New Ammonia Equivalents for the Pd-Catalyzed Amination of Aryl Halides
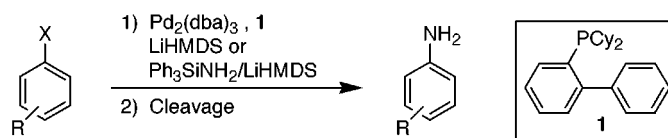
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ABSTRACT

LiN(SiMe$_3$)$_2$, Ph$_3$SiNH$_2$, and LiNH$_2$ can be be used as ammonia equivalents for the Pd-catalyzed coupling of aryl halides. Using these amine derivatives, simple anilines, including *ortho*-substituted ones, as well as di- and triarylamines can be readily prepared.

During the past few years, great progress has been made in the development of the Pd-catalyzed amination of aryl halides.[1] As a result, a wide variety of arylamines can now be efficiently prepared using this methodology. The use of ammonia, the simplest amine, has not yet been reported, however, presumably for reasons of safety and convenience.[2] We previously reported that benzophenone imine can function as an effective ammonia equivalent.[3−5] Coupling reactions with this imine are high yielding and can be performed under extremely mild reaction conditions. Moreover, the resulting *N*-aryl imines can be cleaved using several or-

thogonal methods that are compatible with a variety of protecting groups. Recently, Hartwig described the use of LiN(SiMe$_3$)$_2$ (LiHMDS) as an ammonia equivalent.[6] He showed that this nucleophile could be used with an impressive range of aryl halide substrates. Moreover, many of these transformations could be carried out at room temperature and/or with low catalyst loadings. This report has prompted us to disclose our own work in this area, the majority of which was carried out prior to this recent disclosure.

While investigating the coupling of hindered amines with aryl halides, we queried whether LiHMDS might be useful as an ammonia surrogate. We were pleased to find that, in many instances, it functions well in this role. Shown in Table 1 are a few examples of the Pd-catalyzed preparation of primary anilines. These reactions were typically performed using 0.5 mol % Pd$_2$(dba)$_3$ (1% Pd) and 1.2 mol % of the air-stable, commercially available ligand **1**.[7] Although solid LiHMDS could be employed for this chemistry, it requires the use of a glovebox. We found that comparable results

(1) (a) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046−2067. (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146. (d) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144−1157. (e) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158−1174 and references therein.

(2) Ammonia has been used in the Cu-catalyzed amination of 2-bromopyridines: Lang, F.; Zewge, D.; Houpis, I. N.; Volante, R. P. *Tetrahedron Lett.* **2001**, *42*, 3251−3254.

(3) (a) Wolfe, J. P.; Åhman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367−6370. See also: (b) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernandez-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827−828.

(4) For other ammonia equivalents in Pd-catalyzed aminations, see: (a) Hori, K.; Mori, M. *J. Am. Chem. Soc.* **1998**, *120*, 7651−7652. (b) Jaime-Figueroa, S.; Liu, Y.; Muchowski, J. M.; Putman, D. G. *Tetrahedron Lett.* **1998**, *39*, 1313−1316. (c) Lim, C. W.; Lee, S. *Tetrahedron* **2000**, *56*, 5131−5136. (d) Bolm, C.; Hildebrand, J. P. *Tetrahedron Lett.* **1998**, *39*, 5731−5734

(5) In situ generated CuHMDS has been used in the stoichiometric amination of aryl iodides: King, F. D.; Walton, R. M. *J. Chem. Soc., Chem. Commun.* **1974**, 256−257.

(6) Lee, S.; Jørgensen, M.; Hartwig, J. F. *Org. Lett.* **2001**, *3*, 2729−2732.

