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Amination of aryl chlorides in water catalyzed by cyclopalladated ferrocenylimine complexes with commercially available monophosphinobiaryl ligands

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Abstract—The easily accessible, air- and moisture-stable cyclopalladated ferrocenylimine complex **3** was found to be a highly active one-component precatalyst for the amination of aryl chlorides in water in the presence of inexpensive KOH and *t*-BuOH as a base and an additive, respectively.

The palladium-catalyzed coupling of amines with aryl halides or sulfonates, commonly dubbed Buchwald–Hartwig amination, has evolved into a versatile and efficient synthetic transformation for the preparation of aromatic amines.[1] A number of Pd complexes derived from bulky and electron-rich alkylphosphine ligands are reported to be effective catalysts for the coupling of notoriously unreactive but relatively cheap aryl chlorides with amines. Some of the notable examples include the Buchwald's monophosphinobiaryl ligand family,[1b,2] Hartwig's ferrocenylalkylphosphines,[1c,3] Beller's di-1-adamantyl(*n*-butyl)phosphine and pyrrole-, indole- or imidazole-based alkylmonophosphines[4] as well as several lately developed alkylphosphines.[5] In addition, other strategies such as using bicyclic triaminophosphines,[6] sterically hindered *N*-heterocyclic carbenes (NHCs)[7] as ligands, and palladacycles as the precatalysts,[8] also provide efficient catalytic systems for this transformation.

The Buchwald–Hartwig aminations with the abovementioned catalytic systems were usually run in an organic solvent in the presence of strong bases such as *t*-BuONa or *t*-BuOK and an excess of ligand was required (commonly 2-fold with respect to Pd precursors) except for those one-component precatalysts such as palladacycles. From an economic and practical point of view, a process featuring an efficient and easy-to-handle catalytic system in combination with an inexpensive solvent and base would be highly desirable. Water has clear advantages as a solvent in organic synthesis because it is cheap, readily available and nontoxic.[9] To our knowledge, only one account has been reported concerning the aminations of limited substrates in water in the presence of an inexpensive KOH base.[2c] There have been, however, several reports which demonstrated that the addition of water did not impede the amination or could even be beneficial.[10]

We have found cyclopalladated ferrocenylimine–tricyclohexylphosphine complexes are very efficient for the Suzuki reaction of aryl chlorides with phenylboronic acid.[11] These precatalysts combine the stability imparted by a palladacycle framework with the high activity commonly associated with alkylphosphine ligands. Following this work, we prepared two new cyclopalladated ferrocenylimine complexes **2** and **3** from the reaction of cyclopalladated ferrocenylimine dimer **1** with commercially available 2-(dicyclohexylphosphanyl)biphenyl (DCPB) or 2-dicyclohexylphosphanyl-2′-(*N*,*N*-dimethylamino)biphenyl (DCPAB) (Scheme 1).

The two complexes are air- and moisture-stable both in the solid state and in solution. Despite the fact that complex **2** could, in principle, exist in both cis and trans

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Keywords: Amination; Aryl chloride; Water; Cyclopalladated ferrocenylimine complex; Monophosphinobiaryl ligand.

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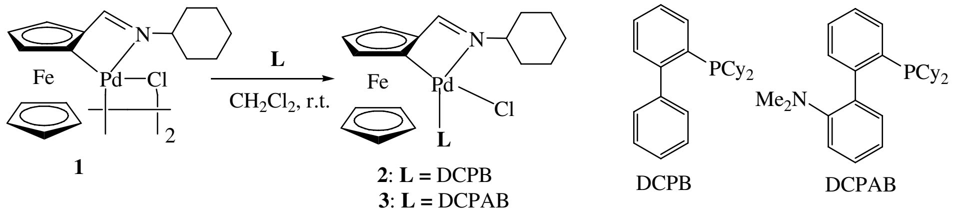


Scheme 1.

