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2,6-Bis(diphenylphosphino)pyridine: a simple ligand showing high performance in palladium-catalyzed C—N coupling reactions

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ABSTRACT

The use of commercially available 2,6-bis(diphenylphosphino)pyridine as a ligand in conjunction with K_2CO_3, DMAc and TBAB is an effective method for the palladium-catalyzed C—N coupling of a variety of aryl halides with anilines, N-heterocyclic aromatic amines, and a cyclic secondary amine. The reactions proceed in good to excellent yield (up to 98%) while the loading of $Pd(OAc)_2$ was as low as 0.025 mol %.

To date, many different strategies have been reported for the synthesis of aryl amines. Despite the potential utility of classical methods such as nucleophilic substitution,[1] reductive amination,[2] and Ullmann-type amination,[3] several have one or more certain drawbacks including harsh reaction conditions, low functional group compatibility, and the necessity of using excess reagents or catalyst. On account of its high tolerance to different functional groups and mild reaction conditions, Pd-catalyzed amination has been the subject of extensive study since the pioneering works of Buchwald[4] and Hartwig[5] (Scheme 1), and have found widespread application in the synthesis of pharmaceuticals and fine chemicals.[6,7]

Several modifications have been reported including variation of the ligands, palladium source, solvent, and bases in order to perform the coupling reaction more efficiently. It is well known that a careful selection of the ligand in terms of its electronic and steric characteristics is extremely crucial in various Pd-catalyzed C—C and C-heteroatom bond-forming reactions. As a result, numerous efforts have been dedicated to the search for more efficient and versatile ligands for expanding the applications of Pd-catalyzed reactions. Phosphines are among the most utilized ligands in transition metal complex catalyzed reactions since their electronic (σ-donating ability with π-accepting capacity) and steric characteristics can be easily varied by introducing different substituents.

The juxtaposition of a pyridine and two phosphine moieties, presenting a P–N–P framework, in a 2,6-relationship of the type shown in Figure 1, has found considerable attention in the field of organometallic chemistry.[8–10] Within this family of ligands, 2,6-bis(diphenylphosphino)pyridine $(Ph_2P)_2py$ (**1**), is more rigid than other examples (**2**–**4**) due to the absence of the methylene groups connecting the phosphorus atoms and the pyridine ring.

In recent work, we reported our results concerning the utility of $(Ph_2P)_2py$ in Heck coupling reactions of various aryl halides.[11] Considering the importance of the Buchwald–Hartwig type amination reaction in organic synthesis, and in continuation of our studies on Pd-catalyzed carbon–carbon coupling reactions,[11–19] in this Letter we report a series of experiments on the carbon–nitrogen coupling reaction using $(Ph_2P)_2py$ as a supporting ligand.

Using ligand **1**, we initially conducted the reaction between bromobenzene and aniline following a reported procedure using 0.025 mol % of $Pd(OAc)_2$, *N*,*N*-dimethylacetamide (DMAc) as the solvent, sodium carbonate (K_2CO_3) as the base, and tetrabutylammonium bromide (TBAB) as the additive.[11,20] The reaction proceeded successfully to afford diphenylamine in 94% yield after one hour. This result was encouraging, and we evaluated the efficiency of the $Pd(OAc)_2/(Ph_2P)_2py$ system with other substrates. We began by examining the aryl bromide partner (Table 1, entries 1–8). The desired products were obtained in good to excellent yields within 1–3 h without obvious discrimination of the electronic nature of the benzene substituents. However, 1-bromo-4-nitrobenzene gave a yield of 74% after five hours, probably due to a competitive dehalogenation reaction which has been reported in the literature

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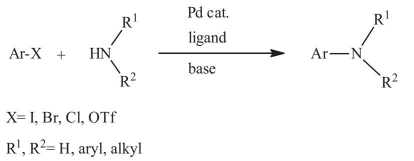
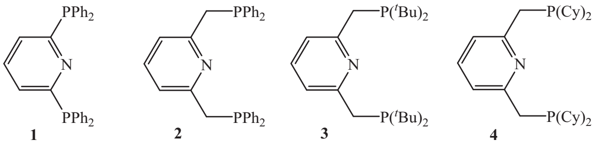


Scheme 1. Palladium-catalyzed Buchwald–Hartwig reaction.



