J|A|C|S
COMMUNICATIONS

Published on Web 08/02/2007

Selective Palladium-Catalyzed Arylation of Ammonia: Synthesis of Anilines as Well as Symmetrical and Unsymmetrical Di- and Triarylamines

David S. Surry and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received June 26, 2007; E-mail: sbuchwal@mit.edu

Traditionally di- and triarylamines have been prepared by the reaction of an aromatic amine and an aryl halide mediated by palladium,[1] copper,[2] or nickel.[3] The palladium-catalyzed conversion of aryl halides and pseudo-halides to anilines with ammonia surrogates[4] has also become a process of increasing importance in pharmaceutical research,[5] materials science,[6] and synthetic chemistry.[7] The coupling of ammonia with aryl halides as a means to access aromatic amines is thus an attractive goal.[8,9] Recently the first example of such a transformation to yield anilines was reported by Hartwig employing a Josiphos-ligated palladium complex.[10] In this paper it was quite reasonably suggested that a tightly chelating ligand was necessary to achieve selective monoarylation. Our recent studies in the production of phenols by the arylation of KOH[11] prompted us to examine the reaction of ammonia and aryl halides using monodentate ligands. We now report that with a judicious choice of ligand it is possible to prepare, in a selective manner, not only anilines but also symmetrical and unsymmetrical di- and triarylamines.

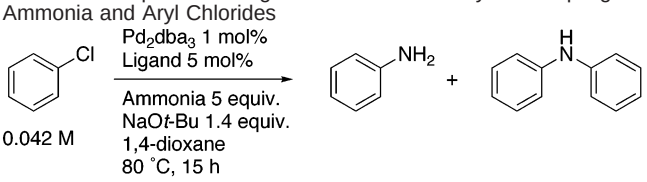
These new investigations revealed that an efficient catalyst for the synthesis of anilines was formed from the combination of 1.0 mol % Pd_2dba_3 and 5.0 mol % of biaryl phosphine ligand **4** in the presence of 5 equiv of ammonia and NaO*t*-Bu (1.4 equiv) at 80 °C in a sealed test tube (Table 1). Use of 1,4-dioxane as solvent provided the optimal yield of product and allowed a convenient protocol to be developed in which a commercially available solution of ammonia 0.5 M in 1,4-dioxane could be used as the source of ammonia (thereby allowing accurate control over the stoichiometry of the reaction). The identity of the dialkylphosphino group of the ligand was important, ligands bearing a dicyclohexylphosphino group (ligands **1**, **3**, and **5**) gave predominantly diarylamine products under these conditions, whereas those with a di(*t*-butyl)phosphino group yielded mainly the aniline (ligands **2**, **4**, and **6**). The concentration of the reactants was also found to be significant, when the concentration of aryl halide was increased above 0.05 M, the diarylamine became the major product with all ligands examined, in accordance with Hartwig's results. The process had a broad scope and was equally useful for electron-deficient and electron-rich aryl chlorides and bromides with or without ortho substituents (Table 2).

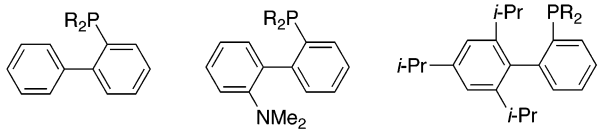
We next turned our attention to the synthesis of symmetrical diarylamines. The best yield of the desired products was achieved by using ligand **5** and performing the reactions at a slightly higher concentration of the aryl halide (0.0625 M) in the presence of 3 equiv of ammonia at 80 °C.

Triarylamines have a wide range of optoelectronic applications because of their ability to act as hole transport materials.[12] In a similar fashion to that employed for the preparation of diarylamines, high yields of triarylamine could be obtained using **5** at a higher concentration of aryl halide (0.66 M) and at 100 °C.

The results described above indicated an ability to selectively mono-, di-, and triarylate ammonia using the same aryl halide. A more challenging task was to devise a process that enabled us to convert ammonia to unsymmetrical di- and triarylamines using two or three different aryl halides.[13] After some experimentation, it proved possible to devise a protocol in which different aryl halides were coupled with ammonia by sequential addition to the same

Table 1. Comparison of Ligands for the Pd-Catalyzed Coupling of Ammonia and Aryl Chlorides

