

Palladium/1,2-bis(diphenylphosphino) ethane catalysed amination of aryl halides with aliphatic/aromatic amines

Mayur J. Bhanushali, Nitin S. Nandurkar, Malhari D. Bhor, Bhalchandra M. Bhanage*

Department of Chemistry, Institute of Chemical Technology, N. Parekh Marg, Matunga, Mumbai 400019, India

Received 17 May 2006; received in revised form 3 June 2006; accepted 7 June 2006

Available online 18 July 2006

Abstract

The Ullmann coupling of amines with aryl iodide and bromides has been carried out efficiently using Pd(OAc)₂/1,2-bis(diphenylphosphino) ethane [DPPE] in toluene as a solvent. The effects of various parameters such as temperature, solvent, base, catalyst loading and metal–ligand ratio on the reaction system were studied. The reaction is applicable to a wide variety of substituted aryl amines and alkyl amines with different steric and electronic properties.

© 2006 Elsevier B.V. All rights reserved.

Keywords: Ullmann coupling; Aryl halides; Amines; Homogeneous catalyst

1. Introduction

Amines constitute an important class of compounds, which is useful in day-to-day life. Lower aliphatic amines are used as organic intermediates for the synthesis of drugs, bactericides, herbicides, rubber accelerators, corrosion inhibitors, extraction agents in the production of penicillin, surface active agents, etc. [1]. Fatty amines and its derivatives are useful softening agents, wetting agents, dye fixers, asphalt emulsifiers, pigment dispersing agents, petroleum additives, ore floatation agents and additives for cosmetic preparations [2]. Especially aryl amines are important substructures in natural products and organic materials [3]. They are found in biologically active compounds such as pharmaceuticals [4] and agrochemicals [5]. Traditionally the preparation of aryl amines has been carried out under Ullmann-type conditions, which involve the coupling of amines with aryl halides [6]. Although these copper promoted reactions are useful, they require higher temperatures.

The palladium catalysed coupling [7–15] of amines with aryl halides devised by Buchwald and Hartwig offers a milder route towards the synthesis of such amines. The reaction system is composed of a palladium precursor along with a variety of phos-

phines and a base. There are several reports for such coupling reactions depending upon the type of metal precursor and ligands used, such as Pd(dba)₂/P(*t*-Bu)₃ [16], Pd(OAc)₂/DPEPhos [17], Pd₂(dba)₃/phospho-adamantane [18]. Apart from these, various tailor made ligands are also employed for the coupling of amines with aryl halides. Solvent free reactions [19] and microwave techniques [20] have also been reported for the amination reactions. Most of this work has focused on the reaction of industrially relevant aryl chlorides and bromides. It is also important to develop appropriate reaction conditions for aryl iodides, as they are widely used as substrate for palladium catalysed cross coupling reactions.

Many of the reaction systems reported are not useful for the coupling of aryl iodides and hence this study aims to develop a suitable catalyst system for the amination of aryl iodides as well as bromides. The present reaction system deals with amination of aryl iodides and bromides using Pd(OAc)₂/DPPE as the catalyst, NaOMe as a base and toluene as a solvent.

2. Experimental

2.1. General

Palladium acetate was made available from commercial sources. Triphenylphosphine, DPPM, DPPE, DPPP, DPPB were purchased from Lancaster. Amines and aryl halides were pur-

* Corresponding author. Tel.: +91 22 24145616; fax: +91 22 24145614.

E-mail addresses: bhalchandra.bhanage@yahoo.com, bmb@udct.org (B.M. Bhanage).

chased from S.D. Fine Chem. Ltd. and used without further purification. The conversions were based on GC analysis (Eshika). The isolated products were characterized by spectral analysis (NMR spectra recorded on Varian).

2.2. General procedure for arylation of amines

In a typical experimental run, 0.05 mmol (11 mg) of Pd(OAc)₂, 0.1 mmol (39 mg) of DPPE and 5 ml toluene was taken in a 50 ml two neck round bottom flask and stirred for 10 min at 110 °C. Then 1 mmol of iodobenzene and 1 mmol of aniline in 5 ml of toluene was added to the round bottom flask, followed by 1.1 mmol of NaOMe and stirred for 24 h. The reaction was cooled to room temperature and the solvent was removed by rotary evaporator. The product was isolated by silica gel chromatography using (8:2) hexane/ethyl acetate system.

