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Palladium-catalyzed arylation of *N*,*N*-dialkylhydrazines and the subsequent conversion to anilines

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Abstract—Palladium-catalyzed aminations of different ArBr with *N*,*N*-dialkylhydrazines are described. The reaction proceeded in moderate to excellent yield (up to 90%) with good functional groups compatibilities as cyano, ester, ketone and Boc-amine groups are all well tolerated. Several hydrazines were proved to be good coupling partners and this process provided a general method for the isosteric replacement of benzyl amines with arylhydrazines. Moreover, a method for the N–N bond cleavage of arylhydrazines was discovered, and this two-step sequence could be employed as an alternative synthesis of aniline derivatives.

Isosteric replacement is one of the most important strategies employed in the exploration of structure activity relationship.[1] The replacement of $-CH_2-$ with –O– or –NH– is frequently encountered[1] because such a change in structure will not alter the steric properties of the molecule, thereby allowing one to focus on the electronic effect without complications. Benzyl amine moieties are frequently seen as drug fragments.[1] One of their isosteric counterparts is the phenylhydrazine derivative (Fig. 1). Compared to benzylamines, the corresponding phenylhydrazines are different in terms of pK_a and hydrogen bonding properties. As a result, such replacement would provide a tool to understand the electronic requirement for the potent binding of drugs containing such a moiety to their targets. Based on these reasons, a general synthesis of phenylhydrazine derivatives is highly desirable.

With the recent advancement in palladium-catalyzed aminations from the Hartwig[2] and Buchwald[3] groups, we envisaged that these phenylhydrazine derivatives could originate from a palladium-catalyzed amination of aryl halides with readily available *N*,*N*-dialkylhydrazines. A few aminations using hydrazines have been published,[4a] which involved hydrazines with an sp[2] hybridized carbon attached to one of the nitrogens. However, at the time of our research, little was published on amination with *N*,*N*-dialkylhydrazines and the yield was poor (24%), using an earlier generation of catalyst system developed in Hartwig and Buchwald's labs.[4b] After we completed this research, two groups, Cacchi[4c] and Pujol,[4d] independently published N-arylations of *N*,*N*-dialkylhydrazines. However, the method by Cacchi[4c] using Xantphos as a catalyst requires the generation of *N*,*N*-dialkylhydrazine/2LiCl adducts and a change of solvent for the subsequent arylation reactions. Furthermore, the use of a strong base, NaO–*t*-Bu, limited the tolerance of functional groups to the reaction conditions. Replacing NaO–*t*-Bu with a weaker base Cs_2CO_2 gave only trace amount of the product. Pujol[4d] reported only three examples of N-arylation of

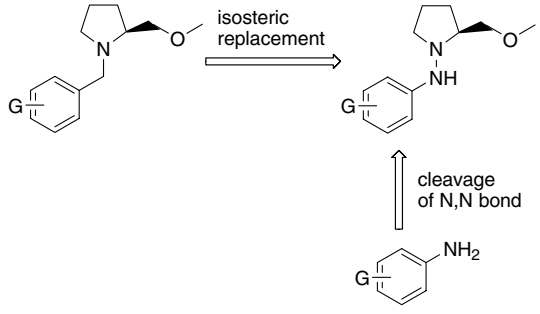

Figure 1.

Keywords: *N*,*N*-Dialkyl-*N*′-arylhydrazine; Aniline; Amination; Arylation.
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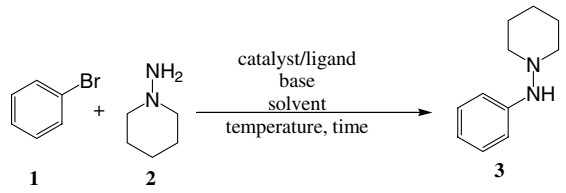


Scheme 1.

N,*N*-dimethylhydrazine, using $Pd[P(o\text{-tolyl})_3]_2Cl_2$ and BINAP or PPh_3 and Cs_2CO_3. The reactions were carried out at 150 °C without solvent and the scope of this methodology is not clear. Herein, we wish to report our effort in the synthesis of *N*,*N*-dialkylarylhydrazines and their conversion into anilines.