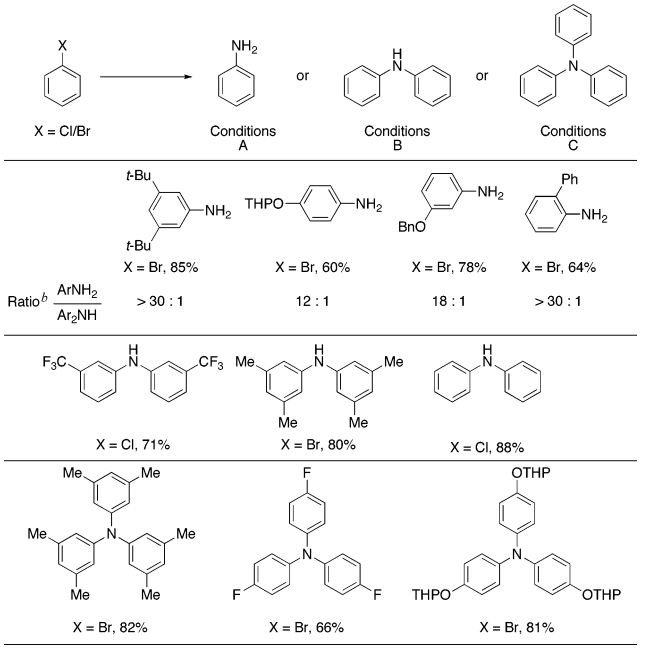




1, R = Cy
2, R = *t*-Bu
3, R = Cy
4, R = *t*-Bu
5, R = Cy
6, R = *t*-Bu

ligand	1	2	3	4	5	6
conversion (%)	46	91	64	100	100	100
$PhNH_2$ (%, GC)	0	52	0	86	15	66
Ph_2NH (%, GC)	28	26	45	7	73	21

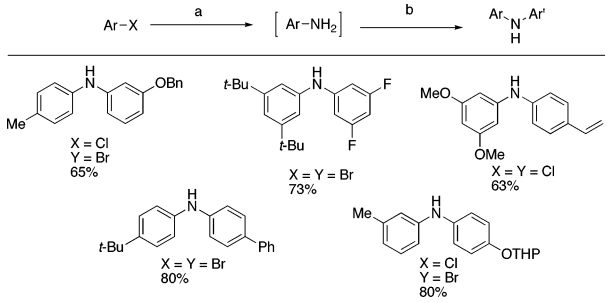
Table 2. Pd-catalyzed Synthesis of Anilines and Symmetrical Di- and Triarylamines from Ammonia and Aryl Halides[a]



[a] All yields are isolated and the average of two runs. Conditions A: (i) Pd_2dba_3, 1 mol %; ligand **4**, 5 mol %; NaO*t*-Bu, 1.4 equiv; NH_3, 5 equiv; 0.042 M, 1,4-dioxane; 80 °C. Conditions B: Pd_2dba_3, 1 mol %; ligand **5**, 5 mol %; NaO*t*-Bu, 1.4 equiv; NH_3, 3 equiv; 0.0625 M, 1,4-dioxane; 80 °C. Conditions C: Pd_2dba_3, 1 mol %; ligand **5**, 5 mol %; NaO*t*-Bu, 1.4 equiv; NH_3, 0.75 equiv; 0.66 M, 1,4-dioxane; 100 °C. [b] Estimated from ^1H NMR spectrum of crude reaction mixture.

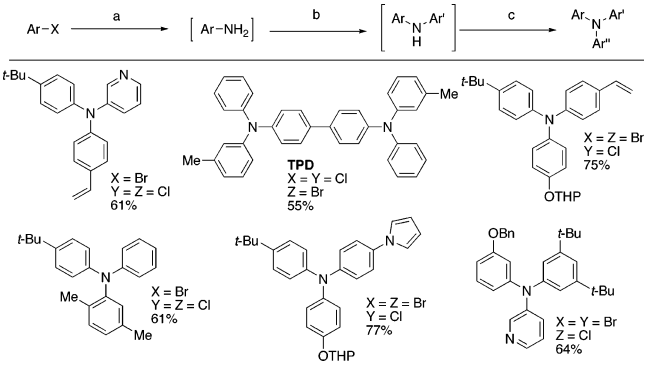
10.1021/ja074681a CCC: $37.00

Table 3. Synthesis of Unsymmetrical Diarylamines from Aryl Halides and Ammonia



[a] Conditions: Pd_2dba_3, 1 mol %; ligand **4**, 5 mol %; NaO*t*-Bu, 2.8 equiv; NH_3, 5 equiv; 1,4-dioxane; 80 °C, 3 h. [b] Conditions: (i) -NH_3, (ii) reduce volume, (iii) Ar′Y, 0.9 equiv; ligand **5**, 5 mol %; 80 °C, 16 h.