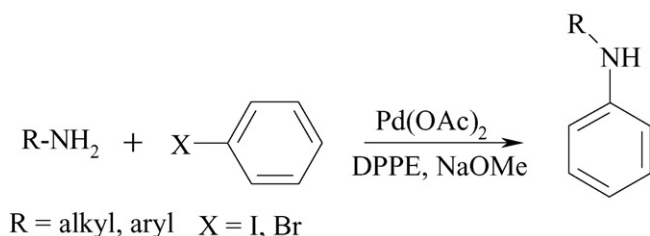
The typical ¹H NMR values for the products are:

- Diphenylamine: ¹H NMR (400 MHz, CDCl₃) δ 7.33–7.29 (td, *J* = 8.0, 2 Hz, 4H), 7.12 (d, *J* = 8.0, 4H), 6.99–6.95 (td, *J* = 8.0, 2 Hz, 2H), 5.73 (br s, 1H).
- 4-Methoxydiphenylamine: ¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, *J* = 7.5 Hz, 2H), 7.11 (d, *J* = 7.5 Hz, 2H), 6.87 (m, 5H), 5.51 (s, 1H), 3.84 (s, 3H).
- 4-Methyldiphenylamine: ¹H NMR (400 MHz, CDCl₃) δ 7.30–7.28 (dd, *J* = 7.6 Hz, 8.8 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.02–7.06 (m, 4H), 6.91 (t, *J* = 7.2 Hz, 1H), 5.63 (br s, 1H), 2.34 (s, 3H).
- *N*-Phenylbenzylamine: ¹H NMR (400 MHz, CDCl₃) δ 7.38 (m, 5H), 7.30 (m, 2H), 6.83 (t, *J* = 7.3 Hz, 1H), 6.74 (d, *J* = 7.7 Hz, 2H), 4.32 (s, 2H), 4.06 (br s, 1H).

3. Results and discussion

This work aims at developing a suitable catalyst for the coupling of aryl iodides/bromides with aliphatic or aromatic amines as shown in Scheme 1.

The scope of the palladium catalysed aryl amination was explored by using Pd(OAc)₂ as the metal precursor, DPPE as the ligand, NaOMe as the base, and toluene as the solvent. The results obtained are as shown in Table 1. The coupling reaction of aryl halides with various primary amines was carried out using this catalyst and the desired amination products were obtained in moderate to good yields. Electron deficient and electron rich anilines and iodobenzene were found to give good yields of the desired product. The system also permits the use of sterically



Scheme 1. *N*-Arylation of amines.

Table 1
Pd (DPPE) catalysed reaction of aryl halides with primary amines

Entry	Aryl halide	Amine	Product	Isolated yield (%)
1				82
2				84
3				74
4				79
5				83
6				77
7				76
8				72
9				71
10				77
11				67
12				65

Reaction conditions: 0.05 mmol Pd(OAc)₂, 0.1 mmol DPPE, 1.1 mmol NaOMe, 1 mmol aryl halide, 1 mmol amine, 10 ml toluene, temperature = 110 °C, time = 24 h.

hindered amine such as *o*-toluidine (entry 8), which gave good yield. Both hexyl amine (entry 10) and benzyl amine (entry 4) also reacted to a considerable extent. To check the overall compatibility of the reaction, aryl bromides were also used as the aryl source. The reaction of aniline with bromobenzene gave 71% yield of diphenylamine (entry 9). Benzyl amine gave 65% yield of the desired product when reacted with bromobenzene. The amination products obtained were exclusively secondary aryl amines. No diarylation product was observed. This was confirmed when secondary amine was taken as a substrate and no reaction occurred under above conditions. Thus a methodology, which selectively gave secondary aryl/aryl alkyl amines, was developed.

Table 2
Influence of temperature

Entry	Temperature	Conversion (%)
1	50	22
2	80	46
3	110	85
4	130	88

Reaction conditions: 0.05 mmol Pd(OAc)₂, 0.1 mmol DPPE, 1.1 mmol NaOMe, 1 mmol iodobenzene, 1 mmol aniline, 10 ml toluene, time = 24 h.

