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# Pd catalyzed coupling of 1,2-dibromoarenes and anilines: formation of *N*,*N*-diaryl-*o*-phenylenediamines

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**Abstract**—1,2-Dibromoarenes were coupled with aniline derivatives to yield *N*,*N*-diaryl-*o*-phenylenediamines in moderate to good yield using a palladium/phosphine or palladium/carbene catalyst system. Under similar conditions, 1,2,4,5-tetrabromobenzene was coupled with aniline derivatives to produce the corresponding tetrasubstituted derivatives which are oxidized on workup to yield azophenines. The sequential reaction of two different anilines with 1-chloro-2-iodobenzene afforded mixed *N*,*N*-diaryl-*o*-phenylenediamines.

The palladium catalyzed coupling of aryl halides and aryl amines has been the subject numerous studies since the groups of Hartwig[1] and Buchwald[2] developed efficient synthetic protocols to carry out this transformation. Generally the coupling is carried out using a Pd(0) or Pd(II) catalyst precursor with an appropriate phosphine ligand and a base. More recently Nolan and co-workers have reported that similar coupling reactions occur when an Arduengo carbene replaces the phosphine as the ancillary ligand.[3] Although many Pd catalyzed couplings of aryl halides and aryl amines have been carried out, the synthesis of *N*,*N*-diaryl-*o*-phenylenediamine derivatives have not been reported using this methodology. The compound, *N*,*N*-diphenyl-*o*-phenylenediamine has been known for some time[4] and various other *N*,*N*-diaryl-*o*-phenylenediamine derivatives have been synthesized[5] however, the procedures reported here are relatively simple and can be used to produce *N*,*N*-diaryl-*o*-phenylenediamine derivatives in moderate to good isolated yields.

The *N*,*N*-diaryl-*o*-phenylenediamines were synthesized[6] by the procedure shown in Scheme 1, which follows that reported by Hartwig for the synthesis of triarylamines.[7] Compounds **2a**, **4a**, and **4b** were prepared using the carbene, 1,3-bis(2,6-diisopropylphenyl)-4,5-dimethyl-imidazol-2-ylidene,[8] instead of $P^tBu_3$, following the same procedure except that only 2 equiv of the carbene were used. Generally, the reactions were allowed to proceed for 12–16 h but in most cases are finished in a much shorter time. For example, the reaction to produce **2b** was followed by GC and was completed in less than 5 h.

Compounds **1**–**5** were isolated as light brown or light green crystalline solids and shown to be pure by $^1$H and $^{13}$C NMR and C, H, N analysis. When rigorously purified, the *N*,*N*-diaryl-*o*-phenylenediamine complexes are colorless. In the $^1$H NMR spectra the N–*H* resonances typically appeared as broad singlets in the range $\delta$ 4.8–5.2. Full experimental procedures and characterization are given in the Supplementary data.

Using $P^tBu_3$ as the supporting ligand, the reaction of one equivalent of aniline derivative with a 1,2-dibromoarene yielded the disubstituted products **1**–**5** as the sole or major product. Thus it appears that the coupling of the second equivalent of aniline to the intermediate monobromodiaryl amine is faster than addition of the first equivalent of aniline to the 1,2-dibromoarene. However, the use of 1-chloro-2-iodobenzene afforded monosubstituted products that could then be further

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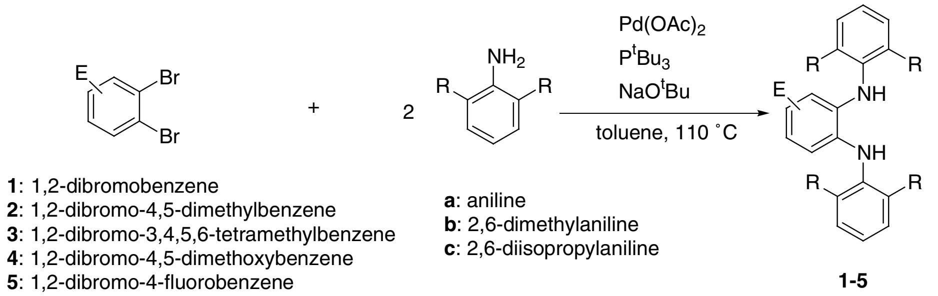
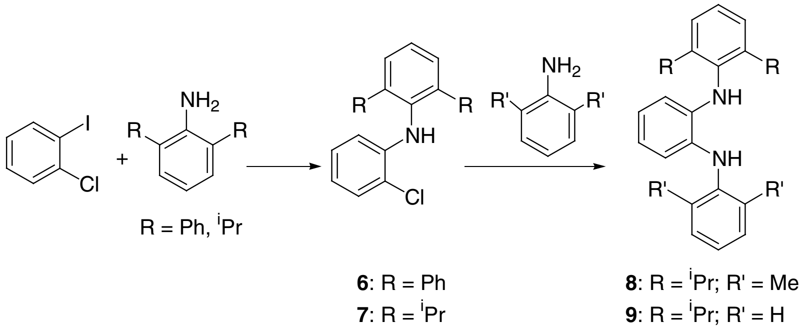