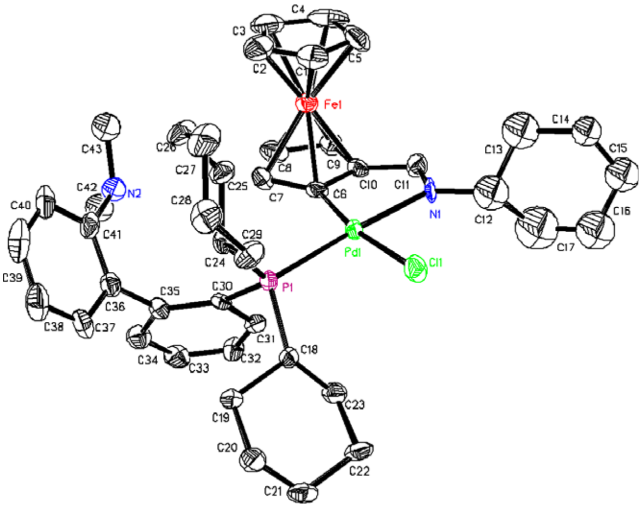
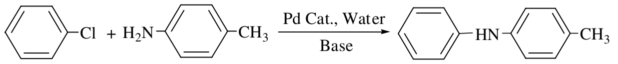


Figure 1. Molecular structure of complex **3**. Hydrogen atoms are omitted for clarity, thermal ellipsoids at 30% probability. Selected bond lengths (Å) and angles (°): Pd(1)–C(6) 2.010(8), Pd(1)–N(1) 2.149(7), Pd(1)–P(1) 2.271(2), Pd(1)–Cl(1) 2.404(2) and C(6)–Pd(1)–N(1) 79.6(3), C(6)–Pd(1)–P(1) 90.6(3), P(1)–Pd(1)–Cl(1) 92.79(8), N(1)–Pd(1)–Cl(1) 92.1(2).

forms corresponding to the relative disposition of the coordinate P-ligand to the imino nitrogen, the only signal at δ 59.5 ppm in ^{31}P NMR spectra suggested the formation of a single isomer. While complex **3** showed two peaks at δ 65.7 and 64.7 ppm, suggesting the formation of isomers in solution.[11] The single-crystal X-ray analysis confirms that complexes **2** and **3** are trans complexes in the solid state and the molecular structure of complex **3** is shown in Figure 1.

We first chose the coupling of chlorobenzene with *p*-toluidine as the model reaction to evaluate the effectiveness of the new palladacycles in the amination of aryl chlorides in water and to optimize the reaction conditions (Table 1).[12] It was disappointing to find at the beginning that the isolated yield of the coupled product was only 31% with 1 mol % of **3** in the presence of 3 equiv of KOH (entry 1). However, when the strong organic base *t*-BuOK was used, the yield increased dramatically to 98% (entry 2). Since *t*-BuOK would hydrolyze to give *t*-BuOH and KOH in water, 4 equiv of *t*-BuOH was added with KOH as the base in the following experiments. As expected, chlorobenzene could be coupled very efficiently with *p*-toluidine giving 4-methyldiphenylamine in a 98% yield (entry 3). On the basis of this finding, we also examined the effect of some other alcohols such as EtOH, *n*-BuOH, *i*-PrOH and cyclohexanol. However, all the four alcohols proved to be ineffective (yields in 28%, 42%, 35% and 33%, respectively; data not shown). Testing different bases (e.g., NaOH, K_2CO_3, Na_2CO_3, K_3PO_4) in the presence of *t*-BuOH revealed that KOH was the most effective base

Table 1. Optimization of reaction conditions for the coupling of chlorobenzene with *p*-toluidine



Entry	Catalyst (mol %)	Base	Yield[a](%)
1[b]	**3** (1)	KOH	31
2[b]	**3** (1)	*t*-BuOK	98
3	**3** (1)	KOH	98
4	**3** (1)	NaOH	63
5	**3** (1)	K_3PO_4	20
6	**3** (1)	Na_2CO_3	44
7	**3** (1)	K_2CO_3	22
8	**2** (1)	KOH	44
9	**1** (1)	KOH	0
10	**1**/PCy_3 (0.5/2)	KOH	0
11	**1**/DCPAB (0.5/2)	KOH	68
12	$PdCl_2$/DCPAB (1/2)	KOH	24
13	$Pd(OAc)_2$/DCPAB (1/2)	KOH	59
14	$Pd_2(dba)_3$/DCPAB (0.5/2)	KOH	50

Conditions: PhCl/*p*-toluidine/base/*t*-BuOH = 1:1.2:3:4 (molar ratio), H_2O, reaction temperature 95 °C, 24 h.

[a] Isolated yield.

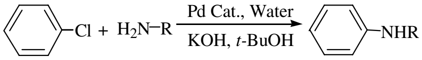
[b] *t*-BuOH was not added.

