



## A Highly Active Palladium Catalyst System for the Arylation of Anilines

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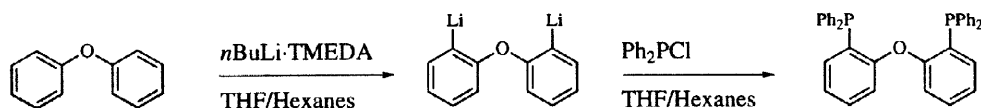
**Abstract.** The chelating ligand bis[2-(diphenylphosphino)phenyl] ether (DPEphos), in combination with palladium acetate, forms a highly active catalyst system for the coupling of anilines with aryl bromides. The bisphosphine is easily prepared in large quantity and at low cost by a known procedure. The catalyst system is effective in coupling reactions involving a variety of substrates, including electron-poor anilines or electron-rich aryl bromides. In addition, it tolerates a high degree of steric congestion at both the aniline and the aryl bromide. © 1998 Elsevier Science Ltd. All rights reserved.

The use of late transition metal catalysis in the formation of carbon-nitrogen bonds has emerged as an important method for the preparation of a wide variety of arylamines. Convenient protocols have been developed for the reaction of alkylamines and anilines with aryl bromides,<sup>1a, b, c</sup> chlorides,<sup>1d</sup> iodides<sup>1b, e</sup> and triflates.<sup>1f, g, h</sup> Related processes have been used in the N-arylation of imines,<sup>1i, j</sup> azoles,<sup>1j</sup> and diarylamines.<sup>1k, l</sup>

Our synthesis of linear oligoaniline derivatives<sup>2</sup> relied on the coupling of primary anilines with aryl bromides, using the Pd[BINAP] catalyst system; we found that relatively high catalyst loadings were necessary for the substrate system employed. Although the reactions proceeded cleanly, the need to use several mole percent of the moderately expensive *rac*-BINAP in large-scale reactions prompted us to search for a more efficient catalyst system, or for potentially inexpensive alternatives to BINAP. At the same time, in our ongoing examination of the efficiency of various phosphine ligands in other C-N bond formation reactions, we sought a convenient route to a family of chelating bisphosphine derivatives, in which steric and electronic properties could be easily modified.

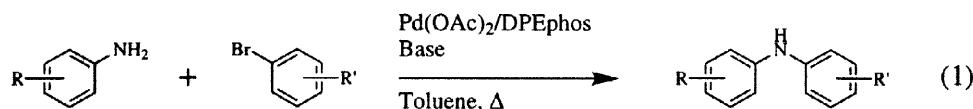
Recently, a number of new chelating bisphosphines have been prepared by van Leeuwen *et al.*<sup>3</sup> The general method consists of the directed double lithiation of diphenyl ether, or of heterocycles containing this structural motif, followed by reaction of the *in situ*-generated aryllithium with chlorodiphenylphosphine. The preparation of the parent compound, bis[2-(diphenylphosphino)phenyl] ether (DPEphos), is shown in Scheme 1.

Scheme 1: Synthesis of DPEphos<sup>3</sup>



These ligands were first examined in the rhodium-catalyzed hydroformylation of olefins;<sup>3</sup> the bite angles of several complexes of the phosphines with zerovalent palladium have been measured by X-ray crystallography.<sup>4</sup>

In view of its efficient, one-pot synthesis on multigram scale, from inexpensive starting materials, DPEphos is potentially attractive as a ligand in palladium-catalyzed aryl amination reactions.<sup>5</sup> We have found that the Pd(OAc)<sub>2</sub>/DPEphos system is an efficient catalyst for the arylation of primary anilines by aryl bromides (Eq 1);<sup>6</sup> the results are summarized in Table 1. For comparison, coupling reactions using the ligands *rac*-BINAP and DPPF under the same conditions are shown. In preliminary studies, the new catalyst system has not been efficient in the coupling of aryl bromides with alkylamines or N-alkylanilines, both of which give rise to large amounts of arene side products.



The coupling of relatively unhindered anilines and aryl bromides proceeds fairly rapidly in toluene at 80 °C, using 0.5 mol % Pd(OAc)<sub>2</sub>/DPEphos (L/Pd = 1.5) in the presence of sodium *tert*-butoxide as base. Even an electron-rich aryl bromide such as 2-bromoanisole, expected to be a less active substrate than the electronically neutral bromides, reacts rapidly and completely under these conditions. In this reaction, DPEphos is as effective a ligand as *rac*-BINAP, and considerably more effective than DPPF. The efficiency of the new catalyst is particularly evident in the coupling of *o*-anisidine with 2-bromo-*p*-xylene, under solvent-free conditions, at a catalyst loading of 0.05 mol %.