Table 4. Synthesis of Unsymmetrical Triarylamines from Aryl Halides and Ammonia



[a] Conditions: Pd_2dba_3, 1 mol %; ligand **4**, 5 mol %; NaO*t*-Bu, 4.2 equiv; NH_3, 5 equiv; 1,4-dioxane; 80 °C, 3 h. [b] Conditions: (i) -NH_3, (ii) reduce volume, (iii) Ar′Y 0.9, equiv; ligand **5**, 5 mol %; 80 °C, 3 h. [c] Conditions: Ar″Z, 0.9 equiv; 100 °C, 16 h.

reaction vessel (Tables 3 and 4). The key to success was to remove excess ammonia from the solution of the aniline initially formed and to reduce the solvent volume before addition of the second aryl halide and **5**.[14] It is interesting that **5** can efficiently displace **4** from the palladium center; this is presumably due to the smaller size of the cyclohexyl- versus *tert*-butylphosphino substituents.[15] Under these conditions functional groups such as alkenes and THP-protected phenols and heterocycles such as pyridines and pyrroles were tolerated. Of particular note is the ability to make the diamine TPD, a molecule which has numerous applications as an organic photoconductor and hole transporter.[16]

In summary we have developed new systems for the palladium-catalyzed coupling of ammonia with aryl halides which allow the selective synthesis of either anilines or di- or triarylamines as desired.

Acknowledgment. We thank the National Institutes of Health (Grant GM-058160) for supporting this work. We thank Merck, Amgen, and Boehringer Ingelheim for additional unrestricted support. We thank Saltigo for a gift of **5**. D.S.S. thanks the Royal Commission for the Exhibition of 1851 for a Research Fellowship.

Supporting Information Available: Complete refs 5b and 5c and experimental information and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Jiang, L.; Buchwald, S. L. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004, p 699.

(2) (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed*. **2003**, *42*, 5400. (b) Kunz, K.; Schloz, A.; Ganzer, D. *Synlett* **2003**, 2428.

(3) (a) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054. (b) Desmarets, C.; Schneider, R.; Fort, Y. *J. Org. Chem*. **2002**, *67*, 3029. (c) Omar-Amrani, R.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett*. **2003**, *5*, 2311. (d) Chen, C.; Yang, L.-M. *Org. Lett*. **2005**, *7*, 2209. (e) Kelly, R. A., III; Scott, N. M.; Díez-González, S.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2005**, *24*, 3442.

(4) (a) Wolfe, J. P.; Åhman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367. (b) Jaime-Figuerosa, S.; Liu, Y.; Muchowski, J. M.; Putman, D. G. *Tetrahedron Lett.* **1998**, *39*, 1313. (c) Hori, K.; Mori, M. *J. Am. Chem. Soc.* **1998**, *120*, 7651. (d) Lim, C. W.; Lee, S.-G. *Tetrahedron* **2000**, *56*, 5131. (e) Huang, X. H.; Buchwald, S. L. *Org. Lett*. **2001**, *3*, 3417. (f) Lee, S.; Jørgensen, M.; Hartwig, J. F. *Org. Lett.* **2001**, *3*, 2729. (g) Lee, D. Y.; Hartwig, J. F. *Org. Lett*. **2005**, *7*, 1169.

(5) For recent examples see: (a) Denni-Dischert, D.; Marterer, W.; Bänziger, M.; Yusuff, N.; Batt, D.; Ramsey, T.; Geng, P.; Michael, W.; Wang, R.-M. B.; Taplin, F., Jr.; Versace, R.; Cesarz, D.; Perez, L. B. *Org. Process Res. Dev*. **2006**, *10*, 70. (b) Li, Q.; et al. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 2000. (c) Huang, H. C.; et al. *J. Med. Chem.* **2005**, *48*, 5853. (d) Humphries, A. C.; Gancia, E.; Gilligan, M. T.; Goodacre, S.; Hallett, D.; Merchant, K. J.; Thomas, S. R. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 1518.

(6) For recent examples see: (a) Kang, H.; Facchetti, A.; Jiang, H.; Cariati, E.; Righetto, S.; Ugo, R.; Zuccaccia, C.; Macchioni, A.; Stern, C. L.; Liu, Z.; Ho, S.-T.; Brown, E. C.; Ratner, M. A.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, *129*, 3267. (b) Lukey, C. A.; Tymichova, M.; Brown, H. R. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 1282. (c) Agou, T.; Kobayashi, J.; Kawashima, T. *Org. Lett*. **2006**, *8*, 2241. (d) Flatt, A. K.; Chen, B.; Taylor, P. G.; Chen, M.; Tour, J. M. *Chem. Mater*. **2006**, *18*, 4513. (e) Kang, H.; Facchetti, A.; Stern, C. L.; Rheingold, A. L.; Kassel, W. S.; Marks, T. J. *Org. Lett.* **2005**, *7*, 3721.