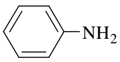
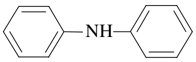
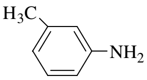
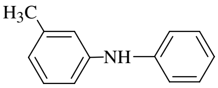
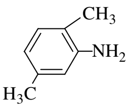
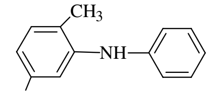
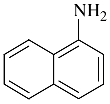
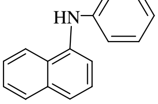
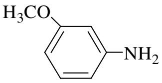
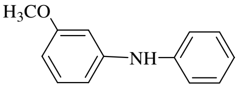
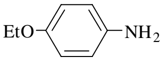
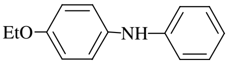
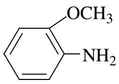
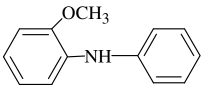
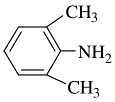
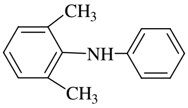
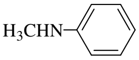
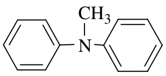
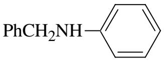
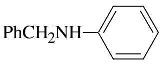
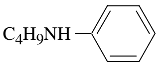
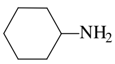
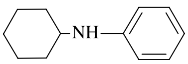
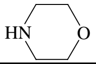
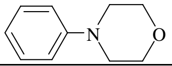
(entries 4–7). The second effective base was NaOH, which is also a hydroxide base and gave a moderate yield (63%, entry 4).

Then the activities of several related catalytic systems in the same model reaction were investigated. Among them, complex **3** was found to be the most active one-component precatalyst. The similar complex **2** without a *N*,*N*-dimethylamino group in comparison with complex **3** generated the coupled product only in a 44% yield under the same conditions (Table 1, entry 8). The dimeric complex **1** and **1**/PCy_3 system were inactive although PCy_3 was an excellent ligand for the Suzuki coupling of aryl chlorides[11] (entries 9–10). A significant increase in activity was observed with **1**/DCPAB system (68%, entry 11) and it was more active than the commonly used Pd(0) or Pd(II) precursors ($Pd_2(dba)_3$ or $PdCl_2$ and $Pd(OAc)_2$) in combination with DCPAB (entries 12–14).

With the optimized reaction conditions (complex **3** as precatalyst, KOH, *t*-BuOH, water) in hand, the coupling reactions between chlorobenzene and a variety of amines were carried out to explore the scope of this system (Table 2). The desired coupled products were obtained in excellent yields (90–96%) with 1 mol % of

Table 2. Arylation of various amines with chlorobenzene catalyzed by **3**



Entry	Amine	Catalyst (mol %)	Product	Yield[a] (%)
1		1		92
2		1		96
3		1		90
4		1		93
5		1		88
6		1		90
7		1		72
8		2		66
9		1		81
10	$PhCH_2NH_2$	0.5		72
11	$PhCH_2NH_2$	1		96
12	$C_4H_9NH_2$	1		51
13		1		67
14		1		73

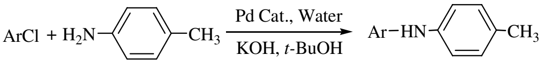
Conditions: PhCl/amine/KOH/*t*-BuOH = 1:1.2:3:4 (molar ratio), H_2O, reaction temperature 95 °C, 24 h.

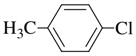
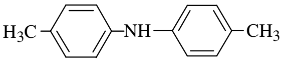
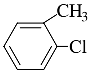
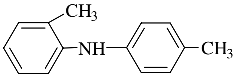
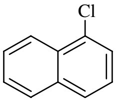
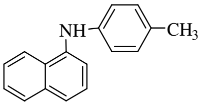
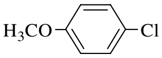
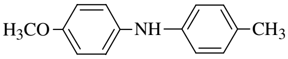
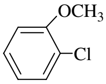
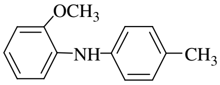
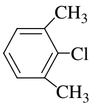
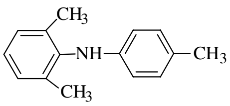
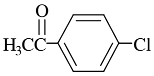
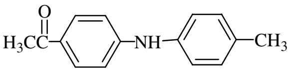
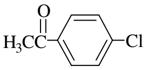
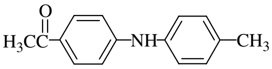
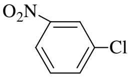
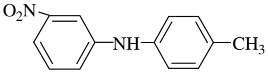
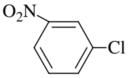
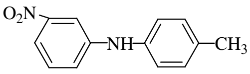
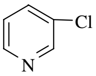
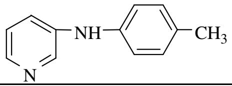
[a] Isolated yield.

