Pergamon

Tetrahedron Letters, Vol. 38, No. 27, pp. 4807-4810, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01038-1

Palladium-Catalyzed Amination of Aryl Chlorides

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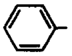
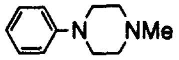
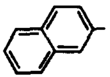
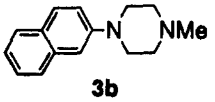
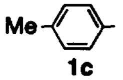
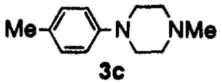
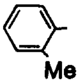
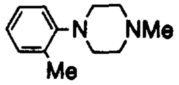
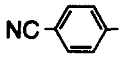
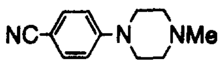
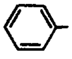
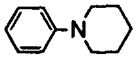
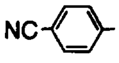
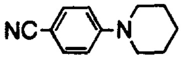
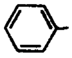
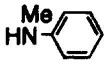
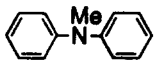
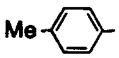
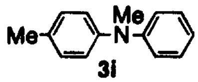
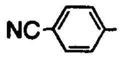
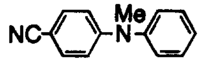
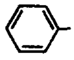
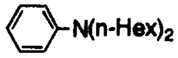
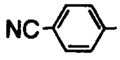
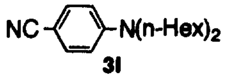
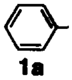
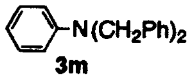
Abstract: **$Pd(PCy_3)Cl_2$ (Cy = cyclohexyl) catalyzed the reaction of aryl chlorides and secondary amines in the presence of NaO^tBu to give the corresponding aryl amines in good to excellent yields. In some of the reactions, an excess amount of aryl chloride (aryl chloride/amine = 2) improved the yields.**

Palladium-catalyzed amination of aryl halides with primary or secondary amines is a convenient synthetic route for aryl amines and a landmark development in C-N bond formation studies. Buchwald and Hartwig independently reported that $Pd/P(o\text{-}Tol)_3$ complex efficiently catalyzed the amination of aryl bromides and iodides.[1,2] In a recent report, Buchwald also disclosed a superior catalytic system which involved Pd/BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) system for the amination of aryl bromides.[3] Hitherto, the amination reactions have been, however, limited to only aryl bromides or iodides. Considering the ease of availability and cost factors, a catalytic system for the amination of aryl chlorides is of practical importance. However, catalytic systems based on the $P(o\text{-}Tol)_3$ or BINAP ligands cannot promote the amination of aryl chlorides since the reactivity of a C-Cl bond is much lower than that of C-Br or C-I. Our approach is based on the fact that a metal center coordinated by bulky and electron-rich phosphine ligands such as PCy_3 and P^iPr_3 can effectively cleave C-Cl bonds of aryl chlorides[4]. Although, activation of C-Cl bonds of aryl chlorides[4,5] has been the subject of long-standing interest, amination of aryl chlorides has not been documented.[6] During our on-going studies on the transformations of aryl chlorides, we realized that $Pd(PCy_3)_2Cl_2$ effectively catalyzed the reaction of aryl chlorides with amines to give the corresponding aryl amines (eq 1).

$$\begin{array}{ccccc} \text{Ar-Cl} & + & \text{R'(R)NH} & \xrightarrow[\text{NaO}^t\text{Bu, toluene}]{\text{Pd(PCy}_3)_2\text{Cl}_2} & \text{Ar-N(R)R'} \\ \mathbf{1a\text{-}e} & & \mathbf{2a\text{-}e} & 120\ ^\circ\text{C, 6-12 h} & \mathbf{3a\text{-}m} \end{array} \qquad (1)$$

The results of palladium-catalyzed amination of aryl chlorides are summarized in Table 1. In most of the cases, two sets of the reactions were carried out using different ratios of reactants; aryl chloride/ amine = 1 or 2. Typically, aryl halide **1** (0.5 or 1 mmol), amine **2** (0.5 mmol), NaO^tBu (0.7 mmol), $Pd(PCy_3)_2Cl_2$ (0.01 mmol) and toluene (2 ml) were placed in a dried Pyrex tube under argon. The glass tube was sealed and heated

Table 1. Palladium-Catalyzed Amination of Aryl chlorides[a]

