Palladium-Catalyzed Amination of Aryl Bromides: Use of Phosphinoether Ligands for the Efficient Coupling of Acyclic Secondary Amines

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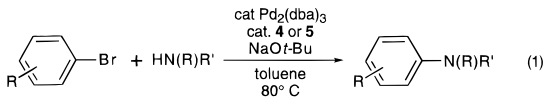
Recent developments in the palladium-catalyzed amination of aryl halides[1−7] offer considerable advantages over the classical methods, which require either activated substrates or severe reaction conditions.[8] While these new methods, based on the use of the monophosphine ligand P(*o*-tolyl)$_3$ or bis-phosphine ligands BINAP and DPPF, lead to efficient coupling of primary amines and secondary cyclic amines, the arylation of secondary acyclic amines remains problematic; the corresponding tertiary aromatic amines are generally formed in low yields. This was especially true when electron-rich arenes were used as coupling partners.[9] These reactions are usually plagued by the reduction of the starting aryl bromide, leading to the formation of the byproduct arene via a *β*-hydride elimination pathway from amidopalladium intermediate **1** (Scheme 1).

Since tri(*o*-tolyl)phosphine was first employed for the tin-free palladium-catalyzed aryl amination reaction,[1] none of the reported catalyst systems has proven to be generally satisfactory for the coupling of secondary amines. Toward this goal, we decided to explore the reactivity of different ligands and to study the effect of their structure on the outcome of the amine-coupling reaction. For this purpose, we chose to examine Hayashi-type[10] ferrocenyl-derived ligands due to their ease of preparation and the availability of known procedures for further structural modification.[11] The ligands surveyed are shown in Figure 1.

Herein, we report that palladium complexes derived from ligands (*rac*)-PPFA (**4**)[10] and (*rac*)-PPF-OMe (**5**)[10,12] are highly effective for the aryl amination reaction of acyclic secondary amines (eq 1).



We first compared the reaction between *tert*-butylbromobenzene and di-*n*-butylamine using $Pd_2(dba)_3$ in the presence of the different ligands that have been used in relevant carbon−nitrogen bond forming procedures; the reactions conditions and results are described in Table 1. Whereas P(*o*-tolyl)$_3$ gave 77% of the desired 4-*tert*-butyl-*N*,*N*-di-*n*-butylaniline after 48 h (entry 1), the use of BINAP and DPPF led to the formation of *tert*-butylbenzene as the major product of the reaction (entries 2 and 3). Employing a reaction protocol based on the reported conditions[5] using DPPF, while providing a moderate yield of the desired product, still resulted in the formation of a large quantity of arene side product (entry 4). We then tried ferrocenyl ligands BPPFA (**2**)[10] and $FcPPh_2$ (**3**).[13] Relative to DPPF (under our standard conditions for comparison), both **2**, which has an added dimethylamino substituent, and **3**, which lacks a second diphenylphosphino substituent, gave slightly improved yields (entries 5 and 6). This prompted us to investigate the use of **4**,[10] which combined the two previous structural modifications; its use caused the yield to increase to 89% (entry 7). Employing the related phosphino ether ligand **5**[10,12] significantly enhanced the rate of the reaction while raising the yield to 93% (entry 8). The amine-coupling procedure with **5** minimized the undesired

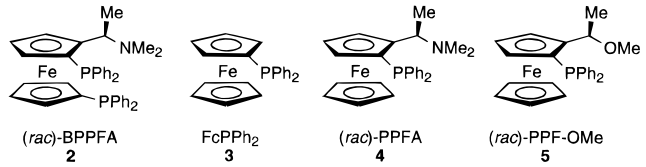


Figure 1.

Scheme 1

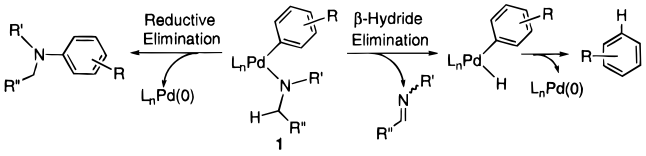
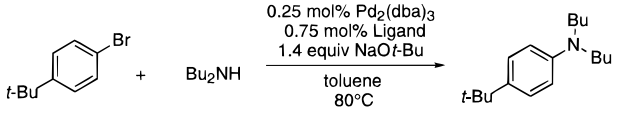


