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Palladium-Catalyzed Coupling of Ammonia and Lithium Amide with Aryl Halides

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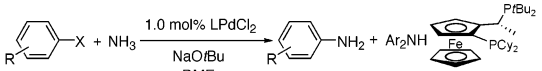
Ammonia is among the largest volume and least expensive bulk chemicals. Although ammonia is a common nitrogen source in chemical synthesis,[1] it is rarely used as a reagent in catalytic processes.[2] Because primary arylamines are important intermediates in the manufacture of agrochemicals, pharmaceuticals, dyes, pigments, and rubber,[4] the palladium-catalyzed amination[3] to form primary aromatic amines from aryl halides would be a synthetically valuable catalytic transformation of ammonia. However, no such reaction of ammonia has been reported.[5] Instead, the palladium-catalyzed synthesis of primary arylamines has typically been accomplished with ammonia surrogates.[6−9]

Three problems make the palladium-catalyzed amination with ammonia challenging: first, the dative ancillary ligands can be displaced by ammonia to form a catalytically unreactive complex;[10] second, reductive elimination from an Ar−Pd−NH_2 complex has never been observed, perhaps because complexes of the parent amido group often adopt stable bridging structures;[11] and third, if reductive elimination did form the arylamine, this product would likely be more reactive than ammonia and would further react to form the diarylamine. Thus, a catalyst is needed whose ancillary ligand resists displacement by ammonia, prevents bridging structures, induces reductive elimination from parent amido complexes, and favors reaction of ammonia over the product arylamine. We report that complexes generated from the Josiphos ligand CyPF-*t*-Bu[12] meet these challenges and catalyze the selective synthesis of primary arylamines from aryl halides and ammonia or lithium amide.[7] As part of this work, the first organopalladium complex with a terminal −NH_2 ligand has been isolated, and this complex reductively eliminates arylamine.

We initially assessed catalyst activity by conducting the coupling of ammonia with 1-*tert*-butyl-4-bromobenzene because reactions of unhindered haloarenes would be the most challenging. Reactions conducted with 1.0 mol % of CyPF-*t*-BuPdCl_2 as catalyst in DME (1,2-dimethoxyethane) with an excess (80 psi) of ammonia at 90 °C for 24 h with NaO*t*-Bu (2.0 equiv) as base formed 4-*tert*-butyl aniline in high yield with excellent monoarylation versus diarylation selectivity (17:1; Table 1, entry 1). The pressure of the ammonia and the concentration of the reaction were crucial to observe high conversion and selectivity. To ensure that the solution was saturated with ammonia, the solution was stirred for 30 min at 80 psi NH_3 prior to heating. Reactions with a lower pressure of ammonia proceeded to lower conversions and with lower monoarylation to diarylation selectivities. Reactions conducted with a higher 0.2 M concentration of haloarene occurred to full conversion but with a lower 9.6:1 selectivity. Reactions of ammonia conducted with weaker carbonate or phosphate bases occurred to low conversions. Reactions in THF, dioxane, and toluene also occurred to lower conversions or with lower selectivity. Consistent with the importance of the steric hindrance and tight chelation of the Josphos ligand, reactions conducted under these conditions with P*t*-Bu_3,[13] Q-phos,[14] X-phos,[8] IPr,[15] DPPF, or BINAP as ligand also did not occur.

Table 1 summarizes reactions conduced under our optimized conditions. Electron-rich bromoarenes coupled with ammonia in excellent yields and selectivities. The more sterically hindered substrates coupled in high yield, even at higher concentrations (entries 7 and 10). This result is important because the convenient ammonia equivalent $LiN(SiMe_3)_2$ does not couple with ortho-substituted bromoarenes.[9] Heteroaryl bromides also coupled with ammonia with excellent selectivities (entries 8 and 9).

Table 1. Coupling of Aryl Halides with Ammonia, Catalyzed by CyPF-*t*-BuPdCl_2[a]



entry	substrates	concentration	condition	products	yield[b] (%)	ratio[c] (A/B)
1	X = Br	0.05 M	90 °C, 24h		86	17:1
2	OTf[d]	0.05 M	90 °C, 24h		-	-
3	X = Cl	0.05 M	90 °C, 24h		69	23:1
4	Br	0.05 M	90 °C, 24h		86	>50:1
5	I	0.05 M	90 °C, 24h		79	>50:1
6		0.05 M	90 °C, 24h		94	31:1
7		0.25 M	90 °C, 20h		89	>50:1
8	R_1, R_2 = H, Br	0.05 M	90 °C, 20h	R_1, R_2 = H, NH_2	80	>50:1
9	R_1, R_2 = Br, H	0.25 M	90 °C, 20h	R_1, R_2 = NH_2, H	70	>50:1
10		0.25 M	90 °C, 20h		92	>50:1

[a] Reactions conducted in a Parr bomb with 1.0 mol % of Pd(CyPF*t*-Bu)Cl_2, 1 mmol of ArBr, and 2.0 equiv of NaO*t*-Bu at 90 °C in DME (20.0 mL). [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude product. [d] No product; only the phenol was observed.

