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# SBA-15-functionalized melamine–pyridine group-supported palladium(0) as an efficient heterogeneous and recyclable nanocatalyst for *N*-arylation of indoles through Ullmann-type coupling reactions

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SBA-15-functionalized melamine-pyridine group-supported palladium(0) was found to serve as a heterogeneous and recyclable nanocatalyst for *N*-arylation of indoles with aryl iodides under a low catalyst loading (0.3 mol% of Pd) through Ullmann-type C-N coupling reactions. A variety of aryl iodides could be aminated to provide the *N*-arylated products in good to excellent yields without the need of an inert atmosphere. Also, this catalyst was found to be an efficient system for the *N*-arylation of other nitrogen-containing heterocycles with aryl iodides. The heterogeneous palladium catalyst could be recovered by simple filtration of the reaction solution and reused for six cycles without significant loss in its activity. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords: Ullmann coupling; indole; C-N bond formation; palladium; nanocatalyst

## Introduction

The indole ring system is present in numerous natural products, pharmaceuticals, agrochemicals and other compounds of importance.<sup>[1–8]</sup> Particularly, *N*-arylated indole motifs are very important as they exhibit nanomolar affinity for  $\alpha_1$ -adrenoceptors in addition to their affinities for dopamine D<sub>2</sub> and serotonin 5-HT<sub>2A</sub> receptors.<sup>[9]</sup> Also, *N*-arylated indoles are prevalent in compounds that are materials of interest.<sup>[10]</sup>

Of the many methods for the synthesis of *N*-arylindoles, the Fisher indole synthesis is the best known and most widely used.<sup>[4,11]</sup> Ullmann-type coupling methodology, involving the combination of an indole with an aryl halide in the presence of base and a copper catalyst at high temperatures, is an important alternative.<sup>[12]</sup> Methods that operate under milder conditions and utilize aryl bismuth<sup>[13]</sup> and aryl lead<sup>[14]</sup> reagents have been developed. Finally, the synthesis of *N*-arylindoles may also be achieved by nucleophilic aromatic substitution in instances in which the aryl halides are activated by the presence of one or more electron-withdrawing groups.<sup>[15–17]</sup> While each of these methods is useful in its own right, each suffers from one or more limitations including a lack of generality, the use stoichiometric quantities of toxic reagents or the need to employ harsh reaction conditions.

The palladium-catalysed *N*-arylation of heterocycles is an alternative method under mild reaction conditions.<sup>[18]</sup> However, use of expensive palladium salts and high oxophilicity associated with phosphine ligands limit the attractiveness of this method for industrial applications. To overcome these problems, the development of highly efficient and recyclable heterogeneous catalysts, such as immobilization of catalytically active species, e.g. organometallic complexes, onto a solid support to produce a

molecular heterogeneous catalyst, is essential.<sup>[19]</sup> Heterogeneous catalysis also helps to minimize wastes derived from reaction workup, contributing to the development of green chemical processes.<sup>[20]</sup> So, encouraged by our previous works on C–C, C–N and C–O coupling reactions,<sup>[21–24]</sup> we designed and prepared an SBA-15/CCPy/Pd nanocatalyst by grafting of melamine bearing pyridine groups on SBA-15 and subsequent deposition of Pd nanoparticles as a new and stable catalyst which is employed in the coupling of phenylboronic acid with aryl halides (Suzuki coupling).<sup>[21]</sup> The wide scope of this catalyst led us to investigate the *N*-arylation of indoles from the corresponding aryl iodides and indoles under mild conditions (Scheme 1).

