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Air-stable palladium(0) phosphine sulfide catalysts for Ullmann-type C–N and C–O coupling reactions

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ABSTRACT

This paper describes an efficient procedure for palladium(0)-catalyzed *N*-arylation and *O*-arylation of aryl halides by Ullmann-type cross coupling reaction under mild reaction conditions in a short reaction time. Two phosphine sulphide ligands and their corresponding Pd(0) complexes namely [Pd(p_2S_2)(dba)] and [Pd(pp_3S_4)(dba)], were synthesized, where p_2S_2 is 1,2-bis(diphenylphosphino)ethane disulfide, pp_3S_4 is tris[2-(diphenylphosphino)ethyl]phosphine tetrasulfide and dba is dibenzylideneacetone. Optimal reaction conditions were determined for the arylation reactions using iodobenzene and benzimidazole by varying temperature, solvent, base and catalyst loading. The cross coupling reactions were carried out taking iodobenzenes/bromobenzenes and a wide variety of substituted aryl amines/phenols/alcohols with different steric and electronic properties to afford the desired *N*-aryl amines/diaryl ethers/alkyl aryl ethers in good to excellent yield (70–94%).

Introduction

N-arylamines and diaryl ethers are very important structural motifs due to their occurrence in biologically active natural products, pharmaceuticals and their applications in materials research [1]. Amongst the methods used for the preparation of such compounds the classical Ullmann cross coupling reaction is widely used. The original protocol for the Cu-mediated coupling reaction required the stoichiometric amounts of copper salts together with high reaction temperatures ($\geq$200 °C) and long reaction times [2]. A drawback of the use of copper salts and copper-ligand complexes in copper based-protocols (copper salt is present in catalytic amount) is their poor solubility and stability in the commonly used organic media [3]. The recent interest in Ullmann chemistry has been spurred by the tremendous success of the palladium catalyzed arylation of amines and phenols at lower temperature [4]. $Pd(PPh_3)_4$, Pd(II)-salt/PPh_3 (excess) and related arylphosphine complexes are the traditional reagents usually used for these types of coupling reactions as phosphines have been regarded as effective ligands to stabilize Pd(0) [5]. However, phosphines are often relatively sensitive to exogenous oxygen and moisture due to oxidation of the ligands and hence, they might not be the ideal ligands in large-scale application on industrial and semi-industrial scale [6]. It implies that, significant limitations still exist in this area and therefore, researchers are in a quest for more active and stable catalyst systems. On the other hand, in case of phosphine-free systems i) if, the ligands are strongly bonded to Pd(0), then the catalytic cycles are blocked to give low catalytic activity and ii) if the ligands are weakly bonded to Pd(0), then the complexes become unstable and decompose into inactive “palladium black”. These problems of phosphine ligands can be overcome by using phosphine sulfide ligands [7]. Though doubly-bonded sulfur atom in the phosphine sulfide can protect the phosphorus atom from its oxidation, the catalysis by Pd(0)-phosphine sulfide complexes has been sparsely studied. The sulfur–phosphorus π bond is not stabilized, and consequently the unoccupied π^* orbital is moderately low and may accept electron from Pd(0) to stabilize the lower oxidation state of Pd. The schematic structures are shown in Scheme 1. Moreover, as phosphine sulfide is not strongly σ-bonding functional group for Pd(II), formation of the Pd(II)-substrate adduct and subsequent reaction processes are not likely to be blocked. The

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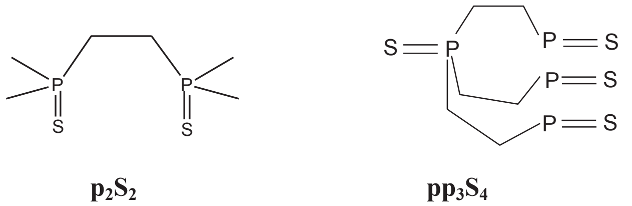


Scheme 1. Schematic diagrams of phosphine sulfide ligands.

Table 1
Effect of solvents and bases for C–N coupling reaction with [Pd(pp_3S_4) (dba)].

Entry	Base	Solvent	Time (h)[a]	Yield (%)[b]
1	Cs_2CO_3	Isopropanol	3	94
2	Cs_2CO_3	DMSO	24	44
3	Cs_2CO_3	DMF	6	83
4	Cs_2CO_3	CH_3CN	6	83
5	Cs_2CO_3	Nitromethane	8	79
6	Cs_2CO_3	Methanol	10	83
7	Cs_2CO_3	Toluene	12	64
8	Cs_2CO_3	Ethyl acetate	12	64
9	Cs_2CO_3	Dichloroethane (EDC)	14	84
10	Cs_2CO_3	Water	24	44
11	KOH	Isopropanol	3	75
12	K_2CO_3	Isopropanol	3	70
13	NaOH	Isopropanol	3	55

[a] Monitored using TLC, until all the benzimidazole was found consumed.
[b] Isolated yield, after column chromatography of the crude product.

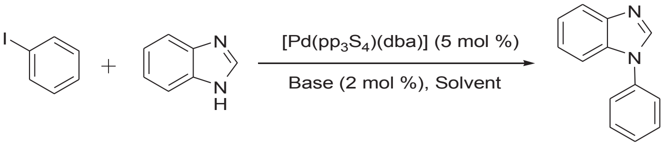
relatively labile Pd(II)–sulfur bond can be cleaved reversibly to generate a free coordination site for incoming stronger binding substrate which facilitates the catalytic process involving oxidative addition and subsequent reductive elimination [7,8].