We began our studies with the model reaction as shown in Scheme 1. The commercially available 1-aminopiperidine, **2**, was coupled with phenyl bromide, **1**, under various conditions to give hydrazine **3**. The yields were obtained through the analysis of the GC chromatograms, with trimethoxybenzene as an internal standard. As expected, the reactions worked best with bulky, electron-rich phosphines such as $P(t\text{-Bu})_3$ as ligands;[2,3] PPh_3, PCy_3, BINAP and DPPF failed to produce significant amounts of product with Cs_2CO_3 as the base, in toluene. Using $Pd_2(dba)_3/P(t\text{-Bu})_3$ as the catalyst system, we also tested different bases in this reaction. Although strong bases such as KO–*t*-Bu were effective, anhydrous solvents were needed and functional groups were less tolerated. Both K_2CO_3 and K_3PO_4 were suitable bases, however, Cs_2CO_3 provided the best yield. The reaction proceeded in DME giving **3** in a yield similar to the one run in toluene, whereas the use of DMF as a solvent gave inferior results. It is necessary to point out that the reactions gave comparable yields regardless of the moisture content in the solvent, toluene.

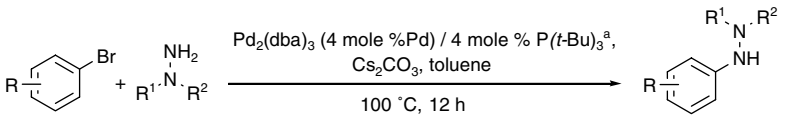
With these results in hand, we then set out to explore the scope of this reaction. One equivalent of ArBr was coupled with 1.5 equiv of hydrazines in the presence of $Pd_2(dba)_3$ (4 mol % Pd) as a catalyst, 4 mol % $P(t\text{-Bu})_3{\cdot}HBF_4$[5] as a ligand and 2.5 equiv of Cs_2CO_3 as a base in toluene at 100 °C [Although the reactions were generally carried out using 4 mol % Pd as a catalyst, phenyl bromide was successfully coupled with 1-aminopiperidine using 1 mol % Pd as a catalyst to provide **3** in 71% isolated yield (Table 1, entry 1).][6] Electron-neutral ArBr and sterically hindered ArBr were suitable substrates as the *o*-tolyl bromide and *o*,*o*-dimethylphenyl bromide were aminated in excellent yields (entries 3 and 5). Aryl bromides bearing electron withdrawing groups such as *m*-trifluoromethyl also reacted with 1-aminopiperidine to give the desired product in 61% yield (entry 6). ArBr bearing strong electron donating groups, such as 4-*N*,*N*-dimethylamino-phenylbromide, were also tested, however, the results were much poorer (data not shown).

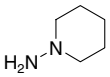
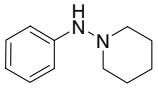
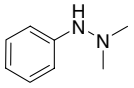
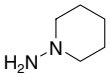
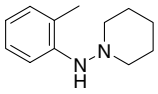
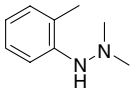
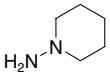
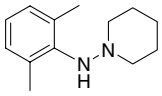
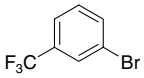
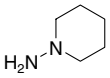
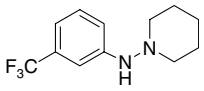
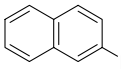
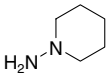
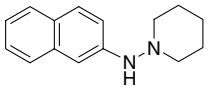
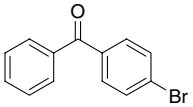
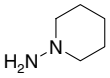
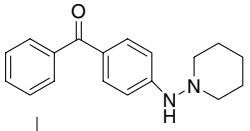
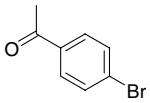
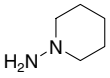
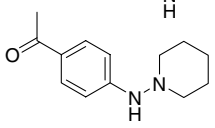
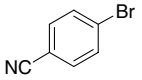
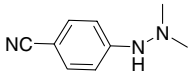
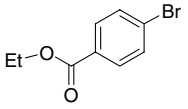
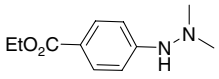
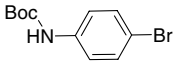
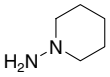
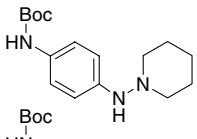
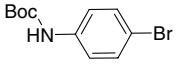
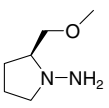
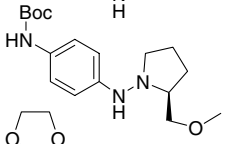
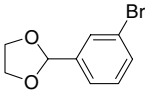
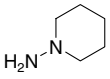
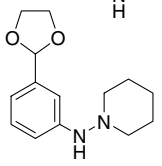
A variety of functional groups such as cyano, ester, ketone (entries 8–11) were tolerated in the reaction. Especially in the case of *p*-bromoacetophenone, even though the acetyl group[7] is vulnerable to nucleophilic attack and potential enolization, the reaction still proceeded to afford the desired product in 61% yield (entry 9). The success of this reaction might be due to the possibilities that the ketone arylation was slower than the amination, or the hydrazine reacted with the ketone to form a hydrazone thus protecting it from arylation at the α methyl group. However, the failure to obtain product from an arylbromide carrying a formyl group suggested that the protection mechanism is less likely. The reaction was also found to be effective in the presence of an acidic N–H group (entries 12 and 13): the 4-Boc-amino phenyl bromide was aminated with 1-aminopiperidine in 74% yield.