complex **3** in the case of electron-neutral primary arylamines even including the one with an *o*-CH_3 group (entries 1–4). For electron-rich primary arylamines with an alkoxy group in the *meta* or *para*-position, the yields decreased slightly but still were very high (88% and 90%, entries 5–6). A further decrease in the yield was observed when the alkoxy group was located in the *ortho*-position (72%, entry 7). The very sterically hindered 2,6-dimethylaniline could provide the corresponding arylamine in a 66% yield with 2 mol % of catalyst (entry 8). A secondary arylamine gave a good yield (81%, entry 9). Compared with the results of arylamines, the present catalytic system was found to be less effective for the coupling of aliphatic primary or secondary amines with the exception that benzylamine afforded an excellent yield (entries 10–14). Finally, it needed to be pointed out that the coupling of arylamines containing $–NO_2$, –OH or –CO– group with chlorobenzene was unsuccessful.

The scope of the amination was further investigated by varying the aryl chlorides under the optimized conditions (Table 3). Similar to the results of varying amine part, good to excellent yields (87–97%) were obtained with 1 mol % of the catalyst in the reactions between *p*-toluidine and the electron-neutral aryl chlorides including *o*-chlorotoluene (entries 1–3). Even the electron-rich 4-chloroanisole could afford the desired product in an excellent yield (94%, entry 4). Also similarly, an obvious decrease in yields was observed in the case of 2-chloroanisole and very sterically hindered 2-chloro-*m*-xylene (entries 5–6). For electron-deficient aryl chlorides such as 3-chloronitrobenzene and 4-chloroacetophenone, the coupling proceeded very efficiently with a catalyst loading as low as 0.5 mol % and 73% yield could still be obtained with 0.2 mol % of the catalyst (entries 7–10). Since the coupling of arylamines containing $–NO_2$ or –CO– group were found to be unsuccessful in the previous study, the efficient coupling of aryl chlorides containing $–NO_2$ or –CO– group provided a valuable complement for the preparation of the corresponding arylamines. Finally, the coupling of a heteroaryl chloride (3-chloropyridine) with *p*-toluidine gave the desired product in a 78% yield (entry 11).

Table 3. Amination of various aryl chlorides with *p*-toluidine catalyzed by **3**



Entry	Aryl halide	Catalyst (mol %)	Product	Yield[a] (%)
1		1		97
2		1		87
3		1		97
4		1		94
5		1		81
6		2		61
7		0.5		98
8		0.1		39
9		0.1		52
10		0.2		73
11		1		78

Conditions: aryl chloride/*p*-toluidine/KOH/*t*-BuOH = 1:1.2:3:4 (molar ratio), H_2O, reaction temperature 95 °C, 24 h.

[a] Isolated yield.

In conclusion, we have demonstrated that easily accessible, air- and moisture-stable cyclopalladated ferrocenylimine complex **3** is an effective precatalyst for the coupling of a variety of electronically and structurally diverse aryl chlorides with various amines in water. The advantages of the present process include an easy-to-handle one-component precatalyst, the use of water as a solvent as well as inexpensive KOH and *t*-BuOH as a base and an additive, respectively.

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Supplementary data

Electronic supplementary data: general experimental procedure for the synthesis of complexes **2** and **3**, their characterization data including crystal structure data, crystal structure of **2** including selected bond lengths and angles. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.130.

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12. General amination procedure: In a Schlenk tube, a solution of prescribed amount of catalyst, aryl chloride (0.5 mmol), amine (0.6 mmol), base (1.5 mmol) and *tert*-butanol (0.192 mL, 2 mmol) in water (3.0 mL) was evacuated and charged with nitrogen. The operation was repeated three times. Then the reaction mixture was heated at 95 °C (reaction temperature) for 24 h. After cooling, the reaction mixture was extracted three times with dichloromethane. The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated to dryness. The products were isolated by flash chromatography on silica gel, and analyzed by ^{1}H NMR.