Entry	Ar	Amine	Time (h)	Product	Yield(%)[b] ArCl/Amine ratio 1	Yield(%)[b] ArCl/Amine ratio 2
1	 **1a**	 **2a**	12	 **3a**	64	88 (83)
2	 **1b**	"		 **3b**	61	75 (72)
3	 **1c**	"	"	 **3c**	62	81 (76)
4	 **1d**	"	"	 **3d**	25	36 (31)
5	 **1e**	"	"	 **3e**	62 (55)	60
6	 **1a**	 **2b**	"	 **3f**	44	65 (59)
7	 **1e**	"	"	 **3g**	48	56
8	 **1a**	 **2c**	6	 **3h**	60	60
9	 **1c**	"	"	 **3i**	57 (54)	
10	 **1e**	"	"	 **3j**	87 (82)	
11	 **1a**	HN(n-Hex)$_2$ **2d**	"	 **3k**	20	
12	 **1e**	"	"	 **3l**	23	
13	 **1a**	HN(CH$_2$Ph)$_2$ **2e**	"	 **3m**	12	

[a] Reaction conditions: Aryl chloride, 0.5 mmol or 1 mmol; amine, 0.5 mmol; NaO^{t}Bu, 0.7 mmol; Pd(PCy$_3$)$_2$Cl$_2$, 0.01 mmol; temperature, 120 °C. [b] NMR yields; all the yields are based on the charged amount of amine; isolated yields (referred to analytically pure compounds) are given in parentheses.

at 120 °C for 6 to 12 h.[7]

When equimolar amounts of phenyl chloride **1a** and 1-methylpiperazine **2a** (Table 1, entry 1) were heated for 6 h under the present catalytic conditions, NMR of the reaction mixture showed about 70% conversion of 1-methylypiperazine and 64% yield of 1-methyl-4-phenylpiperazine **3a**. When the reaction was continued for 18h, no improvement in the conversion of amine **2a** or yield of product **3a** was observed . This indicated that the catalytic cycle was virtually terminated (*vide infra*). Use of 2-fold excess of phenyl chloride (1 mmol) under similar conditions, however, resulted in an increase of the yield of **3a** up to 88% (based on the amount of charged amine). Similar observation was made in the case of *p*-chlorotoluene **1c** (entry 3). However, *o*-chlorotoluene **1d** gave poor yields under similar conditions (entry 4). The hydrogenolysis of the C-Cl bond can be expected as side-reaction in the amination reactions.[8] Indeed, the reaction of 2-naphthyl chloride **1b** with **2a** (**1b**/**2a** = 1) produced 20% of naphthalene along with 61% of **3b** (entry 2). Aryl chlorides bearing electron-withdrawing substituents are more reactive in oxidative addition to transition metal and expected to afford higher yields. However, *p*-chlorobenzonitrile **1e** (entry 5), when reacted with **2a**, gave a significant amount of benzonitrile (30% as estimated by GC) and a decreased yield of **3e**, although the starting materials were completely consumed. Understandably, the use of 2-fold excess of aryl chloride did not give higher yield in this reaction. In the amination reactions of **1a** and **1e** with piperidine **2b** (entries 6 and 7), the trend was similar to the reactions of **2a**, although the yields were relatively low.

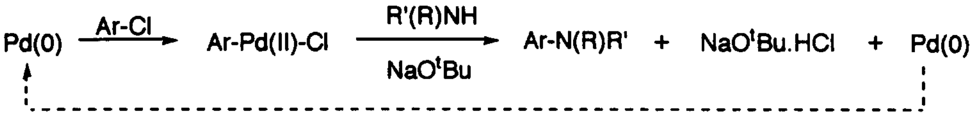
The reactions of aryl chlorides with N-methylaniline **2c** produced moderate to excellent yields depending upon the nature of the substituent. In the case of *p*-chlorobenzonitrile **1e**, an excess amount of aryl chloride was not needed since equimolar amounts of reactants gave a high yield of product **3j** (entry 10). In the reactions of phenyl chloride (entry 8) and *p*-chlorotoluene (entry 9), formation of imine type products[9] retarded the yields and also the ratio of aryl chloride/amine did not show any effect on the yields.

The reactions with open-chain dialkylamines such as dihexylamine **2d** and dibenzylamine **2e** did not afford high yields of aminated products because of extensive dehydrogenation reaction giving the corresponding imine derivatives. In an attempted amination of **1a** with **2e** for instance, N-benzylidenebenzylamine was formed in 85% yield and the yield of the desired aminated product **3m** was only 12% (entry 13). The reactions of **1a** and **1e** (entries 11 and 12) with dihexylamine **2d** also resulted in poor yields of aminated products and several unknown products (probably derived from byproduct imine species) were also produced as byproducts.