In addition to 1-aminopiperidine, other *N*,*N*-dialkylhydrazines have also been employed in the amination studies (entries 2, 4, 10, 11 and 13). 1,1-Dimethylhydrazine reacted with aryl bromides to give yields similar to the ones obtained with 1-aminopiperidine (entries 1–4). The sterically more hindered SAMP [(*S*)-1-amino-2-methoxylpyrrolidine] was also arylated to provide the desired product in 75% yield (entry 13). Since dialkyl hydrazines were readily available through a simple transformation from dialkylamines, the amination chemistry shown here could be used with great convenience in the isosteric replacement of benzyl amines with arylhydrazines (Fig. 1).

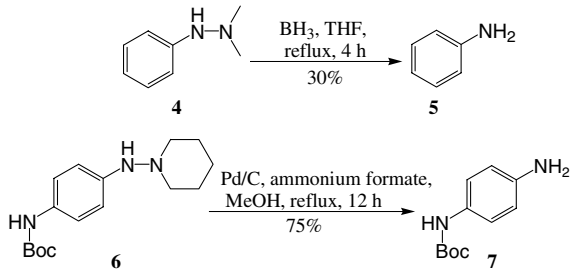
One of the well-known applications of hydrazines in organic synthesis was demonstrated by the Enders group[8] in using SAMP/RAMP [(*R*)-1-amino-2-methoxylpyrrolidine] as a chiral auxiliary to prepare secondary amines enantioselectively. The success of this methodology prompted us to study the possibility of combining our amination chemistry with an easy cleavage method to provide a two-step sequence for preparing aniline derivatives. Many ammonia equivalents[9] were developed for the synthesis of aniline derivatives from aryl bromides, each with its own advantage and limitation. One of the advantages of using the *N*,*N*-dialkylhydrazines as ammonia surrogates is that the arylation chemistry tolerates a variety of functional groups, and methods for cleavage of N–N bonds are known in the literature.[8] Furthermore, after cleavage of the N–N bonds, the byproduct would be low molecular weight *sec*-amines, which could be easily washed away in the workup. With this in mind, we briefly tested our hypothesis. We first heated hydrazine **4** with excess borane[8] in refluxing THF for 4 h, and then released aniline **5** from the borane complex via methanolysis. To our dismay, the aniline was isolated only in 30% yield (Scheme 2). We then turned our attention to palladium-catalyzed transfer hydrogenation to cleave the N–N bond. The Boc-protected amine **6** was heated at reflux with ammonium formate and 10 mol % Pd/C in MeOH for 12 h. To our delight, the desired aniline **7** was obtained in 75% yield. As predicted, purification of the product was easy via a simple aqueous workup to wash away the byproduct piperidine. This result demonstrated the potential use of these *N*,*N*-dialkylhydrazines as ammonia surrogates.

Table 1. Scope of the amination of aryl bromides with *N*,*N*-dialkylhydrazines



Entry	ArBr	Hydrazine	Product	Yield[b] (%)
1	PhBr			71[c]
2	PhBr			72
3	*o*-Tolyl bromide			90
4	*o*-Tolyl bromide			75
5				83
6				61
7				71
8				72
9				61
10				75
11				46
12				74
13				75
14				45

[a] $P(t\text{-Bu})_3 \cdot HBF_4$ was used in the reaction for easy handling. A small run using free $P(t\text{-Bu})_3$ gave similar results.
[b] Isolated yields on 0.5 mmol scale.
[c] 1 mol % Pd and 2 mol % ligand were used.