3.1. Influence of temperature

Temperature effect on coupling of aniline with iodobenzene is shown in Table 2. It was observed that at 50 °C the reaction was very slow and conversion of iodobenzene was found to be 22%, while at 80 °C, an increase in conversion upto 46% was observed. Whereas a further increase in the temperature 110 °C (85%), 130 °C (88%) significantly improves the conversion.

3.2. Influence of solvent

The effect of various solvents on the reaction system was investigated as shown in Table 3. It was observed that toluene and xylene were effective providing higher conversions whereas polar solvents like NMP, DMF, dioxane showed no conversion. It has been observed that after prolonged exposure of the catalyst at higher temperature, i.e. above 100 °C in polar solvents leads to decomposition of homogeneous Pd–DPPE catalyst and Pd(II) gets reduced to Pd(0) particles. The aryl halide, which is one of the starting materials, dehalogenated to the corresponding arene confirmed by gas chromatographic analysis. Such undesired side reaction is a common feature in Heck reaction using Pd–TPP catalysts, which resembles with current catalyst. Similar observation is also reported elsewhere [21]. Such decomposition is not observed in toluene and catalyst remains homogeneous.

3.3. Influence of base

The effect of various organic and inorganic bases on the reaction system was studied and the results are presented in Table 4. It was observed that inorganic bases like potassium carbonate, potassium hydroxide and potassium phosphate were also effective, but gave lower conversions. While the organic bases like NaOMe, KO^tBu provided higher conversions. The probable reason for the difference in the results obtained due to the use of organic and inorganic bases may be due to the higher solubil-

Table 3
Influence of solvent

Entry	Solvent	Conversion (%)
1	Toluene	85
2	Xylene	75
3	NMP	–
4	DMF	–

Reaction conditions: 0.05 mmol Pd(OAc)₂, 0.1 mmol DPPE, 1.1 mmol NaOMe, 1 mmol iodobenzene, 1 mmol aniline, 10 ml solvent, time = 24 h.

Table 4
Influence of base

Entry	Base	Conversion (%)
1	NaOMe	85
2	KO ^t Bu	75
3	K ₂ CO ₃	69
4	KOH	60
5	K ₃ PO ₄	52

Reaction conditions: 0.05 mmol Pd(OAc)₂, 0.1 mmol DPPE, 1.1 mmol base, 1 mmol iodobenzene, 1 mmol aniline, 10 ml toluene, time = 24 h.

ity of alkoxide bases in organic solvents. While the inorganic bases like KOH will require proper choice of catalyst, reaction medium and phase transfer catalyst to carry the hydroxide ion to the corresponding organic phase, which would assist in the rate of deprotonation of the intermediate amido complex. Similar results were also obtained by Zim and Buchwald [9].

3.4. Influence of ligand

Owing to the fact that the ligand plays a key role, various phosphine ligands were screened as shown in Table 5. It was observed that monodentate ligand like triphenylphosphine gave 52% conversion. In a number of transition metal complexes, the use of chelating bisphosphine ligand has been found to inhibit beta-hydride elimination from the Pd-amido intermediate. Hence, further studies were carried out using chelating bidentate phosphine ligands. When a bisphosphine ligand like 1,2-bis(diphenylphosphino) methane (DPPM) was used, it gave increase in conversion up to 58%. 1,2-Bis(diphenylphosphino) ethane (DPPE), improved conversion up to 75%. However, ligands like 1,2-bis(diphenylphosphino) propane (DPPP) and 1,2-bis(diphenylphosphino) butane (DPPB) did not have much effect on the conversion and showed conversion similar to that of DPPM.

3.5. Influence of metal–ligand ratio

In the process of optimization, the effect of ratio of Palladium acetate to the ligand was investigated as shown in Table 6. Initially when the metal: ligand ratio of 1:1 and 1:1.5 was used, fair conversions were obtained. The increase in the ratio to 1:2 favours the formation of Pd/DPPE complex significantly improving the conversion upto 85%. However, further increase in the ratio to 1:3 did not have much effect on the reaction.

Table 5
Influence of ligand

Entry	Ligand	Conversion (%)
1	DPPE	75
2	DPPB	63
3	DPPM	58
4	DPPP	54
5	PPh ₃	52

Reaction conditions: 0.05 mmol Pd(OAc)₂, 0.1 mmol ligand, 1.1 mmol KO^tBu, 1 mmol iodobenzene, 1 mmol aniline, 10 ml toluene, time = 24 h.