(7) **General Procedure A.** An oven-dried resealable Schlenk tube was charged with Pd$_2$(dba)$_3$ (4.6 mg, 5.0 μmol, 0.50 mol %) and 2-dicyclo-hexylphosphinobiphenyl (**1**) (4.2 mg, 12 μmol, 1.2 mol %). The Schlenk tube was evacuated and back-filled with argon. Aryl halide (1.0 mmol) and LiHMDS (1.2 mL, 1 M solution in THF, 1.2 mmol) were added via syringe. The Schlenk tube was then sealed with a Teflon screw cap and placed in a preheated oil bath at 65 °C for 15 h. After cooling of the reaction mixture to room temperature, aqueous HCl (5 mL, 1 M) was added, and the mixture was stirred at room temperature for 5 min. The solution was

Table 1. LiHMDS as an Ammonia Surrogate in the Pd-Catalyzed Coupling of Aryl Halides[7]

entry	substrate	product	T (°C) solvent	cleavage	yield (%)[a]
1	(4-Cl, OMe phenyl)	(4-NH₂, OMe phenyl)	65 THF	H⁺	95
2	(3-Br phenyl dioxolane)	(3-NH₂ phenyl dioxolane)	65 THF	TBAF	94[b]
3	(4-Br, CONEt₂ phenyl)	(4-H₂N, CONEt₂ phenyl)	80 dioxane	H⁺	99[c]
4	(4-Br, tBu phenyl)	(4-H₂N, tBu phenyl)	65 THF	H⁺	99
5	(2-Cl pyridine)	(2-NH₂ pyridine)	65 THF	TBAF	96

[a] Isolated yields (average of two runs) of compounds determined to be >95% pure by ¹H NMR and GC or combustion analysis. [b] 2.2 equiv of LiHMDS was used. [c] Xantphos was used as ligand, and solid LiHMDS was used. See Supporting Information for details.

could be obtained with commercially available solutions of LiHMDS. The latter method is considerably more practical since it obviates the need of a glovebox in order to set up the reaction. For the coupling that required temperatures higher than 65 °C, solid LiHMDS and dioxane were used (entry 3). While these reactions were performed at 65–80 °C, ligand **1** was reported to be quite effective in room-temperature coupling reactions using LiHMDS.[6] One significant limitation of this LiHMDS chemistry is that it fails in the case of *ortho*-substituted aryl halides. It seemed reasonable that the problem lies in the significant bulk of the two trimethylsilyl groups. We reasoned that the use of commercially available aminotriphenylsilane, which possesses a single large silyl group, might allow us to overcome this limitation. A protocol was developed where a slight excess of LiHMDS was added to the reaction mixture containing aminotriphenylsilane (Table 2).[8] Presumably, an equilibrium exists between the different silyl amides; how-

then neutralized by the addition of aqueous NaOH. The aqueous phase was extracted with CH₂Cl₂ three times. The combined organic layers were combined, dried over Na₂SO₄, filtered, and concentrated in vacuo. The product was purified by flash chromatography.

Table 2. Amination of Hindered Aryl Halides with Aminotriphenylsilane[8]

entry	substrate	product	yield (%)[a]
1	(2-Cl, OMe phenyl)	(2-NH₂, OMe phenyl)	98[b]
2	(2-Br, CH(Me)Me phenyl)	(2-NH₂, CH(Me)Me phenyl)	90
3	(2-Br biphenyl)	(2-NH₂ biphenyl)	85
4	(2-Br, Cl phenyl)	(2-NH₂, Cl phenyl)	92
5	(2-Br, vinyl phenyl)	(2-NH₂, vinyl phenyl)	88

[a] Isolated yields (average of two runs) of compounds determined to be >95% pure by ¹H NMR and GC or combustion analysis. [b] 2 mol % of Pd and 2.4 mol % of **1** were used.

ever, the much less sterically hindered triphenylsilylamide reacts preferentially. Deprotection using aqueous acid provided the *ortho* aniline derivatives in excellent yield. As is evident from entries 2 and 3, even hindered substrates are readily transformed to the corresponding anilines. Notably, *ortho*-bromostyrene is efficiently transformed without observable Heck-type side products (entry 5).