**1**: 1,2-dibromobenzene
**2**: 1,2-dibromo-4,5-dimethylbenzene
**3**: 1,2-dibromo-3,4,5,6-tetramethylbenzene
**4**: 1,2-dibromo-4,5-dimethoxybenzene
**5**: 1,2-dibromo-4-fluorobenzene

**a**: aniline
**b**: 2,6-dimethylaniline
**c**: 2,6-diisopropylaniline

**1-5**

**Scheme 1.**

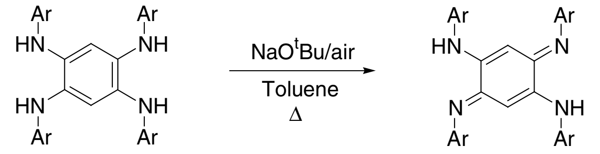


R = Ph, $^i$Pr

**6**: R = Ph
**7**: R = $^i$Pr

**8**: R = $^i$Pr; R' = Me
**9**: R = $^i$Pr; R' = H

**Scheme 2.**



**11b**: Ar = 2,6-dimethylaniline
**11c**: Ar = 2,6-diisopropylaniline

**10b**: Ar = 2,6-dimethylaniline
**10c**: Ar = 2,6-diisopropylaniline

**Scheme 3.**

substituted to make mixed derivatives as shown in Scheme 2. Monosubstituted compound **6** and the compounds **8** and **9** were isolated as crystalline solids. Compound **7** was isolated as an oil of about 90% purity (by $^1$H NMR); this proved to be suitable for further reactions.

1,2,4,5-Tetrabromobenzene reacted with 2,6-dimethylaniline and 2,6-diisopropylaniline to produce the azophenines **10b** and **10c**. The reaction of 1,2,4,5-tetrabromobenzene with 2,6-dimethylaniline was conducted with 1,3-bis(2,6-diisopropylphenyl)-4,5-dimethylimidazol-2-ylidene as the ancillary ligand and the crude azophenine **10b** was obtained as a mixture that contained the unoxidized 1,2,4,5-tetrakis(2,6-dimethylamino)benzene derivative **11b** (Scheme 3). The mixture of unoxidized tetramine **11b** and azophenine **10b** was oxidized cleanly to the azophenine derivative **10b** by heating a toluene solution of the mixture and NaO$^t$Bu in air. The reaction with 2,6-diisopropyl aniline was conducted with P$^t$Bu$_3$ as the ancillary ligand and the azophenine **10c** was obtained in low yield as the sole isolated product.

At 25 °C both azophenine derivatives showed single N–H proton resonances, indicative of rapid tautomerization on the NMR time scale.[9] These resonances occur significantly upfield from those in the diamines **1**–**5** [$\delta$ 7.87 for both **10b** and **10c** in $CD_2Cl_2$]. The IR shifts were also in the expected region (**10b**: $\nu_{N-H} = 3303\,cm^{-1}$; **10c**: $\nu_{N-H} = 3308\,cm^{-1}$).[10]

Presumably the azophenine **10c** is also derived from oxidation of the initially formed 1,2,4,5-tetrakis(2,6-diisopropylamino)benzene derivative **11c**, which was not isolated or observed spectroscopically. Some *N*-alkyl substituted 1,2,4,5-tetra(alkylamido)benzenes are also oxidized during work-up in air.[11] In fact, all of the *N*,*N*-diaryl-*o*-phenylenediamines **1**–**5** are readily oxidized in air in the presence of a base such as NaO$^t$Bu. The nature of these products will be the subject of a future report. Oxidation of the diamines **1**–**5** during work-up was avoided by quenching the excess base present in the reaction mixture via addition of an aqueous $NH_4Cl$ solution immediately upon exposure of the reaction mixture to air.

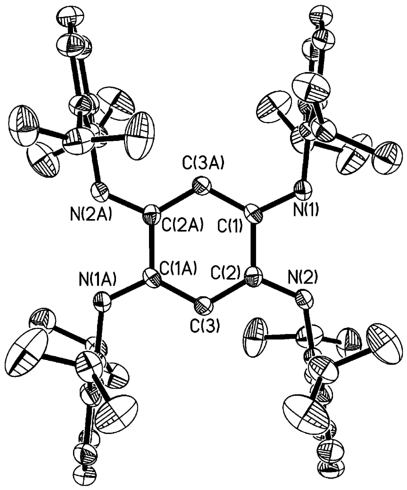


**Figure 1.** ORTEP drawing of azophenine derivative **11c**. Selected bond lengths (Å): N(1)–C(1) 1.312(4); N(2)–C(2) 1.339(4); C(1)–C(2) 1.498(4); C(2)–C(3) 1.378(4); C(3)–C(1A) 1.398(4). Selected bond angles (°): N(1)–C(1)–C(2) 115.2(3); C(1)–C(2)–N(2) 114.6(3); N(2)–C(2)–C(3) 125.6(3).