Table 6
Influence of metal:ligand ratio

Entry	Ratio	Conversion (%)
1	1:3	85
2	1:2	85
3	1:1.5	57
4	1:1	51

Reaction conditions: 0.05 mmol Pd(OAc)₂, DPPE, 1.1 mmol NaOMe, 1 mmol iodobenzene, 1 mmol aniline, 10 ml toluene, time = 24 h.

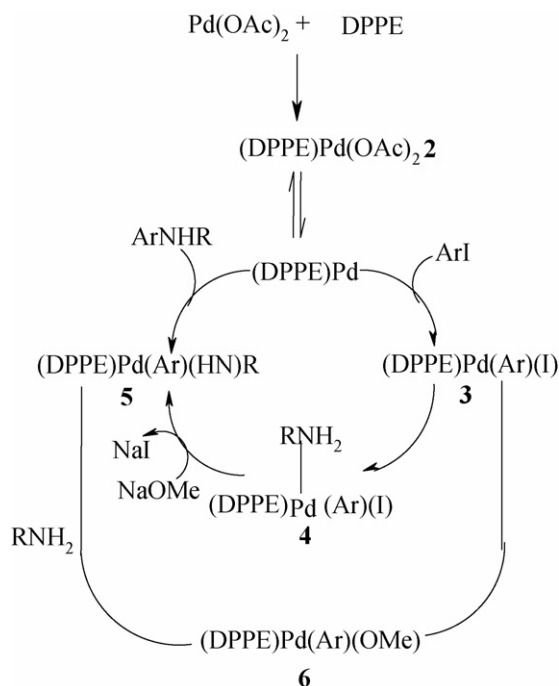
Table 7
Influence of catalyst concentration

Entry	Concentration (mol%)	Catalyst (mmol)	Conversion (%)	TON	TOF (h)
1	7.5	0.075	87	11.6	0.48
2	5	0.050	85	17	0.70
3	2.5	0.025	55	22	0.91
4	1	0.010	53	53	2.2

Reaction conditions: Pd(OAc)₂, 2 equiv. DPPE with respect to Pd(OAc)₂, 1.1 mmol NaOMe, 1 mmol iodobenzene, 1 mmol aniline, 10 ml toluene, time = 24 h. TON: moles of reactant consumed/moles of catalyst, TOF: moles of reactant consumed/moles of catalyst taken/h.

3.6. Influence of catalyst concentration

In an effort to evolve the best concentration of the catalyst, various catalyst concentrations were studied as shown in Table 7. It was found that, optimum results with respect to conversion (85%) were obtained when 5 mol% of Pd(OAc)₂ was used with respect to the reactants. Thus an increase in the conversion was observed with an increase in catalyst concentration. However, TON and TOF are better with the lower catalyst concentration as shown in Table 7.



Scheme 2. Reaction mechanism.

3.7. Mechanism of reaction

The probable mechanism for the amination of aryl halides is as shown in Scheme 2. It is similar to that for the reaction catalysed by BINAP–palladium complexes [19a]. Initially, mixing DPPE with Pd(OAc)₂ leads to the formation of complex (DPPE)Pd(OAc)₂ (2) which then undergoes dissociation to give (DPPE)Pd. Oxidative addition of aryl iodide to the above complex gives (DPPE)Pd(Ar)(I) (3). Co-ordination of the amine to (3) followed by deprotonation forms amido complex (DPPE)Pd(Ar)(HN)R (5) which then undergoes reductive elimination to form the desired product and to regenerate the corresponding Pd(0) catalyst.

4. Conclusions

Thus a detailed investigation of *N*-arylation of aliphatic and aromatic amines was carried out using Pd(OAc)₂ and DPPE under homogenous conditions. The methodology was successfully applied to a wide variety of substrates. The reaction is particularly useful in the selective preparation of secondary aryl/aryl alkyl amines.

Acknowledgement

The financial support from BRNS-DAE, Government of India is kindly acknowledged.