(8) **General Procedure B.** An oven-dried resealable Schlenk tube was charged with Pd₂(dba)₃ (4.6 mg, 5.0 μmol, 0.50 mol %), 2-dicyclohexyl-phosphinobiphenyl (**1**) (4.2 mg, 12 μmol, 1.2 mol %), and 1,1,1-triphenylsilylamine (330 mg, 1.2 mmol). The Schlenk tube was evacuated and back-filled with argon, and aryl halide (1.0 mmol) was added via syringe. The Schlenk tube was sealed with a Teflon screw cap and brought into a glovebox. Lithium bis(trimethylsilyl)amide (220 mg, 1.3 mmol) and toluene (1 mL) were added in the glovebox. The Schlenk tube was then sealed with a Teflon screw cap, brought out of the glovebox and placed in a 100 °C oil bath for 16–20 h. After the reaction mixture was cooled to room temperature, the workup described in General Procedure A was performed and the product was purified by flash chromatography.

(9) For a Pd-based route to unsymmetrical triarylamines, see: Harris, M. C.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5327–5333.

(10) **General Procedure C.** An oven-dried resealable Schlenk tube was charged with Pd₂(dba)₃ (9.2 mg, 10 μmol, 1.0 mol %) and 2-(di-*tert*-butylphosphino)biphenyl (**2**) (7.2 mg, 24 μmol, 2.4 mol %). The Schlenk tube was evacuated and back-filled with argon, and aryl halide was added via syringe. The Schlenk tube was sealed with a Teflon screw cap and brought into a glovebox. Lithium amide (23 mg, 1.0 mmol), sodium *tert*-butoxide, and solvent (1 mL) were added in the glovebox. The Schlenk tube was then sealed with a Teflon screw cap, brought out of the glovebox, and placed in a preheated oil bath for 19 h. The reaction mixture was cooled to room temperature, diluted with ether, passed through a pad of Celite, and concentrated in vacuo. The residue was purified by flash chromatography.

Table 3. LiNH$_2$ as a Reagent for the Formation of Di- and Triarylamines[10]

entry	substrate	product	T (°C) solvent	yield (%)[a]
1			80 Dioxane	82
2			100 Dioxane	75
3			100 Dioxane	79[b]
4			80 Toluene	95
5			80 Toluene	94
6			100 Toluene	86
7			100 Toluene	91[c]
8			100 Dioxane	64

[a] Isolated yields (average of two runs) of compounds determined to be >95% pure by ^{1}H NMR and GC or combustion analysis. [b] 5 mol % of Pd and 6 mol % of **2** were used. [c] PtBu$_3$ was used as ligand.

We were also interested in developing protocols that would allow for the ready preparation of symmetrical di- and triarylamines directly from the aryl halide substrate.[9] LiNH$_2$ was an excellent reagent for this purpose. Ligand screening revealed that a catalyst based on commercially available di-*tert*-butylphosphinobiphenyl (**2**) and Pd$_2$(dba)$_3$ was most efficient for such transformations. NaOtBu served as an effective base for the deprotonation of the aniline and/or diarylamine intermediates formed during the reaction without acting as a competitive nucleophile. When *meta*- or *para*-substituted aryl halides were used, the corresponding triarylamines were prepared in good yield (Table 3, entries 1−3).[10] With *ortho*-substituted aryl halides, diarylamines were formed selectively and isolated in moderate to excellent yield (entries 4−8).

In summary, we have reported the use of several silylated amine derivatives as ammonia equivalents in the Pd-catalyzed amination reaction with commercially available **1** as the supporting ligand. While LiHMDS is effective in the amination of *meta*- and *para*-substituted aryl bromides and chlorides, the use of aminotriphenylsilane allows for the efficient reaction of *ortho*-substituted substrates. Additionally, with a **2**/Pd-catalyst, di- and triarylamines can be efficiently prepared using LiNH$_2$ as the nucleophile and NaOtBu as the base. These results, coupled with Hartwig's report,[6] constitute useful new methods for the synthesis of arylamine derivatives.

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

OL0166808