Although, the use of the Pd(0)-phosphine sulfide complexes as catalysts only for C–C coupling reactions have been reported [7–9], but a detailed study in this area is still lacking. This fact prompted us to explore the applicability of these catalysts in other coupling reactions. In this paper, we describe the application of air-stable, easy-to-prepare Pd(0) complexes with multidentate phosphine sulfide ligands in the Ullmann-type C–N and C–O cross coupling reaction for synthesis of *N*-aryl amine and diaryl ethers/alkyl aryl ethers. Of particular significance is that through the use of these catalysts, we were able to successfully perform Pd(0)-catalyzed Ullmann-type cross coupling reactions to provide high yields of the desired product under an ambient condition, whereas in the previous reports, an inert atmosphere was mandatory when Pd(0)/Pd(II)-salts and bulky phosphine ligands were used [1a,1b,10]. To the best of our knowledge, this is the first time that Pd(0)-phosphine sulfide complexes are reported to be the useful catalyst for *N*-arylation of amines and *O*-arylation of phenols with aryl halides through Ullmann-type cross coupling reactions.

Results and discussion

Initially we tried to seek the optimal condition for Pd(0)-catalyzed C–N bond formation reaction. To optimize the reaction conditions for the *N*-aryl amination reaction, iodobenzene and benzimidazole were selected and [Pd(pp_3S_4)(dba)] was used as a catalyst. A variety of reaction conditions were studied in order to evaluate the effects of temperature, solvents, bases and catalysts. In the absence of the palladium catalyst, the reaction hardly proceeded (only 4% yield was observed). We were pleased to find that under optimized condition reactions occurred to deliver the cross-coupled products in excellent yields.

First, we studied the effect of solvents on the cross coupling reactions. The reactions were carried out in various solvents at different temperatures by taking iodobenzene (1.016 mmol) and benzimidazole (0.846 mmol) in presence of 5 mol % of [Pd(pp_3S_4) (dba)] and 2 mol % Cs_2CO_3 of (Scheme 2). Isopropanol was the most efficient solvent among those examined, because it gave the cross-coupling product in 94% isolated yield (Table 1, entry 1). Other solvents such as DMF, acetonitrile, nitromethane, methanol, dichloroethane too produces good yields (Table 1, entries 3–6, 9) whereas DMSO, toluene, ethyl acetate and water gave 44%, 64%, 64% and 44% yields (Table 1, entries 2, 7, 8, 10), respectively. It is noteworthy that DMSO gave us poor yield though it was effective for aryl bromides in the previous report [10k]. Many reports are found in the literature where a polar aprotic solvent like DMF is the most suitable one [11], but in our case the C–N cross coupling reaction proceeded smoothly in low boiling polar protic solvent.



Scheme 2. Coupling reaction of iodobenzene with benzimidazole under the catalysis of [Pd(pp_3S_4)(dba)].

Further investigations showed that Cs_2CO_3 as base gave the best yields of product (Table 1, entry 1) with a reaction time of 3 h among all tested bases such as KOH, K_2CO_3 and NaOH. NaOH was the least effective (Table 1, entry 13), and other two bases namely KOH and K_2CO_3 gave substantial amounts of *N*-aryl amines (Table 1, entries 11 and 12).

When the reaction was carried out using 1 mol % Cs_2CO_3, only a 44% yield was obtained after 14 h. But, the yield enhanced drastically when 2 mol % of Cs_2CO_3 was used (Table 2, entry 2). On the other side, it was observed that only 1 mol % catalyst can produce excellent yield (Table 2, entry 3). The yields did not improve significantly upon increasing catalyst concentration (Table 2, entry 1, 4). Iodobenzene turned out to be the best substrate (Table 2, entry 1) in comparison with bromobenzene (Table 2, entry 5) and cholorobenzene (Table 2, entry 6).

Table 2
Optimization of base and catalyst mol % and substrate for C–N coupling reaction with [Pd(pp_3S_4)(dba)] in isopropanol.

Entry	Base (mol %)	Catalyst (mol %)	Substrate	Time (h)[a]	Yield (%)[b]
1	Cs_2CO_3 (2)	Pd(pp_3S_4)(dba) (5)	Iodobenzene	3	94
2	Cs_2CO_3 (1)	Pd(pp_3S_4)(dba) (5)	Iodobenzene	14	44
3	Cs_2CO_3 (2)	Pd(pp_3S_4)(dba) (1)	Iodobenzene	3	90
4	Cs_2CO_3 (2)	Pd(pp_3S_4)(dba) (2)	Iodobenzene	3	92
5	Cs_2CO_3 (2)	Pd(pp_3S_4)(dba) (1)	Bromobenzene	3	69
6	Cs_2CO_3 (2)	Pd(pp_3S_4)(dba) (1)	Chlorobenzene	3	55

[a] Monitored using TLC, until all the benzimidazole was found consumed.
[b] Isolated yield, after column chromatography of the crude product.

Table 3
Screening of Pd(0)-catalysts for Ullmann coupling of iodobenzene and benzimidazole in isopropanol at 80 °C.

Entry	Base (2 mol %)	Catalyst (1 mol %)	Time (h)[a]	Yield (%)[b]
1	Cs_2CO_3	[Pd(p_2S_2)(dba)]	3	82
2	Cs_2CO_3	[Pd(pp_3S_4)(dba)]	3	90

[a] Monitored using TLC, until all the benzimidazole was found consumed.
[b] Isolated yield, after column chromatography of the crude product.