11**, 48% yield. [l] With ligand **5**, 78% yield. [m] With 4 mol% $Pd(OAc)_2$, 16 mol% ligand **11**. [n] Isolated yield.

substituted bromides and chlorides (Table 3, entries 1, 4, 5, 8, 11) were allowed to react to give the corresponding aniline derivatives in good to excellent yields (75–96%). Notably, the monoarylation with ammonia also proceeds under atmospheric pressure in a pressure tube under argon at 120 °C. The formation of 1-naphthylamine was observed in a slightly lower yield of 67% (Table 3, entry 2). For selected aryl bromides and chlorides (Table 3, entries 3, 6, and 9) it could be shown that with a lower catalyst loading (1 mol% $Pd(OAc)_2$, 4 mol% ligand **11**) excellent results can be ob-

tained, too, whereas a Pd/ligand ratio of 1:2 (Table 3, entries 7 and 10) gives yields of around 70% under otherwise identical reaction conditions. To our delight, 2-chlorostyrene was converted to the corresponding 2-aminostyrene in good yield (71%; Table 3, entry 12). As expected, the substitution of bromide is preferred, if a bromide ligand competes with a chloride ligand, and no significant amount Cl-substituted product is formed (Table 3, entry 13; 68% yield). Noteworthy is that the reaction of the corresponding 1,2-dihalides selectively yielded the monoaminated products in excellent yields (Table 3, entries 14, 15; 89–99%). The activated 4-bromobenzophenone (Table 3, entry 20; 80% yield) and deactivated bromoarenes such as anisole, thioanisole, and *N*,*N*-dimethylbenzene (Table 3, entries 16–18; 66–70% yield) were also fully converted. The conversion of 2-bromoaniline proceeded smoothly to give the corresponding 1,2-diaminobenzene in 86% yield (Table 3, entry 19). Next, some *N*-heteroaryl bromides and chlorides were investigated.

Full conversion is observed for *N*-methylindole and isoquinoline (Table 3, entries 21 and 23; 70–90% yield), whereas the reaction of pyridine (Table 3, entries 24 and 25; 28–30% yield) gave the desired products in only moderate yields. Notably, in comparison to ligand **11**, the pyrrole-based phosphine **5** gave much better results in the amination of 4-chloroquinaldine (Table 3, entry 22; >99% yield). 1-Chloro-2-(phenylethynyl)benzene (Table 3, entry 26), which was synthesized by a Sonogashira reaction of phenylacetylene and 1-bromo-2-chlorobenzene with ligand **10**, is successfully converted to the corresponding amine in 53% yield.[25]

In summary, a new robust palladium/phosphine catalyst system for the selective monoarylation of ammonia with different aryl bromides and chlorides has been developed. The active catalyst is formed in situ from $Pd(OAc)_2$ and air- and moisture stable phosphines as easy-to-handle pre-catalysts. The productivity of the catalyst system is comparable to that of competitive Pd/phosphine systems;[15,16] full conversion is achieved with most substrates with 1–2 mol% of Pd source and a fourfold excess of ligand. One can conclude that the novel electron-rich and sterically demanding phosphine ligands cannot be displaced from the palladium by ammonia to a significant extent; thus, the deactivation of the catalyst is prevented by the ligands. Furthermore, a subsequent reaction of the resulting aniline derivatives to the corresponding diaryl amines was not observed. Although giving a slightly lower yield of the aniline product, it is demonstrated that the Pd-catalyzed amination process also works at ambient pressure. Notably, the optimized system showed an excellent substrate scope including deactivated, electron-neutral, and activated halides, *o*-, *m*-, and *p*-substituted substrates, aryl chlorides, as well as heterocycles. In contrast to the previously reported Pd-catalyzed procedures, the effective conversion of halostyrenes, haloindoles, and aminoaryl halides is possible with this system. The most active ligands are either commercially available (ligands **5**, **8**)[26] or can be easily synthesized by the previously reported procedure (ligands **11**, **12**).[24b]

Experimental Section

General: All reactions were performed under a nitrogen atmosphere (1–10 bar) using an eightfold parallel autoclave. All starting materials and reactants were used as received from commercial suppliers. Phosphine ligands were stored in Schlenk flasks but weighed under air. NMR spectra were recorded on an ARX300 (Bruker) spectrometer; chemical shifts are given in ppm and are referenced to TMS or the residual non-deuterated solvent as internal standard. Mass spectra were recorded on an AMD 402 double focusing, magnetic sector spectrometer (AMD Intectra). GC-MS spectra were recorded on a HP 5989 A (Hewlett Packard) chromatograph equipped with a quadropole analyzer. Gas chromatography analyses were performed on a HP 6890 (Hewlett Packard) chromatograph using a HP 5 column. All yields were determined by calibration of the corresponding anilines with hexadecane as internal standard and analysis by using gas chromatography.

