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Palladium-Catalyzed Synthesis of Arylamines from Aryl Halides and Lithium Bis(trimethylsilyl)amide as an Ammonia Equivalent

Sunwoo Lee, Morten Jørgensen, and John F. Hartwig*

Department of Chemistry, Yale University, P.O. Box 208107,
New Haven, Connecticut 06520-8107

john.hartwig@yale.edu

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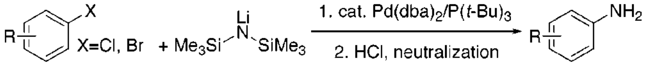
ABSTRACT



A simple, palladium-catalyzed method to convert aryl halides to the parent anilines using lithium bis(trimethylsilyl)amide (LiN(SiMe$_3$)$_2$) is reported. The reaction is catalyzed by Pd(dba)$_2$ and P(*t*-Bu)$_3$ and can be run with as little as 0.2 mol % of catalyst. The reaction is faster than competing generation of benzyne intermediates and, therefore, provides the aniline products regiospecifically.

Palladium-catalyzed aromatic C−N bond formation has become a convenient and general method to form arylamines from aryl halides and sulfonates.[1−5] This reaction occurs with a variety of primary amines, secondary amines, and related nitrogen substrates such as hydrazones,[6,7] carbamates,[8] amides,[9−11] and sulfoximines.[12] However, this reaction does not occur with ammonia and therefore does not form the parent aniline. Instead, the formation of aniline has been accomplished in two steps using ammonia surrogates, such as allyl and diallylamine,[13] benzyl and diphenylmethylamine, and benzophenone imine.[14,15] Some of these substrates require metal-catalyzed cleavage of the protective group, and others are relatively expensive. In contrast, bis(trimethylsilyl)amine or its deprotonated amide would be a less expensive, but easily deprotected substrate to use as a surrogate. Bis(trimethylsilyl)amides are common bases and are available as solutions in hydrocarbon or ether solvents or as solids.

Previous attempts to use these materials as a nitrogen source were unsuccessful. In our experience, we had observed little or no product from palladium-catalyzed chemistry using arylphosphine ligands such as P(*o*-tolyl)$_3$ or DPPF. When we did observe consumption of the aryl halide, the process required elevated temperatures, low yields were observed, and the silylamide product was formed as two regioisomers. We reasoned that redox reactions and the generation of benzyne intermediates occurred under these conditions.[16] Thus, simple, regiospecific conversion of an aryl halide to an aniline would require milder temperatures when using this reagent. While investigating the α-arylation of esters to form products with quaternary carbons, we observed competing formation of bis(trimethylsilyl)arylamines from coupling of the bis(trimethylsilyl)amide base with the aryl halide.[17] Thus, we initiated a study to observe the coupling of bis(trimethylsilyl)amide with aryl halides exclusively. We report the results of this study, which

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(1) Hartwig, J. F. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2000.

(2) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.

(3) Hartwig, J. F. *Synlett* **1997**, 329.

(4) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.

(5) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805.

(6) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2090.

(7) Wagaw, S.; Yang, B.; Buchwald, S. *J. Am. Chem. Soc.* **1999**, *121*, 10251.

(8) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575.

(9) Shakespeare, W. *Tetrahedron Lett.* **1999**, *40*, 2035.

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(13) Jaime-Figueroa, S.; Liu, Y.; Muchowski, J. M.; Putman, D. G. *Tetrahedron Lett.* **1998**, *39*, 1313.

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(15) Wolfe, J. P.; Åhman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367.

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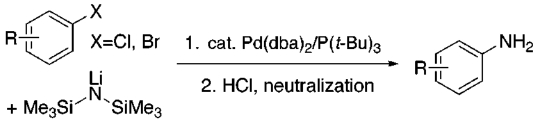
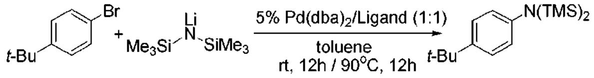
provides a simple method (eq 1) for the conversion of *m*- and *p*-substituted aryl halides to anilines.