The coupling with ammonia is not limited to reactions of bromoarenes. Although reactions of chloro- and iodoarenes have not yet been explored in detail, reactions of 2-chloro- and 2-iodobenzene also formed the substituted anilines in good to excellent yields. To date, however, reactions of aryl sulfonates have led to the formation of phenols (entry 2).

In some settings, reactions of lithium amide would be preferable to reactions of ammonia because it is a solid. As shown in Table 2, aryl and heteroaryl halides also coupled with an excess of $LiNH_2$ (10 equiv) in a small sealed vial to give the primary arylamine in good to excellent yield. The monoarylation/diarylation selectivities for reactions of lithium amide (9.5:1−50:1) were slightly lower than those of reactions with ammonia (entries 1 and 4−12) but were acceptable. The reaction in entry 1 conducted with 0.05 M bromoarene occurred with excellent selectivity, while the same reaction with a higher concentration (0.2 M) of the bromoarene occurred with a lower, albeit useful, selectivity of 5.6:1. Like the reactions of more-hindered bromarenes with ammonia, the reactions of more-hindered bromoarenes with lithium amide could be conducted at higher concentrations. For example, reaction of a 0.5 M solution of 1-bromo-2-isopropylbenzene in DME formed the

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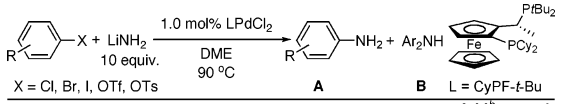
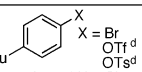
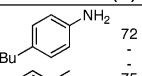
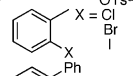
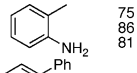
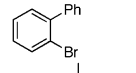
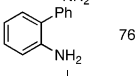
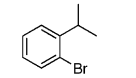
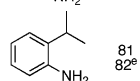
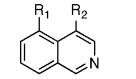
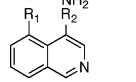
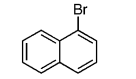
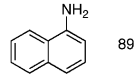
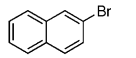
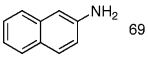
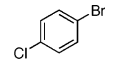
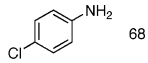
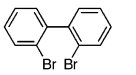
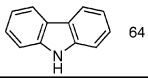
Table 2. Coupling of Aryl Halides with Lithium Amide, Catalyzed by CyPF-*t*-BuPdCl$_2$[a]



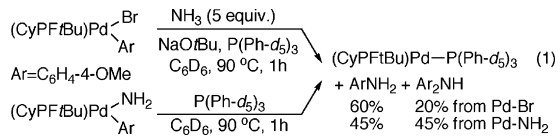
entry	substrates	concentration	condition	products	yield[b] (%)	ratio[c] (A/B)
1	 X = Br	0.05 M	80 °C, 24h		72	9.5:1
2	OTf[d]	0.05 M	80 °C, 24h		-	-
3	OTs[d]	0.05 M	80 °C, 24h		-	-
4	 X = Cl	0.05 M	80 °C, 24h		75	11.1:1
5	Br	0.05 M	80 °C, 24h		86	>50:1
6	I	0.05 M	80 °C, 24h		81	>50:1
7		0.05 M	80 °C, 24h		76	12:1
8		0.5 M	90 °C, 24h		81 82[e]	>50:1 >50:1
9	 R_1, R_2 = H, Br	0.05 M	80 °C, 20h	 R_1, R_2 = H, NH_2	82	>50:1
10	R_1, R_2 = Br, H	0.5 M	90 °C, 24h	R_1, R_2 = NH_2, H	79	>50:1
11		0.25 M	80 °C, 20h		89	>50:1
12		0.25 M	80 °C, 20h		69	8.0:1
13		0.5 M	60 °C, 20h		68	10.9:1
14		0.5 M	90 °C, 24h		64	-

[a] Reactions conducted with 1.0 mol % of Pd(CyPF*t*-Bu)Cl$_2$, 1 mmol ArBr, and 10 equiv LiNH$_2$ in 20 mL DME. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude product. [d] No product, only the phenol was detected. [e] Reaction with 1.99 g of 1-bromo-2-*iso*-propylbenzene (10 mmol).

primary amine in 81% yield with >50:1 selectivity for the monoarylation product. The same reaction conducted on a 2.0 g scale formed the primary amine in a comparable 82% yield. In addition, 2,2′-dibromobiphenyl reacted with LiNH$_2$ to give carbazole in an average yield of 80% for each of two C−N bond-forming processes.