1 2 3 4

Figure 1. Examples of 2,6-disubstituted phosphine-pyridine ligands.

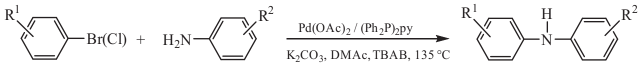
to occur when using aryl halides bearing electron-withdrawing substituents[21,22] (Table 1, entry 7). The reaction with 3-bromothiophene was successfully achieved (entry 5), providing a useful way for the introduction of an amino group on the thiophene ring. It seems that the presence of the S-atom polarizes the aromatic ring, thereby making it prone to oxidative addition.

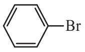
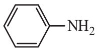
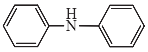
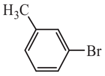
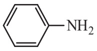
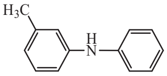
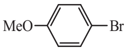
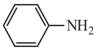
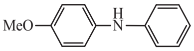
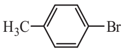
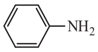
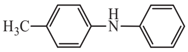
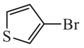
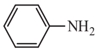
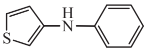
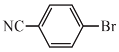
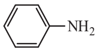
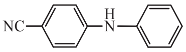
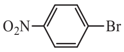
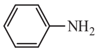
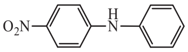
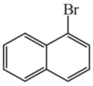
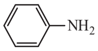
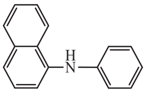
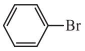
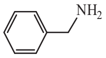
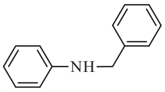
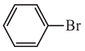
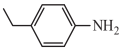
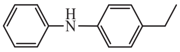
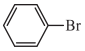
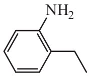
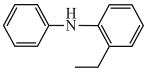
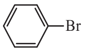
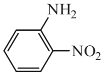
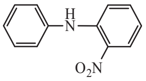
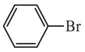
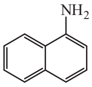
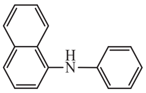
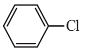
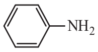
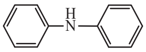
Sterically hindered 1-bromonaphthalene could also be coupled in good yield in a relatively short reaction time (Table 1, entry 8). The coupling between 4-bromobenzonitrile and aniline did not take place under our conditions (Table 1, entry 6). This result was very similar to that of Hong's group for their cobalt-containing P,N-ligand.[23,24] They came to the supposition that the poor reactivity of cyano-substituted bromobenzene might be due to the cyano group coordinating with Pd, therefore interfering with the catalytic role of the Pd species.

The performance of the $Pd(OAc)_2/(Ph_2P)_2py$ system was further evaluated with other substituted anilines (Table 1, entries 9–13). Coupling of benzylamine with bromobenzene worked well, providing the expected product in 98% yield (Table 1, entry 9). Steric hindrance had an effect upon the rate of the reactions. For example, 4-ethylaniline reacted with bromobenzene within one hour to give the desired product in 98% yield (entry 10). However the reaction with 2-ethylaniline occurred over six hours producing the product in 80% yield (Table 1, entry 11).

Encouraged by these positive results, we proceeded to investigate the C—N coupling between aniline and chlorobenzene,

Table 1
Palladium-catalyzed amination of aryl halides[a]



Entry	Aryl halide	Amine	Product	Time (h)	Yield (%)	TON[b]
1				1	94	4760
2				2	83	3320
3				4	76	3040
4				3	80	3200
5				1	80	3200
6				5	No reaction	–
7				5	74	2960
8				2	72	2880
9				1	98	3920
10				1	98	3920
11				6	80	3200
12				2	81	3240
13				3	97	3880
14				3	88	3520

[a] Reaction conditions: aryl halide (4 mmol), amine (4 mmol), K_2CO_3 (4 mmol), $Pd(OAc)_2$ (0.025 mol %), $(Ph_2P)_2py$ (0.05 mol %), TBAB (3 mmol), DMAc (4 mL), 135 °C.
[b] TON = mol product/mol catalyst.

