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A facile access to substituted indoles utilizing palladium catalyzed annulation under microwave enhanced conditions

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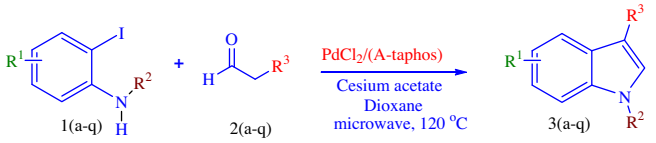
ABSTRACT

A facile access to differently substituted indoles using palladium catalyzed annulation reactions under microwave enhanced conditions has been achieved. A highly active and efficient catalytic system $PdCl_2$/(A-taphos) for the synthesis of indole via palladium catalyzed ring annulation of *ortho* iodo anilines and aldehydes has been developed.

Palladium catalyzed cross-coupling reactions have evolved as one of the efficient and robust methods in the field of organic synthesis for construction of diverse heterocycles. This is largely attributed to the fact that it provides a more general and applicable method for the construction of biaryls,[1] synthesis of various heterocycles which are found in polymers,[2] biologically relevant molecules,[3] ligands, and various materials. The importance of nitrogen based heterocycles as indicated by its role in many aspects prompted us to design more efficient synthetic protocols for a facile access to diverse nitrogen heteroaraomatics. The use of palladium catalyzed cross-coupling reactions in building the heterocyclic core itself was studied in detail by various researchers. Also, the use of heterocyclic fragment as one of the reaction components to access diverse analogues utilizing palladium mediated cross-coupling reactions has also been well explored. Despite these advancements in this field, there still remains a need for an efficient protocol employing low catalyst loadings for the carbon–carbon bond forming reactions of nitrogen derived heteroaromatics. The synthesis and functionalization of indole based structures have been an area of major focus for synthetic organic chemists.[4–8] Due to the wide medicinal relevance of the analogues based on this heterocyclic core, there is always a need for developing efficient synthetic protocols through which diversity oriented synthesis can be employed in generating various analogues. A number of methods are available in the literature in accessing these heterocyclic cores.[9,10] As a part of our research oriented toward microwave mediated palladium catalyzed cross-coupling reactions in the synthesis of nitrogen heterocycles[11] and biologically active molecules,[12] we were interested in the synthesis of some indole based



Scheme 1. Synthesis of substituted indoles utilizing palladium catalyzed annulation reactions under microwave enhanced conditions.

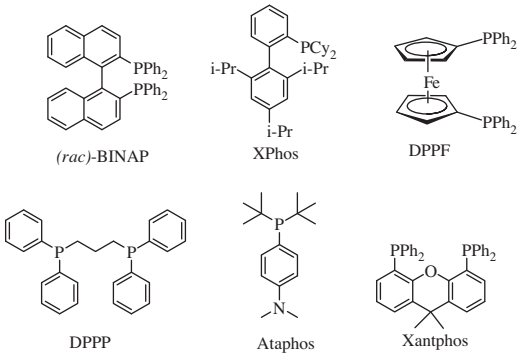


Figure 1. Structures of the ligands used for screening the ring annulation.

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Table 1
Effect of catalyst in synthesis of indoles via palladium catalyzed ring annulation[a]

S. no.	Catalyst	Yield (%)
1	$PdCl_2$/BINAP	22
2	$PdCl_2$/DPPF	38
3	$PdCl_2$/DPPP	20
4	$PdCl_2$/Xphos	41
5	$PdCl_2$/Xantphos	30
6	$PdCl_2$/A-taphos	53

[a] Reaction conditions: **1n** (0.10 mmol), **2n** (0.16 mmol), $PdCl_2$ (5 mol %), ligand (10 mol %), Cs_2CO_3 (0.20 mmol), and DMF, microwave irradiated at 120 °C for 40 min.