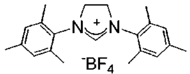
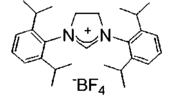
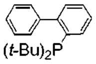
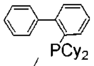
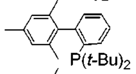
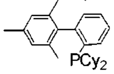
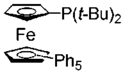


(1)

Table 1 summarizes reactions of lithium bis(trimethylsilyl)amide with 4-*tert*-butylbromobenzene catalyzed by palladium complexes of several ligands. These results show that the first- and second-generation catalysts based on arylphosphines gave little or no coupled product at low temperatures. The catalyst system in entry 7 that is composed of Pd(dba)$_2$ and P(*t*-Bu)$_3$, however, led to efficient formation of the aryl silylamine product. It is the same system we have recently used for room-temperature amination[8] and carbonyl α-arylation[18] and is based on high-temperature work by Nishiyama, Yamamoto, and Koie.[19] The saturated carbene ligand we recently used for room-temperature amination chemistry of aryl chlorides[20] was not useful for this reaction. Some of the ligands developed by Wolfe and Buchwald[21] were suitable at high temperatures, but even the best ligand for this substrate combination at room temperature was inferior to P(*t*-Bu)$_3$.

Table 1. Evaluation of Ligands for Aromatic C−N Coupling of Lithium Bis(trimethylsilyl)amide[a]



entry	ligand	temp.	conversion	GC-yield
1		RT	2%	1%
2		90°C	56%	13%
3		RT	14%	2%
4		90°C	75%	16%
5	PCy$_3$	RT	8%	6%
6		90°C	100%	83%
7	**P(*t*-Bu)$_3$**	**RT**	**100%**	**95%**
8	P(o-tol)$_3$	RT	0%	0%
9		90°C	39%	7%
10	PPh$_3$	RT	8%	0%
11		90°C	90%	51%
12		RT	29%	22%
13		90°C	100%	45%
14		RT	100%	82%
15		RT	10%	1%
16		90°C	100%	45%
17		RT	13%	11%
18		90°C	100%	92%
19		RT	14%	6%
20		90°C	100%	63%
21	BINAP	RT	0%	0%
22		90°C	100%	65%
23	DPPF	RT	0%	0%
24		90°C	94%	22%
25	no ligand	RT	0%	0%
26		90°C	33%	0%
27	no L/no Pd	RT	0%	0%
28		90°C	0%	0%

We evaluated the relative importance of countercation, ligand:metal ratio, solvent, and equivalents of silylamide on the reaction yields using 4-*tert*-butylbromobenzene as a model substrate. Reactions with any of the alkali metal bis(trimethylsilyl)amides occurred in yields exceeding 95% by GC. For consistency, we focused our studies on a single alkali metal derivative, the least expensive lithium salt. Unlike the reaction of amines with aryl halides,[8] reactions of the silylamide occurred with similar rates using 0.5:1, 1:1, or 2:1 ratios of ligand to metal. Reactions occurred most readily in alkane, arene, and dialkyl ether solvents. The reactions were less facile in cyclic ether solvents such as dioxane and THF, and they occurred in less than 20% yield in DMF, mono- and diglyme, and weakly acidic solvents such as acetonitrile. No excess silylamide was necessary to observe high yields, although a slight excess of reagent was not detrimental.

In addition, we attempted to conduct reactions with the silylamine in the presence of base instead of using the alkali metal salts of the silylamine. Reactions in the presence of sodium *tert*-butoxide base occurred, although in lower yield than those conducted in the presence of the silylamide directly. Reactions conducted with weaker bases, such as Na_3PO_4 or Cs_2CO_3, which have been effective for reactions of amines,[8,22] gave no coupled product. Most likely, these bases operate in the amination of aryl halides by deprotonating an arylpalladium complex with coordinated amine, and the silylamide is too sterically hindered to effectively bind palladium.

