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Improved Functional Group Compatibility in the Palladium-Catalyzed Synthesis of Aryl Amines

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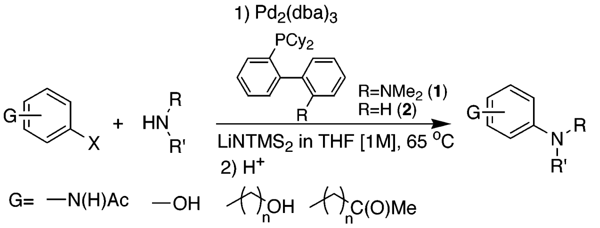
ABSTRACT



The use of Pd$_2$dba$_3$ with bulky, electron-rich ligands 1 or 2 and LiN(TMS)$_2$ as the base for the coupling of amines with aryl halides containing hydroxyl, amide, or enolizable keto groups is described. This protocol expands the utility of palladium-catalyzed C–N bond formation by allowing for the use of aryl halides containing these functional groups, obviating the need for protecting group manipulations.

In recent years the palladium-catalyzed coupling of amines with aryl halides or sulfonates has been widely investigated.[1−3] Despite the improvements to the substrate scope of the palladium-catalyzed C−N bond-forming reactions that utilize weak bases such as K$_3$PO$_4$[4] or Cs$_2$CO$_3$,[5] limitations still exist. Although the use of weak bases allows for the use of substrates containing ester, cyano, nitro and keto groups in the reaction, reactions of aryl substrates containing alcohol, phenol, or amide functional groups have often been problematic. One hypothesis for the incompatibility of these groups is that under the reaction conditions the deprotonated alcohol, amide, or phenol binds to palladium and prevents the desired reaction from occurring.

To synthesize aryl amines containing alcohol, phenol, or amide groups, protecting group strategies have been employed. For example, alcohols have been masked with triisopropylsilyl (TIPS),[6] *tert*-butyldimethylsilyl (TBDMS),[7] and benzyl protecting groups.[8] Likewise, amides have been protected with benzyl[9] or methoxy methyl (MOM)[10] groups. Obviously, the use of protecting groups is inconvenient and inefficient.

A few exceptions to the limitations noted above have been reported. For example, workers at Novartis used the Pd/BINAP catalyst system, with NaOMe as the base, to couple benzophenone imine with an aryl bromide containing a carbamate.[11] Link used Pd$_2$(dba)$_3$/BINAP in combination with NaO*t*-Bu as the base to couple an amine with an aryl bromide containing an amide that was distal to the aryl ring.[12]

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(1) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131.
(2) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.
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(4) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.
(5) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359.
(6) Coleman, R. S.; Chen, W. *Org. Lett.* **2001**, *3*, 1141.
(7) Lakshman, M. K.; Keeler, J. C.; Hilmer, J. H.; Martin, J. Q. *J. Am. Chem. Soc.* **1999**, *121*, 6090.
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(9) De Riccardis, F.; Bonala, R. R.; Johnson, F. *J. Am. Chem. Soc.* **1999**, *121*, 10453.
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(11) Prashad, M.; Hu, B.; Lu, Y.; Draper, R.; Har, D.; Repič, O.; Blacklock, T. J. *J. Org. Chem.* **2000**, *65*, 2612.
(12) Link, J. T.; Sorensen, B.; Liu, G.; Pei, Z.; Reilly, E. B.; Leitza, S.; Okasinski, G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 973.

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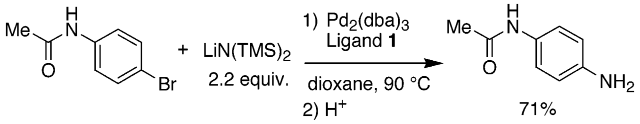
Additionally, Lemière successfully used Pd/BINAP with Cs_2CO_3 as the base to couple benzophenone imine with the triflate of a 5-hydroxyflavone.[13] Although these examples are notable, they remain the exception. Herein, we describe a significantly more general method for the direct coupling of amines with aryl halide substrates containing alcohol, phenol, and amide functional groups.

Scheme 1. $LiN(TMS)_2$ as an Ammonia Surrogate



While investigating the use of lithium bis(trimethylsilyl)-amide as an ammonia equivalent,[14] we observed that the reaction of 4-bromoacetanilide with 2.2 equiv of $LiN(TMS)_2$, followed by acidic hydrolysis, gave 4-aminoacetanilide in 71% isolated yield (Scheme 1). C−N bond-forming reactions with aryl bromides containing an amide group, particularly with a N(H) moiety directly attached to the aromatic ring, had been problematic. The results of this experiment thus prompted us to follow up on our initial study.

