Pergamon

Tetrahedron Letters 40 (1999) 3789–3790

TETRAHEDRON
LETTERS

An Efficient, Palladium-Catalysed, Amination of Aryl Bromides

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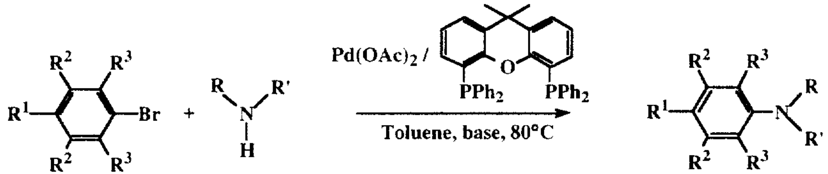
Received 2 February 1999; accepted 8 March 1999

Abstract : Aryl bromides are coupled to primary aliphatic amines, anilines and cyclic secondary amines in an efficient and selective procedure using catalytic amounts of Pd(OAc)$_2$ and the chelating ligand 9,9-dimethyl-4,6-bis(diphenylphosphino)xanthene (Xantphos). This catalyst system accomodating low catalyst loadings (0.5 mol % Pd) allows amination of both electron-poor and electron-rich aryl bromides. Even sterically crowded substrates show good reactivity.

Keywords : Palladium and compounds, Phosphanes, Catalysis, Amines, Arylation.

In recent years, extensive research has been devoted to the development of palladium and nickel-catalysed carbon-heteroatom bond formation.[1] In the search for ligands giving more active catalysts for palladium-catalysed carbon-nitrogen bond formation, recent improvements have been made using bidentate phosphine[2] and aminophosphine[3] ligands. BINAP/Pd was found to be the most active and selective catalytic system for many substrates. Looking for a less expensive and easily accessible alternative to the BINAP ligand, Buchwald et al. reported the use of bis[(2-diphenylphosphino)phenyl]ether (DPEphos)[4] as a highly active palladium catalyst system for the arylation of anilines.[5] Previously, we described a convenient multigram-scale route for the synthesis of a new family of chelating diphosphine derivatives.[4] Here, we report the efficient and selective palladium-catalysed coupling between aryl bromides and primary aliphatic amines, anilines and cyclic secondary amines using the parent 9,9-dimethyl-4,6-bis(diphenylphosphino)xanthene (Xantphos) ligand. As palladium source, Pd(OAc)$_2$ is prefered to Pd(dba)$_2$ as the yields and rates obtained are often superior. The yields and rates obtained using this Pd(OAc)$_2$/Xantphos system are summarised in the table.

Table. Palladium-Catalysed Amination of Aryl Bromides.[a]



Entry	R^1, R^2, R^3	Amine	Time (h)	Yield (%)[b]
1	R^1 = CN; R^2 = R^3 = H	Hexylamine	3	76
2	R^1 = ^{t}Bu; R^2 = R^3 = H	*o*-anisidine	0.5	63
3	R^2 = Me; R^1 = R^3 = H	*o*-anisidine	0.5	92
4	R^1 = R^3 = Me; R^2 = H	*o*-anisidine	68	97
5	R^1 = CN; R^2 = R^3 = H	1-Ethylpiperazine	68	93
6	R^1 = ^{t}Bu; R^2 = R^3 = H	1-Ethylpiperazine	3	66

[a] Reaction conditions : 1.0 mmol aryl bromide, 1.2 mmol amine, 1.4 mmol base (NaO^{t}Bu for entries 2, 3, 4 and 6; Cs$_2$CO$_3$ for entries 1 and 5), cat. Pd(OAc)$_2$ (0.5 mol % Pd), ligand (1.5 equiv./Pd) and 2 mL toluene, 80°C. [b] All yields reported are isolated yields (average of two runs). The compounds are 95 to 99% pure as judged by ^{1}H NMR and GC analysis. These analytically pure products were obtained as solids except the product of entry 4 which was obtained as an oil after flash column chromatography over silica gel.

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PII: S0040-4039(99)00527-4

It is noteworthy that under the conditions used, no product from the halide reduction is observed by GC analysis while a 100% conversion of the aryl bromide is observed demonstrating the good selectivity of this system. Monoarylation of the primary amine (entry 1) proceeds fairly rapidly at 80°C using 0.5 mol % $Pd(OAc)_2$/Xantphos (L/Pd = 1.5) with formation of only small amounts of the diarylated product.[6] For comparison, the DPEphos/$Pd(OAc)_2$ system has been reported not to be efficient in the coupling of aryl bromides with alkylamines giving rise to large amounts of arene side products.[5] The coupling of aryl bromide substrates containing electron donating substituents with *o*-anisidine (entries 2 and 3) proceeds in less than 30 minutes giving only the monoarylated product, demonstrating the effiency of the new catalyst. Arylation of *o*-anisidine using aryl bromides with a high degree of steric congestion is also possible (entry 4) although the reaction is much slower.

The $Pd(OAc)_2$/Xantphos catalytic system has been shown to be inefficient for cross-coupling reactions using acyclic secondary amines. However, efficient coupling of 1-ethylpiperazine can be reached with aryl bromides containing both electron-poor (entry 5) and electron-rich (entry 6) substituents to afford the arylated product selectively in good to excellent yield.

In conclusion, the $Pd(OAc)_2$/Xantphos system is a very efficient and selective catalyst for the amination reaction of both electron-poor and electron-rich aryl bromides with primary aliphatic amines, anilines and cyclic secondary amines.

Acknowledgements : We thank the Netherlands Ministry of Economic Affairs (IOP Katalyse) for support of this research.

References and Footnotes

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(6) General procedure : Upon stirring a solution of $Pd(OAc)_2$ and Xantphos in toluene (at room temperature for 5 minutes) in a Schlenck vessel purged with nitrogen, the aryl bromide (1,0 mmol) and the amine (1,2 mmol) were added. The solution was stirred for 5 minutes and subsequently the base (1,4 mmol) was added. The mixture was allowed to react at room temperature for 5 minutes. The Schlenck vessel was heated to 80°C by immersion in a preheated oil bath. When the aryl bromide had been consumed as judged by GC analysis, the mixture was cooled to room temperature, taken in diphenylether containing 1% Et_3N, passed over a celite column and dried over $MgSO_4$. Evaporation of the solvent under vacuum gave the crude mixture.

(7) Previously reported compounds : (a) 4-hexylamino-benzonitrile (entry 1) : Wolfe, J.P.; Wagaw, S.; Buchwald, S.L. *J. Am. Chem. Soc.*, **1996**, *30*, 7215-7216. (b) (2-Methoxy-phenyl)-(2,4,6-trimethyl-phenyl)-amino (entry 6) : Sundberg, R.J.; Sloan, K.B. *J. Org. Chem.*, **1973**, *11*, 2052-2057. (c) 4-(4-Ethyl-piperazin-1-yl)-benzonitrile (entry 5) : Watanabe, T.; Kakefuda, A.; Kinoyama, I.; Takizawa, K.; Hirano, S. *Chem. Pharm. Bull.*, **1997**, *9*, 1458-1469 and (3,5-dimethyl-phenyl)-(2-methoxy-phenyl)amine (entry 3) : (5).