#### Experimental

#### General Procedure for Synthesis of N-arylindoles

In a typical reaction, 10 mg of the catalyst (10 mg = 0.003 mmol Pd) was placed in a 25 ml flask. Aryl iodide (1.1 mmol) in 5 ml of DMF was added with 1 mmol of indole and 2 mmol of Et<sub>3</sub>N. The mixture was then refluxed for 2 h at 110 °C. After completion of the reaction monitored using TLC, the reaction mixture was cooled to room temperature (the catalyst was recovered by centrifugation) and was extracted with diethyl ether three times (3 × 10 ml). The combined organic layers were washed with brine solution and

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 $\label{eq:Scheme 1. SBA-15/CCPy/Pd(0)-catalysed $N$-arylation of indoles using various aryl iodides.$ 

dried over anhydrous  $Na_2SO_4$  and concentrated *in vacuo*. The crude product was purified using column chromatography on silica gel (60–120 mesh) to afford the *N*-arylindoles.

## **Results and Discussion**

In our initial screening experiments, the *N*-arylation reaction of indole with iodobenzene was investigated to optimize the reaction conditions including Pd concentration, solvent, base and temperature without the protection of an inert gas. The results are summarized in Table 1.

<b>Table 1.</b> Optimization of reaction conditions for <i>N</i> -arylation of indole with iodobenzene <sup>a</sup>								
Entry	Pd (mol%)	Base	Solvent	T (°C)	<i>t</i> (h)	Yield (%) <sup>b</sup>		
1	0.5	Et₃N	CH₃CN	82	12	55		
2	0.5	$Et_3N$	EtOH	78	12	45		
3	0.5	$Et_3N$	Toluene	110	12	70		
4	0.5	Et <sub>3</sub> N	H <sub>2</sub> O	100	12	40		
5	0.5	$Et_3N$	$CH_2CI_2$	40	12	35		
6	0.5	Et₃N	DMSO	110	12	85		
7	0.5	Et <sub>3</sub> N	DMF	110	3	95		
8	0.2	Et₃N	DMF	110	12	70		
9	0.3	$Et_3N$	DMF	110	2	98		
10	0.3	_	DMF	110	12	12		
11	0.0	Et₃N	DMF	110	12	0		
12	0.3	K <sub>2</sub> CO <sub>3</sub>	DMF	110	12	65		
13	0.3	$Na_2CO_3$	DMF	110	12	45		
14	0.3	$K_3PO_4$	DMF	110	12	50		
15	0.3	KOH	DMF	110	12	73		
16	0.3	NaHCO <sub>3</sub>	DMF	110	12	60		
17	0.3	$Et_3N$	DMF	25	12	0		
18	0.3	$\text{Et}_3\text{N}$	DMF	70	12	25		
<sup>a</sup> Reaction conditions: indole (1.0 mmol), iodobenzene (1.1 mmol), Pd catalyst, base (2.0 mmol), solvent (5.0 ml).								

<sup>b</sup>lsolated yield.

Initially, various solvents, namely DMF, EtOH, CH<sub>3</sub>CN, toluene, CH<sub>2</sub>Cl<sub>2</sub>, DMSO and H<sub>2</sub>O, were studied in the presence of 0.5 mol% Pd catalyst and 2 equiv. of Et<sub>3</sub>N at 110 °C (Table 1, entries 1–7). As is evident from Table 1, the best result is obtained in DMF (Table 1, entry 7). Next, bases, namely Et<sub>3</sub>N, KOH, K<sub>3</sub>PO<sub>4</sub>, Na<sub>2</sub>CO<sub>3</sub>, NaHCO<sub>3</sub> and K<sub>2</sub>CO<sub>3</sub>, were explored. Et<sub>3</sub>N gives the best yields (Table 1, entries 1, 12–16). However, a low yield is obtained without any base (Table 1, entry 10).

It is also found that the reaction temperature has a great influence on this transformation (Table 1, entries 9, 17, 18). An obvious improvement in the conversion (98%) is achieved for the reaction at 110  $^{\circ}$ C (Table 1, entry 9).

In addition, when the loading of Pd is reduced from 0.5 to 0.3 mol %, an excellent yield is also afforded. However, when 0.2 mol% of Pd is employed, the reaction yield decreases to 70% (Table 1, entries 7–9). It is important to mention that *N*-arylation of indole does not take place in the absence of Pd catalyst (Table 1, entry 11). In summary, the optimal condition for the *N*-arylation of indole with iodobenzene involves the use of 0.3 mol% of Pd catalyst, 2 equiv. of Et<sub>3</sub>N in DMF at 110 °C for 2 h (Table 1, entry 9).