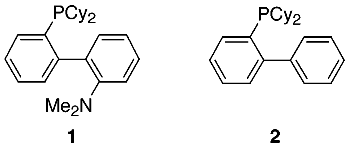
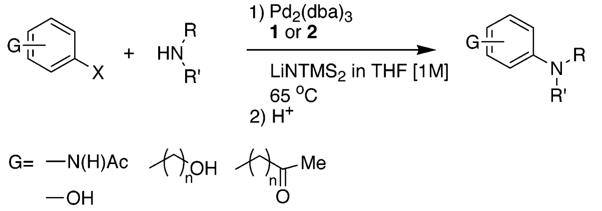


Figure 1. Ligands used for the palladium-catalyzed amination reaction with $LiN(TMS)_2$ as the base.

Expanding on our initial results, we found that $LiN(TMS)_2$ could be used as the base, in many instances, in the coupling reaction of amines with aryl halides containing alcohol, phenol, amide, or keto groups (Scheme 2). Presumably, 1 equiv of the $LiN(TMS)_2$ removes the most acidic proton of the functional group, while the second equivalent is used as the base (or as the nucleophile) in the coupling reaction.

Scheme 2. General Reaction Scheme for Coupling of Amines with Functionalized Aryl Halides



Silylamide bases have been used previously in Pd-catalyzed C−N bond-forming processes[15,16] but not, however, with substrates containing alcohol, amide, phenol, or enolizable keto groups.

In a typical protocol, 1 mol % $Pd_2(dba)_3$, 2.4 mol % of the air-stable, commercially available ligands **1** or **2** (Figure 1), and 2.2 equiv of $LiN(TMS)_2$ (1 M solution in THF)[17] are employed.[18,19] Using this system, aryl halides containing alcohol (entries 1−5), phenol (entries 6−8), amide (entries 11−16), and keto (entries 17−19) groups may be coupled with amines in good to excellent yields. Although the Pd-catalyzed coupling of amines with aryl halides containing an enolizable ketone group has previously been demonstrated using Cs_2CO_3 and K_3PO_4 as base,[20] the method described herein allows for the use of lower temperatures (65 vs 100 °C) to provide products in comparable yields.

Amino alcohols were also investigated as substrates. No reaction was observed when amino alcohols that may chelate to the Pd center (e.g., 1,2- and 1,3-amino alcohols) were employed as substrates. However, reactions of 4-hydroxypiperidine proceeded smoothly, as shown in entries 9 and 10. Since 4-hydroxypiperidine was efficiently coupled with unfunctionalized aryl bromides, we were interested in testing how the presence of multiple functional groups affects this chemistry. We were pleased to find that the reaction of 4-hydroxypiperidine with 3-chloroacetanilide using 3 equiv of $LiN(TMS)_2$ gave product in acceptable yield (entry 16).

Although this method is useful for a variety of substrates, as expected, it is not without its limitations. This transformation works well with secondary amines and anilines; however, primary aliphatic amines afford products in low yields (ca. 30−40%). The reaction of 3-chlorophenethanol with di-*n*-butylamine (entry 1) yields a large amount of 3-(trimethylsilyl)-phenethanol when the reaction is performed at 65 °C.[21] However, by conducting the reaction at room

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(13) Deng, B.-L.; Lepoivre, J. A.; Lemière, G. *Eur. J. Org. Chem.* **1999**, 2683.

(14) Huang, X.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3417.