Table 1. Ligand Effect for the Arylamination of 4-*tert*-Butylbromobenzene with *N*,*N*-di-*n*-butylamine



entry	ligand	time (h)	conversn (%)	ratio of product/ reduced S.M.	GC yield[a] (%)	isolated yield (%)
1	P(*o*-tolyl)$_3$	48	90	12.6:1	83	77
2	BINAP	48	98	1:5.2	8	
3	DPPF	48	100	1:4.9	9	
4	DPPF[b]	3	100	1.4:1	43	
5	**2**	48	100	1.7:1	18	
6	**3**	48	100	3.0:1	54	
7	**4**	24	100	12.5:1	92	89
8	**5**	5	100	39:1	97	93

[a] GC yields were calculated using dodecane as an internal standard. [b] Reaction run under the reported conditions[5] but using commercially available DPPF·$PdCl_2$·CH_2Cl_2 (5 mol %) and DPPF (15 mol %) in THF at 100 °C.

† National Science and Engineering Research Council Postdoctoral Fellow (NSERC, Canada).

‡ Ford Foundation Predoctoral Fellow.

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(5) (a) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217−7218. (b) Use of the complex DPPF·$PdCl_2$ (containing *ca.* 0.25 equiv of DMF) prepared accordingly to the procedure in ref in 5a gave similar results. For this procedure, see: Davies, J. A.; Hartley, F. R.; Murray, S. G. *J. Chem. Soc., Dalton Trans.* **1979**, 1705−1708.

(6) For application in solid-phase synthesis, see: (a) Willoughby, C. A.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 7181−7184. (b) Ward, D.; Farina, V. *Tetrahedron Lett.* **1996**, *37*, 6993−6996.

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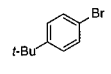
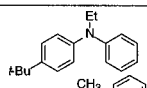
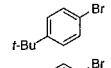
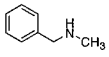
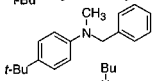
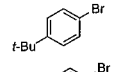
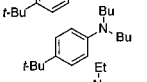
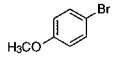
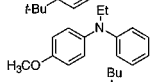
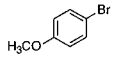
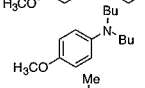
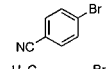
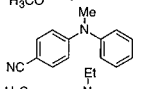
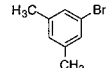
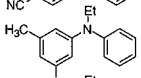
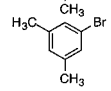
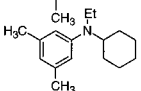
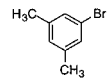
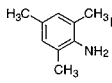
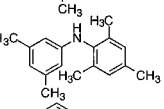
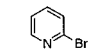
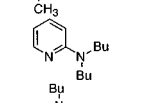
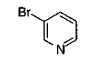
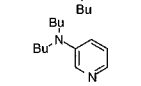
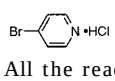
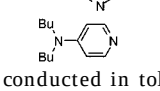
Table 2. Palladium-Catalyzed Arylamination in the Presence of PPF-OMe

Entry	Halide	Amine	Product	Reaction condns[a]	Reaction time (h)	Yield (%)[b]
1				A	6	91 (84)[c]
2				B	10	91
3				A	5	93
4				A	7	92
5				A	6	74
6				B	4	90
7				B	5	91
8				C	9	52
9				A	12	97
10				D	8	84
11				D	12	49-69[d]
12				E	12	60

[a] All the reactions were conducted in toluene at 80 °C in the presence of 1.4 equiv of NaO-*t*-Bu and L:Pd = 1.5:1. Conditions: (A) 0.25 mol % of $Pd_2(dba)_3$ (0.5 mol % of Pd); (B) 0.50 mol % of $Pd_2(dba)_3$ (1.0 mol % of Pd); (C) 2.5 mol % of $Pd_2(dba)_3$ (5.0 mol % of Pd); (D) 1.5 mol % of $Pd_2(dba)_3$ (3.0 mol % of Pd); (E) 2.5 mol % of $Pd(OAc)_2$. [b] Yields refer to the average of at least two isolated yields of >95% purity as determined by GC, ^1H NMR, and elemental analysis. [c] PPFA was used as the ligand. [d] GC yields were consistently higher than 70%. Problems with isolation account for the fluctuation in isolated yields.

β-hydride elimination pathway; less than 3% of arene side product was formed. Quantities as low as 0.75 mol % of ligands **4** and **5** (L:Pd = 1.5:1) also proved to be highly effective for the aryl amination of *N*-ethylaniline with *tert*-butylbromobenzene (Table 2, entry 1).