With these optimum reaction conditions in hand, the scope and generality of the *N*-arylation method were investigated with various aryl iodides and indoles with different substituents. The results are summarized in Table 2.

We examined the reaction of indoles with substituted aryl iodides (Table 2, entries 1–16). All the substituted aryl iodides react with indoles to afford the coupling products in good to high yield. We do not observe any limitation as for aryl iodide derivatives. The reactivity of 2-methylindole is slightly lower than that of indole and 3-methylindole due to the steric effect (Table 2, entries 1, 11, 13).

Table 2. Synthesis of N-arylindoles catalysed by SBA-15/CCPy/Pd(0) <sup>a</sup>							
$ \begin{array}{c}                                     $							
Entry	Aryl iodide	Indole	Yield (%) <sup>b</sup>	Ref.			
1	lodobenzene	Indole	98	[12d]			
2	p-Methoxyiodobenzene	Indole	98	[12d]			
3	p-Chloroiodobenzene	Indole	98	[12d]			
4	p-Nitroiodobenzene	Indole	97	[12e]			
5	p-Bromoiodobenzene	Indole	96	[12d]			
6	p-Acetyliodobenzene	Indole	92	[12d]			
7	p-Methyliodobenzene	Indole	96	[12d]			
8	o-Bromoiodobenzene	Indole	90	[12f]			
9	o-Methoxyiodobenzene	Indole	95	[12d]			
10	m-Nitroiodobenzene	Indole	88	[12f]			
11	lodobenzene	2-Methylindole	90	[12e]			
12	p-Methyliodobenzene	2-Methylindole	92	[18c]			
13	lodobenzene	3-Methylindole	98	[12d]			
14	p-Methoxyiodobenzene	3-Methylindole	96	[12d]			
15	p-Nitroiodobenzene	3-Methylindole	92	[12d]			
16	lodobenzene	1-Methylindole	0	—			

<sup>a</sup>Reactions were carried out under aerobic conditions in 5 ml of DMF, 1.1 mmol aryl iodide, 1.0 mmol indole and 2 mmol Et<sub>3</sub>N in the presence of Pd catalyst (0.010 g, 0.3 mol% Pd) and 110 °C for 2 h. <sup>b</sup>Isolated yield.

<b>Table 3.</b> SBA-15/CCPy/Pd(0)-catalysed N-arylation of various nitrogen- containing heterocycles with iodobenzene <sup>a</sup>							
$ \underbrace{ 0.3 \text{ mol\% SBA-15/CCPy/Pd(0)}}_{\text{Et}_3\text{N, DMF, 110 C}} \xrightarrow{ \text{N-Het}} $							
Entry	Het-NH	Yield (%) <sup>b</sup>	Ref.				
1	1H-benzo[d]imidazole	96	[25]				
2	1 <i>H</i> -imidazole	98	[25]				
3	1 <i>H</i> -pyrrole	92	[25]				
4	1 <i>H</i> -pyrazole	96	[25]				
5	1H-pyrrolo[2-29]pyridine	96	[26]				
<sup>a</sup> Reactions were carried out under aerobic conditions in 3 ml of DME							

\*Reactions were carried out under aerobic conditions in 3 ml of DMF, 1.1 mmol aryl iodide, 1.0 mmol Het-NH and 2 mmol  $Et_3N$  in the presence of Pd catalyst (0.010 g, 0.3 mol% Pd) and 110 °C for 3 h. <sup>b</sup>Isolated yield.