To identify the palladium species that forms the C−N bond, we conducted stoichiometric reactions of Pd(CyPF-*t*-Bu)(4-MeOPh)(Br)[16] **1** with ammonia and base and developed an independent synthesis of the potential arylpalladium amide intermediate. The reaction of complex **1** with 5.0 equiv of ammonia and 1.1 equiv of NaO*t*-Bu at 90 °C (eq 1) for 1 h formed the coupled product in 80% yield with a 3:1 ratio of monoarylation to diarylation product by ^{1}H NMR spectroscopy. This reaction occurred through an intermediate that we detected by ^{31}P NMR spectroscopy and that we suspected to be the arylpalladium amido species.

Thus, we prepared the arylpalladium amido complex containing CyPF-*t*-Bu as ligand by an independent route from the corresponding cationic arylpalladium complex of ammonia. Addition of AgOTf to a solution of **1** and NH$_3$ in CH$_2$Cl$_2$ formed [Pd(CyPF-*t*-Bu)(4-MeOPh)(NH$_3$)]OTf, which was characterized as a 4:1 ratio of stereoisomers by spectroscopic methods. A single crystal of one isomer was obtained and was characterized by X-ray diffraction methods (see Supporting Information). Deprotonation of this species by KN(SiMe$_3$)$_2$ cleanly formed Pd(CyPF-*t*-Bu)(4-MeOPh)(NH$_2$) as a 4:1 ratio of stereoisomers. This mixture of stereoisomers was isolated in 40% yield after crystallization and was characterized by ^{1}H and ^{31}P NMR spectroscopy. Heating of this complex in the presence of PPh$_3$ to trap the Pd(0) product formed a 1:1 ratio of the primary and secondary arylamine in a combined yield over 90% (eq 1). Further studies are clearly needed to understand the factors that control selectivity for formation of the primary amine in this reaction and in the catalytic cycle, but this reaction comprises the first C−N bond-forming reductive elimination of a parent amido complex and one of the few reactions of terminal amido complexes that parallels the typical reactivity of organometallic species. Further studies of reaction scope and the mechanism of the coupling process will be the subject of future work.



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Supporting Information Available: All experimental procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) LeBlanc, J. R. J.; Madhavan, S.; Porter, R. E.; Kellogg, P. *Encyclopedia of Chemical Technology*, 2nd ed.; Wiley: New York, 1963; Vol. 2.
(2) (a) Gross, T.; Seayad, A. M.; Ahmad, M.; Beller, M. *Org. Lett.* **2002**, *4*, 2055. (b) Roundhill, D. M. *Chem. Rev.* **1992**, *92*, 1. (c) Zimmermann, B.; Herwig, J.; Beller, M. *Angew. Chem., Int.* Ed. **1999**, *38*, 2372. (d) Prinz, T.; Driessen-Holscher, B. *Chem.—Eur. J.* **1999**, *5*, 2069. (e) Prinz, T.; Keim, W.; Driessen-Holscher, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1708. (f) Ogo, S.; Uehara, K.; Abura, T.; Fukuzumi, S. *J. Am. Chem. Soc.* **2004**, *126*, 3020.
(3) (a) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. I., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, p 1051. (b) Hartwig, J. F. In *Modern Arene Chemistry*; Astruc, C., Ed.; Wiley-VCH: Weinheim, Germany, 2002, p 107. (c) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131.
(4) (a) Weissermel, K.; Arpe, H. J. *Industrial Organic Chemistry*; Wiley-VCH: Weinheim, Germany, 1997. (b) Lawrence, S. A. *Amines: Synthesis, Properties, and Application*; Cambridge University Press: Cambridge, 2004.
(5) Lang, F.; Zewge, D.; Houpis, I. N.; Volante, R. P. *Tetrahedron Lett.* **2001**, *42*, 3251.
(6) (a) Jaime-Figueroa, S.; Liu, Y.; Muchowski, J. M.; Putman, D. G. *Tetrahedron Lett.* **1998**, *39*, 1313. (b) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernandez-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827. (c) Wolfe, J. P.; Åhman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367. (d) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J. J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (e) Grasa, G. A.; Viciu, M. S.; Huang, J. K.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729. (f) Barluenga, J.; Aznar, F.; Valdes, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 343.
(7) Huang, X. H.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3417.
(8) Huang, X. H.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.
(9) (a) Lee, S.; Jorgensen, M.; Hartwig, J. F. *Org. Lett.* **2001**, *3*, 2729. (b) Lee, D.-Y.; Hartwig, J. F. *Org. Lett.* **2005**, *7*, 1169.
(10) (a) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2755. (b) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 3534. (c) Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030.
(11) (a) Park, S.; Rheingold, A. L.; Roundhill, D. M. *Organometallics* **1991**, *10*, 615. (b) Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *Inorg. Chem.* **1987**, *26*, 971.
(12) (a) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062. (b) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1371. (c) Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180.
(13) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746.
(14) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 10718.
(15) Stauffer, S.; Hauck, S. I.; Lee, S.; Stambuli, J.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423.
(16) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 8704.

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