A brief study of the reaction conditions with PPF-OMe established that, as in our previous protocols, sodium *tert*-butoxide is the most effective base; we also investigated the use of potassium *tert*-butoxide, triethylamine, sodium carbonate, and sodium hydride. In certain cases, the reaction can be performed at lower temperature (60 °C), albeit at a significantly slower rate. Whereas the reaction could be carried out in toluene and to some extent in THF, attempts to employ other solvents such as DMF, Et_2O, or hexane led to poor conversion to product.

As shown in Table 2, the procedure employing the **5**/$Pd_2(dba)_3$ catalyst system is extremely effective in coupling secondary anilines and acyclic secondary amines with both electron-poor and electron-rich aryl bromides. It is also complementary to our previously reported protocol for the combination of bromopyridines with amines using DPPP or BINAP in which acyclic secondary amines were not efficiently coupled.[7] In general, use of this catalyst system is not effective with primary amines including unhindered primary anilines. In contrast, sterically hindered 2,4,6-trimethylaniline could be transformed to the desired product in close to quantitative yield (entry 9). We also note that only poor yields are obtained when ortho-substituted aryl bromides are reacted with secondary amines, although moderate yields were obtained when these were coupled with primary amines.

Ferrocenyl phosphines **4** and **5** represent the first examples in which a (presumably) chelating ligand other than a bis-phosphine has been employed for the palladium-catalyzed aryl amination. That the reaction with **3** as supporting ligand resulted in significantly lower yields supports the notion that the PPF-OMe-catalyzed reactions proceed via intermediates in which the oxygen−palladium interaction is important. The existence of such an interaction has been confirmed by an X-ray structure determination of the product of the oxidative addition step of the **5**/$Pd_2(dba)_3$ catalyst mixture with *p-tert*-butylbromobenzene.[14] The key feature of this structure is the short Pd−O bond distance of 2.215(7) Å. This can be compared to the Pd−O covalent bond distances reported for square planar complexes (2.0−2.16 Å).[15,16]

On the basis of the results presented above, we believe that **5** functions as a chelating ligand in which both the phosphorus and oxygen groups are bound to the palladium center.[17] As we have previously noted,[4] tetracoordinate palladium complexes are less subject to β-hydride elimination than the corresponding tricoordinate species, and hence, we would expect that procedures using **4** or **5** would give better results than those employing nonchelating ligands.[18] Since a methoxy group is a poor σ-donor relative to PAr_2, aryl(amido)-palladium complexes **1** (Scheme 1) with **5** should be less electron-rich than in the analogous intermediates when BINAP or DPPF are used. This diminished electron density at the palladium center enhances the rate of the reductive elimination relative to β-hydride elimination.[19]

In summary, we have shown that PPFA and PPF-OMe are ligands of choice for the palladium-catalyzed aryl amination of acyclic secondary amines.

Acknowledgment. We thank the National Science Foundation and Pfizer, Inc., for their support of this research. J.-F.M. thanks the NSERC (Canada) for a postdoctoral fellowship. S.W. is the recipient of a Ford Foundation Fellowship.

Supporting Information Available: Detailed experimental procedures including analytical and spectroscopic data for all compounds along with tables of bond lengths and bond angles and an ORTEP diagram of PPF-OMe·*p-t*-BuC_6H_4PdBr complex (11 pages).

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(14) Details of the X-ray determination will be fully described elsewhere. The ORTEP diagram is included in the Supporting Information. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(15) (a) Kapteijn, G. M.; Grove, D. M.; Kooijman, H.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. *Inorg. Chem.* **1996**, *35*, 526−533. (b) Bryndza, H. E.; Tam, W. *Chem. Rev.* **1988**, *88*, 1163−1188 and references cited therein. (c) Kiers, N. H.; Feringa, B. L.; Kooijman, H.; Spek, A. L.; Van Leeuwen, P. W. N. M. *J. Chem. Soc., Chem. Commun.* **1992**, 1169−1170.

(16) ^1H NMR (300 MHz) spectra of complex PPF-OMe·*p-t*-BuC_6H_4-PdBr in $CDCl_3$ at room temperature showed that the methoxy protons were shifted by 1.1 ppm downfield compared to the uncomplexed PPF-OMe.

(17) Even though we believe that ligand **5** is chelating most of the time, this does not preclude the possibility that keys steps are occurring via a three-coordinate palladium intermediate.

(18) For related studies on the P(*o*-tolyl)$_3$/Pd catalytic system, see: Hartwig, J. F.; Richards, S.; Barañano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626−3633.

(19) For a discussion about the factors that influence the rate of reductive elimination of transition-metal complexes, see: Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Mill Valley, CA, 1994; p 27 and references cited therein.