The scope of the reaction of lithium bis(trimethylsilyl)amide with aryl halides is presented in Table 2. The aryl bis-silylamine product underwent hydrolysis during chromatography. Thus, the corresponding anilines, instead of the silylamines, were isolated after addition of aqueous or ethereal HCl and neutralization. The product from coupling with 4-*tert*-butyl bromobenzene was, however, isolated in its protected form by distillation.

With few exceptions, the reaction of *m*- and *p*-substituted aryl bromides and chlorides gave high yields of the coupled product. Electron-donating groups were tolerated. Electron-withdrawing groups, such as a trifluoromethyl or an ester group, would favor generation of benzyne intermediates. However, substrates with electron-withdrawing groups reacted at low temperatures and generated the coupled product regiospecifically in high yield. Aryl halides with esters in conjugation with the aryl halide reacted cleanly at the halide and not the ester.

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(18) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473.

(19) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617.

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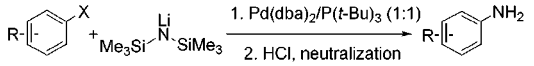
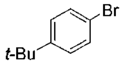
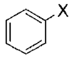
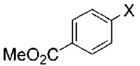
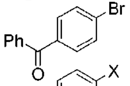
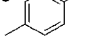
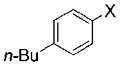
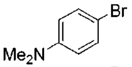
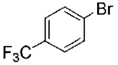
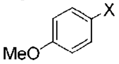
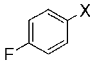
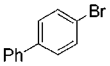
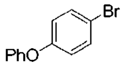
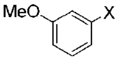
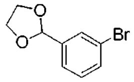
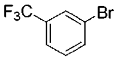
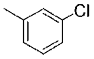
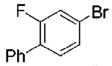
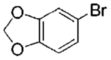
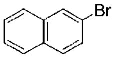
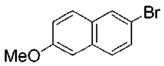
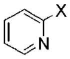
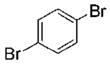
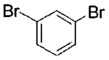
(21) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J. J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

(22) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359.

Table 2. Scope of the Aromatic C−N Coupling of Lithium Bis(trimethylsilyl)amide Using P(t-Bu)$_3$ and Pd(dba)$_2$ (1:1)[a]



entry	substrate	cat. loading	temp.	time	yield
1		2%	rt.	12h	90%
2	 X=Br X=Cl	2% 5%	rt. 50°C	16hr 20h	92% 89%
3	 X=Br X=Cl	3% 5%	rt. rt.	20h 14h	95% 97%
4		5%	rt.	20h	89%
5	 X=Br X=Cl	5% 5%	rt. 50°C	18h 20h	97% 95%
6	 X=Br X=Cl	5% 5%	rt. 50°C	14h 20h	92% 95%
7		5%	rt.	14h	87%
8		2%	rt.	16h	75%
9	 X=Br X=Cl	5% 5%	rt. 50°C	14h 12h	85% 90%
10	 X=Br X=Cl	5% 5%	rt. 50°C	14h 16h	85% 74%
11		2%	rt.	16h	79%
12		2%	rt.	14h	87%
13	 X=Br X=Cl	2% 5%	rt. 50°C	16h 10h	87% 96%
14		2%	rt.	14h	99%
15		5%	rt.	16h	84%
16		2%	50°C	14h	87%
17		5%	rt.	12h	92%
18		5%	50°C	10h	98%
19		2%	rt.	16h	76%
20		2%	rt.	7h	92%
21	 X=Br X=Cl	2% 5%	rt. rt.	16h 14h	88% 64%
22		5%	rt.	20h	80%
23		5%	rt.	20h	85%

Aryl chlorides are generally less reactive than bromides and often require higher temperatures for reaction. If this were the case for reactions of the silylamide reagent, then benzyne and possibly radical intermediates would be generated. However, the high activity of the catalyst derived from Pd(dba)$_2$ and P(t-Bu)$_3$ allowed for reaction of the aryl chlorides under relatively mild conditions. The results in Table 2 show that many aryl chlorides underwent regiospecific reaction with bis(trimethylsilyl)amide to form the parent aniline in high yield. In general, the substrate scope for reactions of aryl chlorides was similar to that for reactions of aryl bromides, but reactions required heating to occur at reasonable rates.