Thus, the efficacy of the present catalysis is highly influenced by the nature of the reactants. Some of the reactions encountered serious limitation due to the side reaction, dehydrogenation of amine to produce imine derivatives with the concurrent hydrogenolysis of aryl chlorides.[8] In addition, when this side reaction competed with the amination, use of excessive aryl chloride had no effect. Cyclic amines (**2a** and **2b**) and N-methylaniline **2c** are more selective towards amination reaction and gave good to excellent yields. Open-chain aliphatic amines were found to be more vulnerable to the dehydrogenation reaction and produced less yields of the aminated products.

The performance of various catalyst precursors was studied in the reaction of **1a** (1 equiv.) and **2a**. Under the identical conditions (**1a**/**2a** = 1, 120 °C, 6 h), $Pd(P^iPr_3)_2Cl_2$ was found to be as active as $Pd(PCy_3)_2Cl_2$ to give 60% NMR yield of **3a**. The catalyst precursors such as $Pd(o\text{-}Tol_3)_2Cl_2$, $Pd(dba)_2$/BINAP (dba = dibenzylideneacetone) and $Pd(dppf)Cl_2$ (dppf = (1,1'-diphenylphosphino)ferrocene), which catalyzed the amination of aryl bromides or iodides, were found to be ineffective, the yields of **3a** being 3, 4 and 7% respectively.

As to the mechanism, the pathway proposed for the amination of aryl bromides[10] can be visualized for aryl chlorides. The initiation of the catalytic cycle obviously depends on the efficacy of oxidative addition of the C-Cl bond to Pd(0) species (Scheme 1). The improvement in conversion of **2a** and yield of **3a** by the use of 2-fold excess of **1a** (entry 1) indicates that as the concentration of aryl chlorides decreases, the coordination of amines (reactant and product) prevents Pd(0) to undergo oxidative addition with aryl chloride.



Scheme 1

In conclusion, Pd(PCy$_3$)$_2$Cl$_2$ effectively catalyzes the amination of aryl chlorides. In some cases, the use of excessive aryl chloride considerably improves the yield. Further studies are under progress to expand the applications to other substrates.

References and Notes

1. a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348-1350. b).Louie, J.; Hartwig, J. F. *TretrahedronLett.* **1995**, *36*, 3609-3612. c) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133-1135.
2. Pd/dppf system was also used for amination of aryl bromides. See Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217-7218.
3. Wolfe, J. P.; Wagaw, S.; Buchwald, S. L.; *J. Am. Chem. Soc.* **1996**, *118*, 7215-7216.
4. Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047-1062.
5. a) For amino carbonylation, see Perry, R. J.; Wilson, B.D. *J. Org. Chem.*, **1996**, *61*, 7482-7485. b) For Heck arylation, see Reetz, M. T.; Lohmer, G. *Chem. Commun.* **1996**, 1921-1922 and references cited therein.
6. While this manuscript was in preparation, Koie, Y. *et al*. reported (72nd Spring Annual Meeting of the Chemical Society of Japan, Abstracts 2PA052 and 2PA053, Tokyo, March 28-31, 1997) a Pd/P^{t}Bu$_3$ catalytic system for the synthesis of aryl piperazines and triaryl amines by treating aryl halides (bromides and chlorides) with piperazine and diaryl amines respectively.
7. The reaction mixture was taken into ether (10 ml) and washed with saturated brine (5-10 ml). The organic layer was dried with MgSO$_4$ and concentrated. The products were purified by preparative TLC (Aluminium oxide 60 F$_{254}$, MERCK) using hexane/ether (4 : 1) as eluent. All the new products gave satisfactory spectral and analytical data.
8. a-Hydrogen-containing amines, when coordinated to a metal complex, tend to undergo dehydrogenation to produce imines and hydrido-metal species. The resulting hydrido-metal complex induces the hydrogenolysis of aryl halides. See ref. 1.
9. The details of these products will be published elsewhere.
10. For more details about the mechanism of amination of aryl bromides, see a) Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics*, **1995**, *14*, 3030-3039. b) Mann, G.; Hartwig, J. F. *J. Am. Chem.* Soc. **1996**, *118*, 13109-13110

(*Received in Japan* 23 *April* 1997; *accepted* 22 *May* 1997)