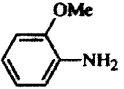
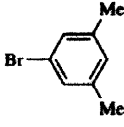
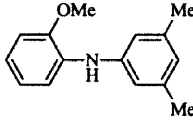

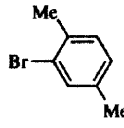
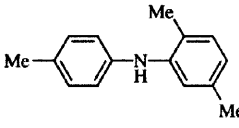

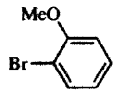
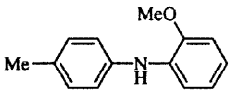
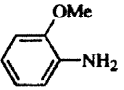
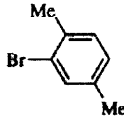
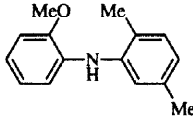

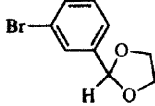
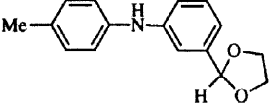
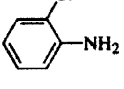
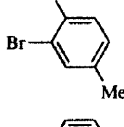
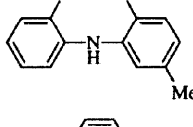
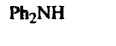
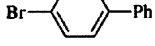
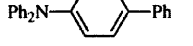
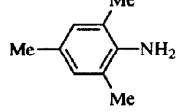
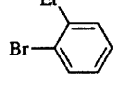
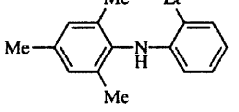
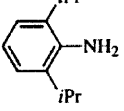
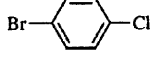
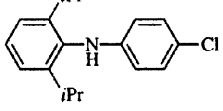
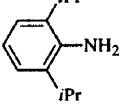
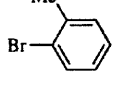
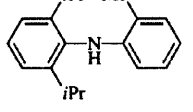
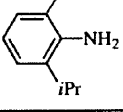
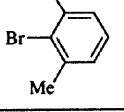
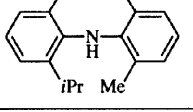
Arylation of 2-aminobenzonitrile, a relatively poor nucleophile, proceeds smoothly in the presence of 2 mol % catalyst, with cesium carbonate as the base. Unlike sodium *tert*-butoxide, cesium carbonate is compatible with substrates containing functional groups such as methyl esters or enolizable ketones, or nitro groups;<sup>1c</sup> in this case, the relatively acidic product appears to deactivate the catalyst when sodium *tert*-butoxide is used as the base.<sup>7</sup> As in the coupling of the electron-rich aryl bromide 2-bromoanisole, DPEphos performs comparably to *rac*-BINAP, and more effectively than DPPF.

Although good selectivities are observed for the monoarylation of anilines under the conditions of this study, with only traces of tertiary amines (if any) observed by GC analysis, diphenylamine has been arylated in good yield, using a catalyst loading of 1 mol % and a reaction temperature of 100 °C.

The Pd(OAc)<sub>2</sub>/DPEphos catalyst system allows the preparation of diarylamines with a high degree of steric crowding. A catalyst loading of 0.5 mol % is sufficient to effect the coupling of 2,4,6-trimethylaniline with 2-ethylbromobenzene, or of 2,6-diisopropylaniline with a para-substituted or even an ortho-monosubstituted aryl bromide. A catalyst loading of 5 mol % allows the coupling of 2,6-diisopropylaniline with the highly hindered substrate 2-bromo-*m*-xylene; the DPEphos ligand is as effective as *rac*-BINAP or DPPF for this reaction.

In conclusion, the chelating ligand DPEphos, in combination with Pd(OAc)<sub>2</sub>, forms a highly active catalyst system for the coupling of primary anilines with aryl bromides. The efficiency of this catalyst system equals that of Pd(OAc)<sub>2</sub>/*rac*-BINAP, and equals or exceeds that of Pd(OAc)<sub>2</sub>/DPPF, in the examples compared. The ready accessibility of DPEphos, a known compound amenable to large-scale synthesis, further increases the utility of this type of aryl amination reaction.