References

- [1] (a) E. Schweizer, R.L. Fowlkes, J.H. McMakin, T.E. Whyte Jr. (Eds.), Kirk-Othmer Encyclopedia of Chemistry and Technology, vol. 2, Wiley, New York, 1978, pp. 272–283; (b) A. Seayad, M. Ahmed, H. Klein, R. Jackstell, T. Gross, M. Beller, Science 297 (2002) 1676.
- [2] H.B. Bathina, R.A. Reck (Eds.), Kirk-Othmer Concise Encyclopedia of Chemical Technology, Wiley, New York, 1985, p. 83.
- [3] (a) J. Buckingham, Dictionary of Natural Products, 1st ed., University Press, Cambridge, MA, 1994; (b) G.D'Aprano, G. Schiavon, G. Zotti, M. Leclerc, Chem. Mater. 7 (1995) 33–42.
- [4] A. Kleeman, J. Engel, B. Kutscher, D. Reichert, Pharmaceutical Substances, 3rd ed., Thieme, Stuttgart, 1999.
- [5] G.W.A. Milne (Ed.), CRC Handbook of Pesticides, CRC Press, Boca Raton, 1994.
- [6] (a) F. Ullmann, Ber. Dtsch. Chem. Ges. 36 (1903) 2382–2384; (b) H.B. Goodbrand, N.X. Hu, J. Org. Chem. 64 (1999) 670–674; (c) S.V. Ley, A.W. Thomas, Angew. Chem. Int. Ed. 42 (2003) 5400.
- [7] (a) J.P. Wolfe, S. Wagaw, S.L. Buchwald, J. Am. Chem. Soc. 118 (1996) 7215–7216; (b) J.P. Wolfe, S. Wagaw, J.F. Marcoux, S.L. Buchwald, Acc. Chem. Res. 31 (1998) 805.
- [8] (a) B.H. Yang, S.L. Buchwald, J. Organomet. Chem. 576 (1999) 125; (b) M.C. Harris, X. Huang, S.L. Buchwald, Org. Lett. 4 (2002) 2885–2888.
- [9] D. Zim, S.L. Buchwald, Org. Lett. 5 (2003) 2413–2415.
- [10] (a) M.S. Driver, J.F. Hartwig, J. Am. Chem. Soc. 118 (1996) 7217–7218; (b) J.F. Hartwig, Synlett (1997) 329.
- [11] J.F. Hartwig, Angew. Chem. Int. Ed. 37 (1998) 2046–2047.
- [12] A.R. Mucci, S.L. Buchwald, Top. Curr. Chem. 219 (2002) 131.
- [13] D. Prim, J.-M. Campagne, D. Joseph, B. Andrioletti, Tetrahedron 58 (2002) 2041.
- [14] J.P. Wolfe, S.L. Buchwald, Angew. Chem. Int. Ed. 38 (1999) 2413.

- [15] (a) A.F. Littke, G.C. Fu, *Angew. Chem. Int. Ed.* 41 (2002) 4176;
(b) A.F. Littke, C. Dai, G.C. Fu, *J. Am. Chem. Soc.* 122 (2000) 4020.
- [16] J.F. Hartwig, M. Kawatsura, S.I. Hauck, K.H. Shaughnessy, L.M. Alcazar-Roman, *J. Org. Chem.* 64 (1999) 5575–5580.
- [17] Y. Guari, D.S. Van Es, J.N.H. Reek, P.C.J. Kamer, P.W.N.M. van Leeuwen, *Tetrahedron Lett.* 40 (1999) 3789–3790.
- [18] D. Gerritsma, T. Brenstrum, J. McNulty, A. Capretta, *Tetrahedron Lett.* 45 (2004) 8319–8321.
- [19] (a) J.P. Wolfe, S.L. Buchwald, *J. Org. Chem.* 65 (2000) 1144;
(b) G.A. Artamkina, M.V. Ermolina, I.P. Beletskaya, *Mendeleev Commun.* (2003) 1.
- [20] (a) J. Heo, Y.S. Song, B.T. Kim, *Tetrahedron Lett.* 46 (2005) 4621–4625;
(b) T.A. Jensen, X. Liang, D. Tanner, N. Skjaerback, *J. Org. Chem.* 69 (2004) 4936.
- [21] M.H. Ali, S.L. Buchwald, *J. Org. Chem.* 66 (2001) 2560.