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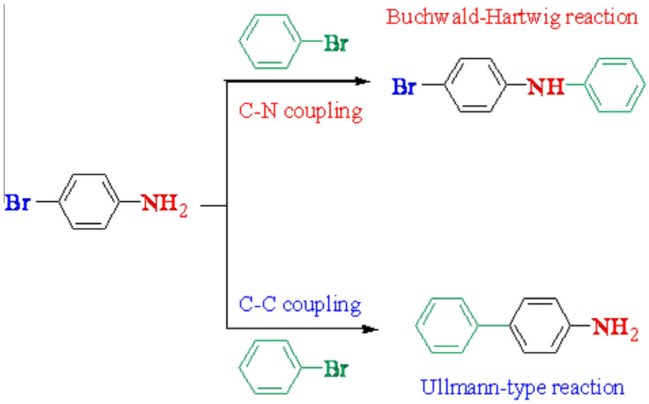
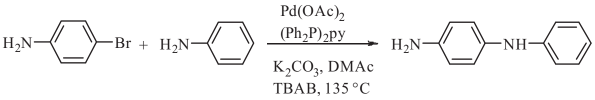


Scheme 2. Two possible pathways for the reaction between 4-bromoaniline and bromobenzene.



Scheme 3. C—N coupling between 4-bromoaniline and aniline.

which is known to be less reactive than the bromo analogue due to the stronger C—Cl bond, which delays the oxidative addition to the Pd(0) species. Fortunately, the coupling was satisfactory with a low loading of only 0.025 mol % of $Pd(OAc)_2$ to give an 88% yield of product after three hours (Table 1, entry 14).

4-Bromoaniline is an interesting test substrate, because it contains two functional groups, both susceptible to coupling reactions. In fact, there are two pathways for the conversion of 4-bromoaniline that involve the NH_2 group for construction of a C—N bond through the Buchwald–Hartwig reaction, or the Br group to form a C—C bond through an Ullmann-type reaction as illustrated in Scheme 2.

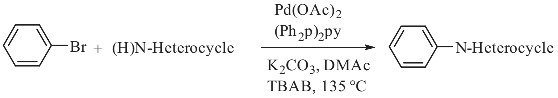
In order to identify which reaction was preferred, we reacted 4-bromoaniline and bromobenzene using our conditions, which gave a mixture of amination product and biphenyl derivative in 70% and 30% yield, respectively. This demonstrates clearly that the amination reaction is much faster than the Ullmann coupling. The Ullmann reaction mechanism involves consecutive oxidative addition of the aryl halide to Pd(0) and Pd(II) species, respectively. The electron-donating ability of the NH_2 group may slow the second oxidative addition step in the catalytic cycle and allow amination to dominate. The application of a 2-fold excess of bromobenzene versus 4-bromoaniline had no effect on the selectivity for the Ullmann reaction and the product ratio remained constant as before, (70:30). However, with prolonged time (17 h) a di-coupled amination product was obtained.

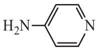
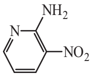
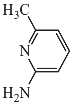
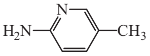
It is important to note that there is another route for the conversion of 4-bromoaniline based on C—N coupling of 4-bromoaniline and aniline as shown in Scheme 3. In this reaction 4-bromoaniline acts as an electrophile and adds oxidatively to the Pd(0) center.

Unfortunately, the reactivity toward aliphatic amines such as *n*-butylamine and isopropylamine, which was observed by others,[25,26] was not achieved with our catalyst system (data not shown), presumably due to the volatility of these substrates under the employed high temperature conditions.