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

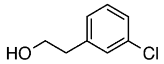
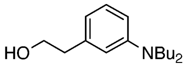
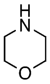
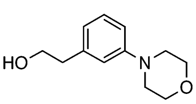
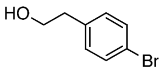
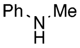
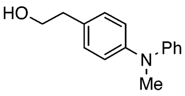
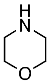
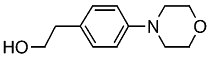
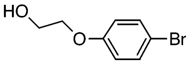
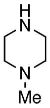
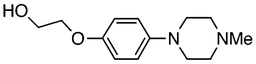
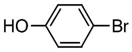
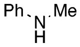
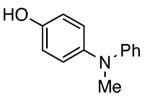
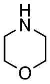
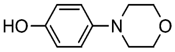
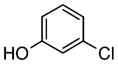
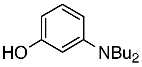
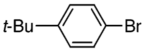
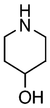
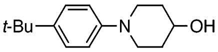
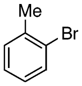
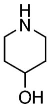
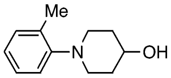
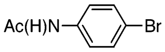
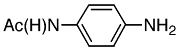
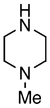
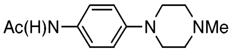
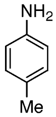
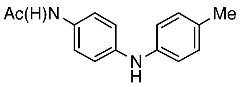
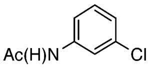
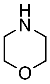
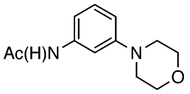
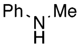
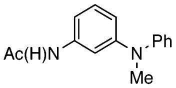
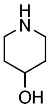
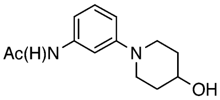
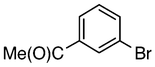
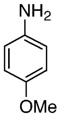
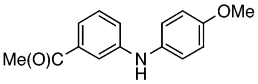
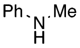
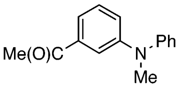
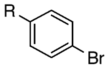
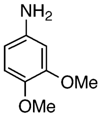
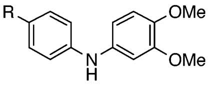
(17) Solid $LiN(TMS)_2$ in dioxane or THF may also be used with comparable results; however, use of the solid is less desirable since the setup requires use of a glovebox.

(18) **General Procedure A.** An oven-dried Schlenk tube was charged with $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol, 2 mol % Pd), ligand **1** (4.2 mg, 0.012 mmol, 2.4 mol %), aryl halide (0.50 mmol), and amine (0.60 mmol). The Schlenk tube was evacuated and back-filled with argon, and the Teflon screwcap was replaced with a rubber septa. The $LiN(TMS)_2$ solution (1 M in THF, 1.1 mL) was added via syringe (substrates that are liquids at room temperature were added at this point). The rubber septum was replaced with the Teflon screwcap, and the reaction vessel was sealed. The reaction mixture was heated at 65 °C with stirring until the aryl halide had been consumed as judged by GC analysis. The reaction mixture was then allowed to cool to room temperature. To the reaction mixture was added 1 M HCl (0.5−1.0 mL), and the mixture was stirred at room temperature for 5 min, followed by neutralization with a saturated $NaHCO_3$ solution (0.5−1.0 mL). Dodecane (113 μL, 0.50 mmol) was added as an internal standard for GC analysis, and the reaction mixture was diluted with ethyl acetate. The organic layer was dried with $MgSO_4$, filtered through a pad of Celite, and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel using mixtures of ethyl acetate/hexanes or methanol/dichloromethane (for very polar compounds) as the eluent.

(19) **General Procedure B.** Same as general procedure A, but with ligand **2** (4.6 mg, 0.012 mmol, 2.4 mol %).

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

Table 1. Synthesis of Aryl Amines Using $LiN(TMS)_2$ as Base[a]

Entry	aryl halide	amine	Product	Yield[b] %
1		$HNBu_2$		64[c,d]
2				84
3				80[e]
4				56
5				61
6				85[e]
7				80
8		$HNBu_2$		71[e]
9				91[e]
10				90[e, f]
11		$LiN(TMS)_2$		71
12				66
13				95[e, f]
14				83
15				92
16				59[e, g]
17				83
18				82
19	 $R=(CH_2)_2C(O)Me$			57[e]

[a] Reaction conditions: (1) 1.2 equiv of amine, 1.0 equiv of aryl halide, 2.2 equiv of $LiN(TMS)_2$ (1 M in THF), 0.5−1.5 mol % $Pd_2(dba)_3$ (1−3 mol % Pd), 1.2−3.6 mol % ligand **1**, 65 °C, 14−25 h. (2) H^+. [b] Yields represent isolated yields of compounds estimated to be ≥95% pure as judged by ^1H NMR, GC, and combustion analysis (average of two runs). [c] Reaction performed at room temperature with a reaction time of 4 d. [d] Reaction proceeded to ∼95% conversion. [e] Reaction performed with **2** as the supporting ligand. [f] Yield represents an average of three runs. [g] 3 equiv of $LiN(TMS)_2$ used.

temperature, we were able to minimize the formation of this silylated material, and the product was obtained in 64% yield.[22] We also observed that the coupling of aryl halides containing functional groups (phenols, alcohols, and amides) ortho to the halide is unsuccessful. However, use of non-functionalized ortho-substituted aryl halides affords the desired product in good yield (entry 10). Surprisingly, aryl halides containing a *N*-BOC moiety are not compatible with this method as cleavage of the BOC group is observed.