The coupling with *p*-haloiodobenzenes exhibits interesting selectivities between halogens. The reactions with *p*-chloroiodobenzene and *p*-bromoiodobenzene afford the corresponding products, *N*-*p*-chlorophenyl and *N*-*p*-bromophenylindoles, with good yields of 96 and 98%, respectively, without touching the bromine and chlorine atoms (Table 2, entries 3, 5). It is very important to mention that the reaction is very selective to give only *N*-arylated product and in none of these cases is *C*-arylation of indole observed.

To ensure that there is no *C*-arylation taking place in the reaction, the reaction was carried out with 1-methylindole and no product is formed (Table 2, entry 16). This shows the high selectivity of SBA-15/CCPy/Pd(0) as catalyst in the *N*-arylation of indole using aryl iodides.



**Scheme 2.** Plausible mechanism for *N*-arylation.



**Figure 1.** Recycling of the SBA-15/CCPy/Pd(0) for the *N*-arylation of indole under similar conditions.

Interestingly, less reactive aryl halides such as bromobenzene and chlorobenzene also couple with indole furnishing *C*-arylindole in good to appreciable yields in longer reaction times.

We were pleased to find that the arylation reactions also proceed with other nitrogen-containing heterocycles such as benzimidazoles, imidazole, pyrrole, pyrazole and 7-azaindole in good yields under the same conditions (Table 3, entries 1–5).

In order to determine whether the catalysis is due to the SBA-15/ CCPy/Pd(0) complex or to a homogeneous Pd complex that comes off the support during the reaction and then returns to the support at the end, we performed the hot filtration test.<sup>[27]</sup> We focused on the N-arylation reaction of indole with iodobenzene. We filtered off the SBA-15/CCPy/Pd(0) complex after 30 min reaction time and the filtered phase of the reaction mixture was kept under reaction conditions for another 2 h. The catalyst filtration was performed at the reaction temperature (110 °C) in order to avoid possible re-coordination or precipitation of soluble palladium upon cooling. The reaction of indole with iodobenzene at 110°C for 30 min before the hot filtration affords *N*-phenylindole in 60% yield. We find that, after this hot filtration, no further reaction is observed. This result suggests that the Pd catalyst remains on the SBA-15 support at elevated temperatures during the reaction and points to a process of a heterogeneous nature. Based on these results we propose a reaction mechanism for Ullmann-type C-N coupling reaction with the prepared nanocatalyst (Scheme 2).<sup>[28]</sup> According to the general mechanism depicted in Scheme 2, the reaction of indole NH with the oxidative addition product **A** in the presence of base leads to a novel **B** complex. When the latter complex undergoes a reductive elimination, the coupled product Narylindole is produced, and the catalyst is released to complete the catalytic cycle.

For a heterogeneous transition metal catalyst, it is important to examine its ease of separation, recoverability and reusability. The recycling performance of SBA-15/CCPy/Pd(0) was investigated in the reaction of iodobenzene and indole. SBA-15/CCPy/Pd(0) was centrifuged from the reaction, washed with hot ethanol and water, and reused in a next reaction. The data presented in Fig. 1 show that SBA-15/CCPy/Pd(0) can be reused six times without significant loss of catalytic activity. The high stability and excellent reusability of the catalyst should result from the chelating action of bidentate pyridine groups on palladium and the mesoporous structure of the SBA-15 support. The result is important from a practical point of view. The high catalytic activity, excellent reusability and easy accessibility of the SBA-15/CCPy/Pd(0) make it a highly attractive heterogeneous palladium catalyst for the parallel solution-phase synthesis of diverse libraries of compounds.

## Conclusions

We have demonstrated a simple and efficient procedure for the synthesis of *N*-arylindoles through the reaction of indoles with aryl iodides using SBA-15-immobilized bidentate pyridine palladium nanoparticles as catalyst under mild reaction conditions. The reactions generated the corresponding *N*-arylindoles in good to excellent yields and were applicable to various indoles and a variety of aryl iodides. In addition, this methodology offers the competitiveness of recyclability of the catalyst without significant loss of catalytic activity, and the catalyst could be easily recovered and reused for at least six cycles, thus making this procedure environmentally more acceptable.

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