N-heterocyclic aromatic amines, especially aminopyridines, occupy important roles in chemistry, being a key structural feature of many natural products, and are present in several classes of pharmaceutical drugs. Thus, we explored further the scope of ligand **1** in the amination of heterocyclic substrates and the results are shown in Table 2.

Table 2
C—N coupling of various aminopyridines with bromobenzene[a]



Entry	Amine	Time (h)	Yield (%)	TON[b]
1		4	91	3640
2		2	94	3760
3		4	No reaction	-
4		4	No reaction	-
5	2-(Aminomethyl)pyridine	1	78	3120

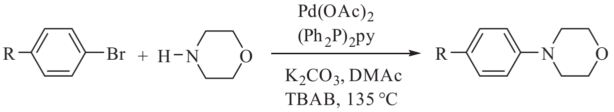
[a] Reaction conditions: bromobenzene (4 mmol), amine (4 mmol), K_2CO_3 (4 mmol), $Pd(OAc)_2$ (0.025 mol %), $(Ph_2P)_2py$ (0.05 mol %), TBAB (3 mmol), DMAc (4 mL), 135 °C.

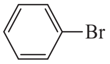
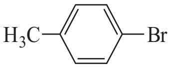
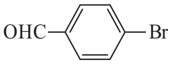
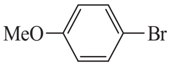
[b] TON = mol product/mol catalyst.

4-Aminopyridine and 2-amino-3-nitropyridine reacted efficiently to give excellent yields of products (Table 2, entries 1 and 2). 2-Amino-6-methylpyridine was unreactive under similar reaction conditions (Table 2, entry 3). At first glance, this result may be attributed to the steric hindrance present in the substrate, but since our effort employing 2-amino-5-methylpyridine was not successful (Table 2, entry 4), we are inclined to assume that the electronic effect of the methyl group is mostly responsible for the decreased catalytic activity. We found that our system could also catalyze the arylation of 2-(aminomethyl)pyridine (Table 2, entry 5).

We considered morpholine as a suitable candidate for further evaluation of the influence of ligand **1** on the C—N coupling of a cyclic secondary amine. The results are summarized in Table 3.

Table 3
C—N coupling of morpholine with aryl bromides[a]



Entry	Aryl halide	Time (h)	Yield (%)	TON[b]
1		3	92	3680
2		3	90	3600
3		4	64	2560
4		3	70	2800

[a] Reaction conditions: aryl bromide (4 mmol), morpholine (4 mmol), K_2CO_3 (4 mmol), $Pd(OAc)_2$ (0.025 mol %), $(Ph_2P)_2py$ (0.05 mol %), TBAB (3 mmol), DMAc (4 mL), 135 °C.

[b] TON = mol product/mol catalyst.

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Our catalytic system showed good activity for the arylation of morpholine. However, in the cases of 4-bromobenzaldehyde and 4-bromoanisole an unidentified product was also observed.

In summary, a highly efficient palladium-catalyzed system using commercially available 2,6-bis(diphenylphosphino)pyridine as the ligand has been developed for the C—N coupling of various aryl halides with anilines, N-heterocyclic aromatic amines and a cyclic secondary amine. Good to high yields of products were obtained with excellent functional group tolerance.

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20. Typical experimental procedure for the Buchwald–Hartwig reaction: A round-bottomed flask was charged with bromobenzene (4 mmol), aniline (4 mmol), TBAB (3 mmol), and K_2CO_3 (4 mmol) under a dry nitrogen atmosphere. A solution of $(Ph_2P)_2py$ (0.05 mol % in 2 mL of DMAc) and a solution of palladium acetate (0.025 mol % in 2 mL of DMAc) was added through a rubber septum, and the resulting mixture was heated at 135 °C for the appropriate time. Upon completion of the reaction, the mixture was cooled to room temperature and quenched with H_2O. After extraction with CH_2Cl_2 (3 × 20 mL), the combined organic layer was dried over $MgSO_4$. The solvent was evaporated and the crude residue was purified by silica gel chromatography, using *n*-hexane/EtOAc as eluent to provide the desired product. The products were characterized by NMR spectroscopy.
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