We were puzzled as to why this transformation works using $LiN(TMS)_2$, but is unsuccessful when other bases, such as NaO*t*-Bu, LiO*t*-Bu, or K_3PO_4 (except in the case of substrates containing a ketone) are employed. We considered the possibility that formation of an in situ protected substrate prevents the amide, alcohol, phenol, or ketone from binding to the palladium (preventing catalyst deactivation). We postulated that because Si−O bonds are significantly stronger than a N−Si bond,[23] perhaps a trimethylsilyl group is

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(21) At this elevated temperature the 3-silated product may result from lithium−halogen exchange, followed by a silyl group transfer.

(22) The reaction only proceeded to ca. 95% conversion.

(23) *Comprehensive Organometallic Chemistry. The Synthesis, Reactions, and Structures of Organometallic Compounds*, 1st ed.; Pergamon Press: New York, 1982; Vol. 2.

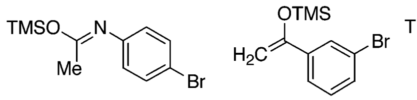


Figure 2. Proposed silylated intermediates.

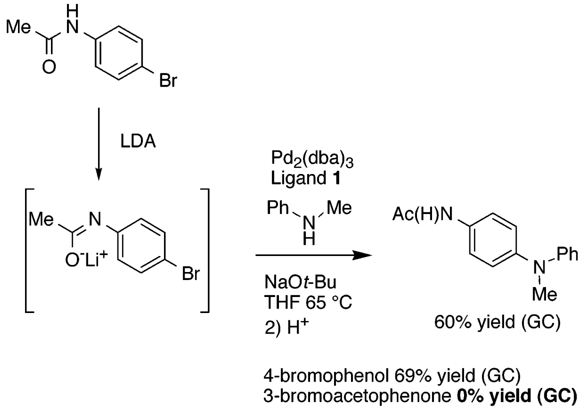
transferred from $LiN(TMS)_2$ to the oxygen atom of the amide, alcohol, or ketone (Figure 2).

To probe the veracity of this hypothesis, we devised a set of experiments to test whether formation of a silylated intermediate was necessary to account for the compatibility of these functional groups. For example, we combined 4-bromoacetanilide with LDA in THF at room temperature. After stirring for 5 min, the contents of this flask were added to a flask containing $Pd_2(dba)_3$, **1**, *N*-methylaniline, and NaO*t*-Bu, and the reaction mixture was stirred at 65 °C (Scheme 3). If formation of a silylated intermediate is necessary for the reaction to proceed, then no product should be observed.

In fact, under these conditions, the desired product was formed in 60% yield (as determined by GC). An identical protocol with 4-bromophenol as the substrate yielded the desired product in 69% yield (GC analysis). However, when 3-bromoacetophenone was used as the substrate, no desired product was formed. Further, coupling reactions with 4-bromoacetanilide or 4-bromophenol with *N*-methylaniline where the LDA deprotonation step was omitted yielded none of the desired product.

The results of these experiments imply that in situ silylation of the oxygen of the phenol or amide is not required for the success of the reaction. Instead, we suggest that perhaps the lithiate or a lithium-amide aggregate[24] of the deprotonated substrate functions as a protecting group, thus inhibiting binding of the oxygen to the palladium center. The experimental results of the reaction with 3-bromoacetophenone, while not conclusive, are consistent with the notion that a silylated intermediate may be required and that in situ silylation may be occurring when $LiN(TMS)_2$ is used as the base.

Scheme 3. Use of LDA to Deprotonate the Acidic Hydrogen and Subsequent Palladium-Catalyzed Coupling Reaction



In summary, we have developed a method for the use of $LiN(TMS)_2$ as the base in Pd-catalyzed C−N bond-forming reactions with substrates containing alcohol, phenol, ketone, or amide groups. This method expands the utility of this methodology by allowing for the use of substrates containing these functional groups. Investigations to understand the factors behind these results are underway.

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

OL0262688

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[24] Lucht, B. L.; Collum, D. B. *Acc. Chem. Res.* **1999**, *32*, 1035.