Scheme 2.

In summary, by using palladium-catalyzed aminations with *N*,*N*-dialkylhydrazines, we were able to provide a general and practical synthesis of *N*,*N*-dialkyl-*N*′-aryl-hydrazines which are isosteres of benzyl amines. Under the reaction condition, various functional groups were tolerated and the yields were moderate to excellent. Moreover, we have demonstrated that the cleavage of the N–N bond could be accomplished in good yield, to provide an alternative method for the synthesis of anilines.

Acknowledgements

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References and notes

1. *Burger's Medicinal Chemistry and Drug Discovery*; Wolff, M. E., Ed.; John Wiley & Sons: New York, 1996; Vol. 5, pp 1–5; Silverman, R. B. *The Organic Chemistry of Drug Design and Drug Action*, 2nd ed.; Elsevier/Academic Press: San Diego, 2004.
2. Hartwig, J. F. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2002; pp 107; Hartwig, J. F. In *Handbook of Organopalladium Chemistry for organic Synthesis*; Negishi, A. de Meijere, Ed.; Wiley: New York, 2002; Vol. 1, pp 1051.
3. Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131; Buchwald, S. L.; Wagaw, S.; Geis, O. WO9943643, 1999.
4. (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2090; Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6621; Lim, Y.; Lee, K.; Cho, C. *Org. Lett.* **2003**, *5*, 979; Arterburn, J. B.; Rao, K. V.; Ramdas, R.; Dible, B. R. *Org. Lett.* **2001**, *3*, 1351; (b) Buchwald; S. L.; Wagaw, S.; Geis, O. WO9943643, 1999; (c) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Licandro, F.; Maiorana, S.; Perdicchia, D. *Org. Lett* **2005**, *7*, 1497; (d) Harrack, Y.; Romero, M.; Constans, P.; Pujor, M. D. *Lett. Org. Chem* **2006**, *3*, 29.
5. Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.
6. *Representative procedure: Piperidin-1-yl-o-tolyl-amine* (Table 1, entry 3): To a round bottom flask were added *o*-bromotoluene (0.179 g, 1.046 mmol), 1-aminopiperidine (0.157 g, 1.557 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.022 g, 0.021 mmol), $P(t\text{-}Bu)_3{\cdot}HBF_4$ (0.014 g, 0.048 mmol) and cesium carbonate (0.814 g, 2.498 mmol). Toluene (8 mL) was then added. The mixture was degassed and heated at 100 °C for 12 h. After the mixture was cooled to room temperature, water was added and the toluene layer was collected and directly loaded on the silica-gel column; the title compound (0.1789 g, 90%) was isolated using 3% EtOAc/hexane as eluent: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (1H, dd, $J = 8.0$ and 1.2 Hz), 7.12 (1H, dt, $J = 8.4$ and 1.2 Hz), 7.02 (1H, d, $J = 7.2$ Hz), 6.70 (1H, dt, $J = 7.2$ and 1.6 Hz), 4.24 (1H, br), 2.66 (4H, br), 2.11 (3H, s), 1.69 (4 H, m), 1.43 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.36, 130.12, 126.99, 121.42, 118.43, 112.87, 57.55, 26.11, 23.77, 17.29; Anal. Calcd for $C_{12}H_{18}N_2$: C, 75.74; H, 9.53; N, 14.72. Found: C, 75.89; H, 9.09; N, 14.71.
7. Lee, D.; Hartwig, J. F. *Org. Lett.* **2005**, *7*, 1169.
8. (a) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253; (b) Enders, D.; Moll, A.; Schaadt, A.; Raabe, G.; Runsink, J. *Eur. J. Org. Chem.* **2003**, 3923.
9. Wolfe, J. P.; Ahman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367; Jaime-Figueroa, S.; Liu, Y.; Muchowski, J. M.; Putman, D. G. *Tetrahedron Lett.* **1998**, *39*, 1313; Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaugnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575; Lee, S.; Jorgensen, M.; Hartwig, J. F. *Org. Lett.* **2001**, *3*, 2729; Huang, X.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3417; Lee, D.; Hartwig, J. F. *Org. Lett.* **2005**, *7*, 1169.