Aryl bromides or chlorides possessing enolizable hydrogens did not couple with the bis(trimethylsilyl)amide reagent. These substrates react by ketone α-arylation,[18,23] and presumably the haloacetophenones generate polymeric or oligomeric products during reaction with the silylamide reagent. In addition, this catalyst system did not allow for reactions of aryl halides with nitro groups, and reactions of those with *p*- or *m*-cyano groups were sluggish. Perhaps direct reaction of the strong base with these substrates interferes with the desired palladium-catalyzed coupling.

Although the process occurred in a fairly general fashion for substrates substituted with meta and para substituents, the reaction did not occur with substrates bearing ortho substituents. These substrates are some of the most effective for reactions with simple amine reagents. However, the silylamide reagent is apparently too bulky to react with the sterically hindered arylpalladium(II) intermediate. For conversion of these substrates to the parent amine, reaction with a different ammonia equivalent[13−15] is necessary at this time.

In addition to evaluating reaction scope, we assessed reactions conducted with low catalyst loadings. Table 3 summarizes these results. Reactions with lower loadings did require higher temperatures, but evidently these temperatures were still low enough to prevent generation of benzyne intermediates.

In some cases high turnover numbers were obtained. For example, 4-*tert*-butylbromobenzene and 3-bromoanisole formed the coupled product in 89% and 91% yields with only 0.2 mol % of catalyst at 70 °C, and 2-bromo-6-methoxynaphthalene reacted in 92% yield with only 0.1 mol % of catalyst. Reactions of aryl chlorides also occurred with lower loadings than the 5% used in the reactions of Table 2, but generally 0.5−1 mol % of catalyst was still necessary for full conversion at temperatures low enough to generate single regioisomeric products.

We also evaluated each reaction in the absence of catalyst at temperatures up to 120 °C. In only a few cases did we see any aniline product at all. 3-Bromoanisole and the dioxolane in entry 14 gave 10% and 6% of the aniline after 12 h at 70 °C, and 4-butylbromobenzene and 4-bromobenzophenone gave roughly 40% and 30% yields after 12 h at 120 °C. Although the protected bromocatechol in entry 18 gave a reasonable 53% yield under these conditions, this yield for the high-temperature, uncatalyzed reaction was much lower than the 99% yield observed at 70 °C using 1% palladium catalyst.

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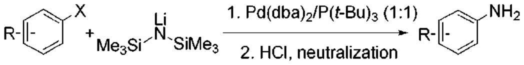
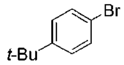
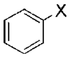
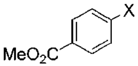
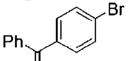
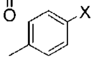
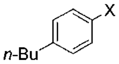
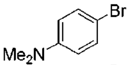
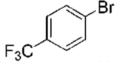
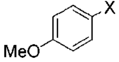
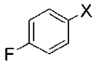
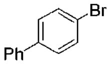
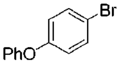
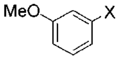
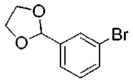
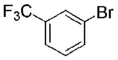
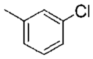
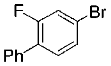
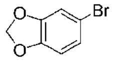
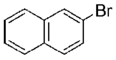
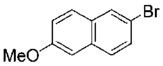
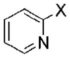
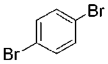
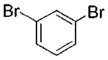
(23) Fox, J. M.; Huang, X. H.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.