(7) For selected examples see: (a) Sato, H.; Fujihara, T.; Obora, Y.; Tokunaga, M.; Kiyosu, J.; Tsuji, Y. *Chem. Commun*. **2007**, 269. (b) Bolm, C.; Frison, J-C.; Le Paih, J.; Moessner, C.; Raabe, G. *J. Organomet. Chem.* **2004**, *689*, 3767. (c) Ball, P. J.; Shtoyko, T. R.; Bauer, J. A. K.; Oldham, W. J.; Connick, W. B. *Inorg. Chem.* **2004**, *43*, 622. (d) Liu, Y.; McWhorter, W. W., Jr. *J. Am. Chem. Soc*. **2003**, *125*, 4240.

(8) Willis, M. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3402.

(9) For synthesis of di- and triarylamines from aryl halides and urea in a process that may involve the in situ generation of ammonia: (a) Artamkina, G. A.; Sergeev, A. G.; Shtern, M. M.; Beletskaya, I. P. *Russian J. Org. Chem.* **2006**, *42*, 1683. (b) Artamkina, G. A.; Sergeev, A. G.; Shtern, M. M.; Beletskaya, I. P. *Synlett* **2006**, 235.

(10) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc*. **2006**, *128*, 10028.

(11) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc*. **2006**, *128*, 10694.

(12) (a) Shirota, Y. *J. Mater. Chem.* **2000**, *10*, 1. (b) Shirota, Y. *J. Mater. Chem.* **2005**, *15*, 75.

(13) (a) Thayumanavan, S.; Barlow, S.; Marder, S. R. *Chem. Mater.* **1997**, *9*, 321. (b) Harris, M. C.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5327. (c) Nozaki, K.; Takahashi, K.; Nakano, K.; Hiyama, T.; Tang, H. Z.; Fujiki, M.; Yamaguchi, S.; Tamao, K. *Angew. Chem., Int. Ed*. **2003**, *42*, 2051.

(14) General procedure for the synthesis of unsymmetrical triarylamines: Pd_2dba_3 (4.6 mg, 0.005 mmol), ligand **4** (8.5 mg, 0.025 mmol), sodium *tert*-butoxide (202 mg, 2.1 mmol), and aryl halide **a** (0.5 mmol) (if solid) were weighed into an oven-dried test-tube which was sealed with a Teflon screw cap. The tube was then evacuated and back-filled with argon. 1,4-Dioxane (5 mL), ammonia (3 mL of a 0.5 M solution in 1,4-dioxane, 1.5 mmol), and the aryl halide **a** (0.5 mmol) (if liquid) were then added by syringe. The tube was then placed in a preheated oil bath at 80 °C for 3 h. At the end of this time the tube was removed from the bath and allowed to cool, and the tube was evacuated and ultrasonicated until the total solvent volume was reduced to approximately 3 mL and back-filled with argon. The Teflon screw cap was then briefly removed, and ligand **5** (11.9 mg, 0.025 mmol) and aryl halide **b** (0.45 mmol) (if solid) were added. If liquid aryl halide **b** (0.45 mmol) was then added by syringe. The tube was then evacuated, back-filled with argon, and replaced in the oil bath at 80 °C for 3 h. At the end of this time the tube was removed from the bath and allowed to cool. If aryl halide **c** were solid the Teflon screw cap was removed and aryl halide **c** (0.45 mmol) was added. The tube was then evacuated and back-filled with argon. If aryl halide **c** was a liquid, the Teflon screw cap was not removed and the aryl halide **c** (0.45 mmol) was added by syringe. The tube was then placed in a preheated oil bath at 100 °C for 16 h. At the end of this time the tube was removed from the bath, the contents diluted with EtOAc, and the mixture filtered through a plug of silica. The solution was then concentrated under reduced pressure, and the residue was purified on the Biotage SP4.

(15) Yang, Q.; Ney, J. E.; Wolfe, J. P. *Org. Lett*. **2005**, *7*, 2575.

(16) TPD = *N*,*N*′-bis(3-methylphenyl)-*N*,*N*′-diphenylbenzidine, for example: Shen, Y.; Klein, M. W.; Jacobs, D. B.; Scott, J. C.; Malliaras, G. G. *Phys. Rev. Lett.* **2001**, *86*, 3867.

JA074681A