A thermal ellipsoid diagram of **11c** is shown in Figure 1.[†] The crystal contains two independent molecules, which are essentially equivalent except for slight differences in bond lengths and angles. The four N atoms and the central ring are co-planar; the N(2)–C(2) and N(1)–C(1) bond lengths are 1.339(4) and 1.312(4) Å, respectively. The bond length of 1.498(4) Å between C(1) and C(2) is significantly longer than the C(2)–C(3) and C(3)–C(1A) bond lengths of 1.378(4) and 1.398(4) Å. Thus the molecule may be described as composed of two equivalent, delocalized, 6-electron π systems, (the N(1)–C(1)–C(3A)–C(2A)–N(2A) unit and the N(2)–C(2)–C(3)–C(1A)–N(1A) unit), which are not conjugated but are joined by C–C bonds.[12,13]

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.07.116. Detailed synthetic procedures and NMR data for all compounds are available. The supplementary data is available online with the paper in ScienceDirect. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 234276. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

## References and notes

1. Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046–2067.
2. Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818.
3. (a) Viciu, M. S.; Kissling, R. M.; Stevens, E. D.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 2229–2231; (b) Stauffer, S. R.; Lee, S. W.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423.
4. (a) Clemo, G. R.; Perkin, W. H.; Robinson, R. *J. Chem. Soc.* **1924**, 1751–1804; (b) Bourson, J. *Bull. Soc. Chim. Fr.* **1970**, *5*, 1867–1872; (c) Chakrabarty, M.; Batabyal, A.; Khasnobis, S. *Synth. Commun.* **2000**, *30*, 3651–3668.
5. (a) Olivier Baudoin, O.; Teulade-Fichou, M.-P.; Vigneron, J.-P.; Lehn, J.-M. *J. Org. Chem.* **1997**, *62*, 5458–5470; (b) Trinks, U.; Buchdunger, E.; Furet, P.; Kump, W.; Mett, H.; Meyer, T.; Mueller, M.; Regenass, U.; Rihs, G.; Lydon, N.; Traxler, P. *J. Med. Chem.* **1994**, *37*, 1015–1027.
6. The general procedure was as follows: Under an inert atmosphere, $Pd(OAc)_2$ (4 mol%; based on dibromobenzene) and $P^tBu_3$ (12 mol%) were added to toluene and the mixture stirred for about 5 min until the $Pd(OAc)_2$ dissolved. Dibromobenzene derivative (1 equiv), aniline derivative (2 equiv) and sodium *tert*-butoxide (3 equiv) were then added, in that order, and the reaction mixture heated for 14 h at 110 °C. The reaction mixture was cooled to room temp and aqueous $NH_4Cl$ was added immediately upon opening the reaction to air. The toluene layer was separated and washed twice with water, dried over $MgSO_4$, filtered, and concentrated to an oil or a solid under vacuum. The product was then recovered by crystallization, the exact conditions of which depended on the identity of the product. Generally, addition of a small amount of methanol to the resulting oil or solid resulted in formation of a powder that was filtered, washed with cold methanol, and dried under vacuum to yield a reasonably pure product (>95% by $^1H$ NMR). Isolated yields (%): **1a** 90; **1b** 87; **1c** 60; **2a** 37; **2b** 75; **2c** 56; **3a** 55; **3b** 62; **3c** 56; **4a** 67; **4b** 35; **4c** 73; **5a** 32; **5b** 30; **5c** 25; **6** 33; **7** 92; **8** 37; **9** 73; **10b** 26; **10c** 9.
7. Goodson, F. E.; Hauck, S. I.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 7527–7539.
8. Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889–9890.
9. Rumpel, H.; Limbach, H. H. *J. Am. Chem. Soc.* **1989**, *111*, 5429–5441.
10. Rumpel, H.; Limbach, H. H.; Zachmann, G. *J. Phys. Chem.* **1989**, *93*, 1812–1818.
11. Siri, O.; Braunstein, B. *Chem. Commun.* **2000**, 2223–2224.
12. Siri, O.; Braunstein, P.; Rohmer, M.-M.; Benard, M.; Welter, R. *J. Am. Chem. Soc.* **2003**, *125*, 13793–13803.
13. Braunstein, P.; Siri, O.; Taquet, J.; Rohmer, M.-M.; Bénard, M.; Welter, R. *J. Am. Chem. Soc.* **2003**, *125*, 12246–12256.

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[†] Crystals of the azophenine **8c**·$0.5CH_2Cl_2$ were grown from slow evaporation of a methylene chloride solution. The crystals contained two half molecules and $CH_2Cl_2$ in the unit cell. Crystal data for **11b**: $C_{55}H_{76}Cl_2$, triclinic, P-1, $a = 13.144(3)$ Å, $b = 13.519(3)$ Å, $c = 15.861(3)$ Å, $\alpha = 68.90(3)°$, $\beta = 81.97(3)°$, $\gamma = 8.70(3)°$.