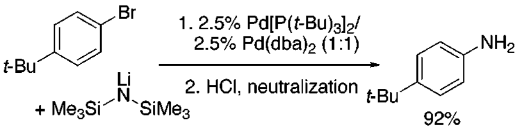
Table 3. Aromatic C−N Coupling of Lithium Bis(trimethylsilyl)amide at Low Loadings of P(t-Bu)$_3$ and Pd(dba)$_2$ (1:1)[a]



entry	substrate		cat. loading	temp.	time	yield
1			0.2%	70°C	12h	89%
2		X=Br X=Cl	0.5% 0.5%	70°C 90°C	18h 16h	76% 90%
3		X=Br X=Cl	0.5% 1%	70°C 90°C	14h 16h	96% 98%
4			0.5%	70°C	16h	93%
5		X=Br X=Cl	0.5% 0.5%	70°C 90°C	14h 16h	92% 99%
6		X=Br X=Cl	0.5% 0.5%	70°C 90°C	12h 16h	90% 74%
7			1%	70°C	30h	86%
8			0.5%	70°C	18h	65%
9		X=Br X=Cl	0.5% 1%	70°C 90°C	36h 16h	83% 90%
10		X=Br X=Cl	0.5% 1%	70°C 90°C	12h 14h	77% 71%
11			0.5%	70°C	8h	94%
12			1%	70°C	8h	88%
13		X=Br X=Cl	0.2% 0.5%	70°C 90°C	12h 14h	91% 92%
14			1%	70°C	14h	99%
15			0.5%	70°C	12h	75%
16			1%	90°C	18h	85%
17			1%	70°C	18h	86%
18			1%	70°C	16h	99%
19			0.5%	70°C	12h	87%
20			0.2%	70°C	16h	95%
21		X=Br X=Cl	0.5% 1%	70°C 90°C	18h 20h	86% 62%
22			1%	70°C	14h	81%
23			1%	70°C	12h	82%

Although the ligand and silylamide reagent used in the catalytic reaction are air sensitive, convenient procedures can be followed without a drybox. Both the silylamide and ligand are commercially available as a solution in hydrocarbon solvents and can, therefore, be delivered to the reaction solution by syringe.

Alternatively, the preformed Pd(0) catalyst Pd[P(t-Bu)$_3$]$_2$ is commercially available and is air stable. Combining this air-stable species with the air-stable and commercially available Pd(dba)$_2$ or Pd$_2$(dba)$_3$ in a 1:1 molar ratio to metal, as done previously by Fu,[24] generates a catalyst that is more active than Pd[P(t-Bu)$_3$]$_2$, albeit less active than the catalyst generated in situ from Pd(dba)$_2$ and P(t-Bu)$_3$. Use of 2.5 mol % of these two catalyst precursors gave 92% yield of the aryl silylamine after 24 h at room temperature for reaction of 4-*tert*-butylbromobenzene with lithium bis(trimethylsilyl)amide.



(2)

The mechanistic data we have obtained for the reactions of aryl bromides are not straightforward, but the data for reactions of aryl chlorides are simpler to interpret. ^{31}P NMR spectra obtained for reactions of aryl chlorides using a 1:1 ratio of Pd(dba)$_2$ and P(t-Bu)$_3$ show that the Pd(0) complex Pd[P(t-Bu)$_3$]$_2$ is the major palladium−phosphine complex in solution. Roughly 20 h after consumption of the aryl chloride, 40% cyclometalated complex[25,26] is formed. In contrast, little Pd[P(t-Bu)$_3$]$_2$ is observed during the reaction of aryl bromides. Two identified complexes with chemical shifts 10−20 ppm upfield of those of the free ligand were observed by ^{31}P NMR spectrometry. These are not formed by reaction of aryl halide or by reaction of the silylamide with Pd[P(t-Bu)$_3$]$_2$. Further studies will be needed to determine the structures of these species.

In conclusion, we have shown that the recently developed catalysts for aryl halide amination now allow for the reaction of lithium bis(trimethylsilyl)amide with *m*- and *p*-substituted aryl bromides at temperatures low enough to form products exclusively from palladium-catalyzed coupling without formation of benzyne intermediates. This catalytic chemistry, therefore, forms products from regiospecific replacement of the halogen by silylamide. After aqueous workup, this reaction generates the parent aniline.

Acknowledgment. We thank the NIH (R29-6M-55382) for support of this work and Neil A. Beare for helpful discussions.

Supporting Information Available: Reaction procedures and characterization of new reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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