X-ray structure determination: $C_{32}H_{39}N_2P$, $M_r = 482.62$, colorless crystal, $0.50 \times 0.30 \times 0.13$ mm, orthorhombic, space group $P2_12_12_1$, $a = 10.3780(3)$ Å, $b = 10.7916(3)$ Å, $c = 25.6151(6)$ Å, $V = 2868.76(13)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.117$ g cm^{-3}, $\mu = 0.117$ mm^{-1}, $T = 200$ K, 41509 measured, 5645 independent reflections ($R_{int} = 0.0439$), of which 4297 were observed ($I > 2\sigma(I)$), $R_1 = 0.0302$ ($I > 2\sigma(I)$), $wR_2 = 0.0595$ (all data), 296 refined parameters. Data were collected on a STOE IPDS II diffractometer using graphite-monochromated $Mo_{K\alpha}$ radiation. The structure was solved by direct methods (SHELXS-97: G. M. Sheldrick, University of Göttingen, Germany, **1997**) and refined by full-matrix least-squares techniques on F^2 (SHELXL-97: G. M. Sheldrick, University of Göttingen, Germany, **1997**). XP (Bruker AXS) was used for graphical representation. All fully occupied non-hydrogen atoms were refined anisotropically. One phenyl ring (C10–C15) is disordered nearly equally over two sites. Hydrogen atoms were placed in idealized positions and refined by using a riding model. CCDC-713326 (**11**) contains 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

General procedure for the amination of aryl halides: A 3.0 mL autoclave was charged with $Pd(OAc)_2$ (0.9 mg, 2 mol%), ligand **11** (7.7 mg, 8 mol%) or ligand **5** (4.6 mg, 8 mol%), and NaO*t*Bu (38.4 mg, 2 equiv). If it was a solid, the (hetero)aryl halide was also added at that point. The filled autoclave was placed into the autoclave device, evacuated, backfilled with argon, and then 1,4-dioxane (0.2 mL) was added and the mixture was stirred at room temperature for 5 min. Then, the corresponding aryl halide (if liquid) (0.2 mmol) and a 0.5 M NH_3 solution (2.0 mL) in 1,4-dioxane (5 equiv NH_3) were added successively under an argon atmosphere. The reaction mixture was pressurized with 10 bar N_2 and heated up to 120 °C for 24 h. After the mixture had been cooled to room temperature, it was laced with hexadecane (20 μL) as an internal standard. The mixture was filtered and the yield was determined by gas chromatography.

2-(Phenylethynyl)aniline (Table 3, entry 21): Following the reaction and cooling to room temperature, the reaction mixture was purified by column chromatography (cyclohexane/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.48$–7.45 (m, 2H), 7.32–7.24 (m, 4H), 7.10–7.04 (m, 1H), 6.72–6.65 (m, 2H), 4.60 ppm (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 147.0$, 132.2, 131.5, 129.8, 128.4, 128.3, 123.3, 118.6, 114.8, 108.5, 94.9, 85.7 ppm; MS (EI): 193 (100) $[M]^+$, 165 (34), 139 (4), 89 (11); HRMS: calcd for $C_{14}H_{11}N$: 193.08860; found:193.08853.

Acknowledgements

We thank Dr. W. Baumann, Dr. C. Fischer, A. Koch, S. Buchholz, S. Schareina, A. Kammer, and S. Rossmeisl for excellent analytical support. We gratefully acknowledge Evonik (formerly Degussa) for financial support as well as the precious gift of different chemicals. We also thank Dr. Kathrin Junge for providing the eightfold parallel autoclave equipment and technical support.

Keywords: amination · anilines · homogeneous catalysis · palladium · phosphanes

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Received: December 18, 2008
Revised: February 9, 2009
Published online: March 25, 2009