Table 1: Catalytic Amination of Aryl Bromides<sup>a</sup>

Entry	Aniline	Bromide	Product (Ref 8)	Conditions <sup>b</sup>	mol % Pd	Rxn Time (h)	Yield (%) <sup>c</sup>
1				A	0.5	2.5	96
2				A	0.5	3	95
3				A Pd(OAc) <sub>2</sub> /DPEphos Pd(OAc) <sub>2</sub> / <i>rac</i> -BINAP Pd(OAc) <sub>2</sub> /DPPF	0.5	3	94 (94) (44)
4				A	0.05	21	90
5				A	0.5	7	80
6				B Pd(OAc) <sub>2</sub> /DPEphos Pd(OAc) <sub>2</sub> / <i>rac</i> -BINAP Pd(OAc) <sub>2</sub> /DPPF	2	16	87 82 20
7				C	1	14	84
8				C	0.5	12	99
9				C	0.5	18	95
10				C	0.5	18	94
11				C Pd(OAc) <sub>2</sub> /DPEphos Pd(OAc) <sub>2</sub> / <i>rac</i> -BINAP Pd(OAc) <sub>2</sub> /DPPF	5	18	90 87 88

<sup>a</sup> Reactions were performed with 1.0 mmol bromide, 1.2 mmol amine, 1.4 mmol base, cat. Pd(OAc)<sub>2</sub>, cat. ligand (1.5 equiv./Pd) and 2 mL toluene/1.0 mmol bromide, except entry 4 (neat, 10 mmol scale) and entry 5 (3 mL toluene/1.0 mmol bromide).

<sup>b</sup> Bases and reaction temperatures: A = NaOtBu, 80 °C; B = Cs<sub>2</sub>CO<sub>3</sub>, 100 °C; C = NaOtBu, 100 °C. <sup>c</sup> Products isolated by flash chromatography on silica gel, except entries 4 and 5 (recryst. from MeOH) and entry 7 (recryst. from EtOH). All yields are an average of two runs. Yields in parentheses obtained by GC using an internal standard; all other yields reported are isolated yields of compounds estimated to be >95% pure by <sup>1</sup>H NMR, GC analysis and combustion analysis. All compounds were characterized by NMR (<sup>1</sup>H, <sup>13</sup>C) and IR.

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### References and Footnotes

- (1) (a) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215–7216. (b) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217–7218. (c) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359–6362. (d) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054–6058. (e) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066–6068. (f) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264–1267. (g) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268–1273. (h) Åhman, J.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6363–6366. (i) Wolfe, J. P.; Åhman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367–6370. (j) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernández-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827–828. (k) Louie, J.; Hartwig, J. F.; Fry, A. *J. Am. Chem. Soc.* **1997**, *119*, 11695–11696. (l) Thayumanavan, S.; Barlow, S.; Marder, S. R. *Chem. Mater.* **1997**, *9*, 3231–3235.
- (2) Singer, R. A.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 213–214.
- (3) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081–3089.
- (4) Kranenburg, M.; Delis, J. G. P.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Vrieze, K.; Veldman, N.; Spek, A. L.; Goubitz, K.; Fraanje, J. *J. Chem. Soc., Dalton Trans.* **1997**, 1839–1849.
- (5) While this manuscript was in preparation, a mechanistic paper was published on the amination of aryl halides using bidentate phosphines, including DPEphos and certain analogues: Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 3694–3703.
- (6) **Representative Procedure:** An oven-dried Schlenk tube was charged with *p*-toluidine (1.20 mmol), palladium acetate (0.005 mmol) and DPEphos (0.0075 mmol), evacuated, and repressurized with argon. 2-Bromoanisole was added to the flask via syringe, followed by toluene (2 mL). The resulting mixture was stirred for 5 min at room temperature, affording a clear yellow solution. The flask was opened and solid sodium *tert*-butoxide (1.40 mmol) was added in one portion, causing the solution to turn a deep red color. The flask was purged for 3 min with argon, and the mixture was heated with stirring to 80 °C until the aryl bromide had been consumed as judged by GC analysis. The mixture was then cooled to room temperature, taken up in diethyl ether (40 mL), and washed with brine. The resulting solution was dried over anhydrous potassium carbonate, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel using 9:1 hexanes:ethyl acetate as the eluant, affording the product as a pale yellow oil in 94% yield.
- Note that the order of addition described above, in which the base is added after the palladium acetate has been mixed with the ligand and the amine, has been found to be important in the activation of the catalyst: Wolfe, J. P.; Buchwald, S. L. Unpublished results.
- (7) The coupling of *p*-toluidine with 4-bromo-*tert*-butylbenzene using 0.5 mol % Pd (reaction condition A; see Table) proceeds quantitatively, as judged by GC analysis, within 2.5 h. In the presence of the cyanodiarylamine product of entry 6 (1 equiv.), this reaction proceeds to *ca.* 30% conversion after 18 h. The use of a larger excess of base did not improve the conversion.
- (8) Previously reported compounds: (a) 2,4',5-trimethyldiphenylamine (entry 2) and 2-methoxy-4'-methyldiphenylamine (entry 3): Sundberg, R. J.; Sloan, K. B. *J. Org. Chem.* **1973**, *38*, 2052–2057. (b) N-biphenyl-4-yl-N,N-diphenylamine (entry 7): Piccard, J.; de Montmollin, F. *Helv. Chim. Acta* **1923**, *6*, 1011–1019.