Table 2
Effect of base in synthesis of indoles via palladium catalyzed ring annulation[a]

S. no.	Base	Yield
1	KOH	5
2	K_2CO_3	35
3	K_3PO_4	49
4	Cs_2CO_3	53
5	CH_3COOCs	72
6	DBU	30
7	DABCO	28

[a] Reaction conditions: **1n** (0.10 mmol), **2n** (0.16 mmol), $PdCl_2$ (5 mol %), A-taphos (10 mol %), base (0.20 mmol), and DMF, microwave irradiated at 120 °C for 40 min.

Table 3
Effect of solvent in synthesis of indoles via palladium catalyzed ring annulation[a]

S. no.	Solvent	Yield
1	Toluene	25
2	THF	42
3	DME	35
4	DMF	30
5	Dioxane	70

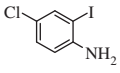
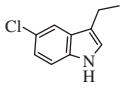
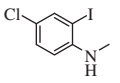
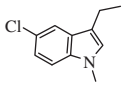
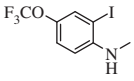
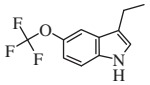
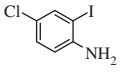
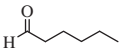
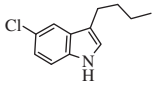
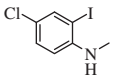
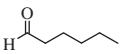
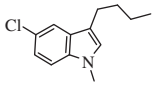
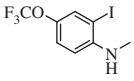
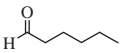
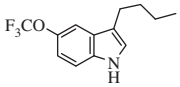
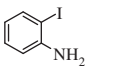
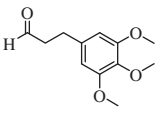
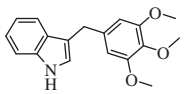
[a] Reaction conditions: **1n** (0.10 mmol), **2n** (0.16 mmol), $PdCl_2$ (5 mol %), A-taphos (10 mol %), and CH_3COOCs (0.20 mmol), solvent, microwave irradiated at 120 °C for 40 min.

analogues utilizing microwave assisted, metal mediated cross-coupling processes.

Microwave assisted organic synthesis (MAOS) plays a vital role in the design of new molecule as well as in the drug discovery laboratories.[13–15] Microwave heating has been shown to dramatically reduce reaction times, increase the product yields and enhance the product purities by reducing unwanted side reactions compared to conventional heating methods. The short reaction times provided by microwave synthesis make it ideal for rapid reaction scouting and optimization of reaction conditions. The use of microwave assisted palladium catalyzed cross-coupling reactions to access various hereto aromatic substrates is nowadays well studied.

In an attempt to synthesize differently substituted indoles utilizing palladium mediated cross-coupling reactions, we herein describe a highly efficient protocol for variously substituted indoles (Scheme 1). In order to set the reaction parameters, a model system and a range of conditions were explored. *ortho* iodo aniline (**1n**) reacted efficiently with an aldehyde (**2n**) in the presence of palladium catalyst ($PdCl_2$/xantphos) and cesium carbonate as a base in DMF. It was heated via microwave irradiation at 120 °C to afford product in 30% yield. The products formed were purified by flash column chromatography. Next we focused on screening various ligand (Fig. 1) combinations with cesium carbonate as a base and palladium chloride as the catalyst. Different ligands were explored along with palladium precursor to find an optimum true catalyst which will facilitate the formation of indoles with high yields (Table 1). The unique effect of cesium salts in palladium catalyzed cross-coupling reactions[16,17] arises from the special properties of cesium cation like very large ionic radius, low charge density and high polarizability. From Table 1 it is clear that the $PdCl_2$/A-taphos combination provided an effective catalytic system which enhanced the formation of indoles in 53% yield. This could be attributed to the fact that this catalytic combination provided a highly active catalytic species[18] which was instrumental for the better conversions to products. Now that we have found an effective catalytic system, we were interested in screening different

Table 4
Synthesis of indoles via palladium catalyzed ring annulation of *ortho* iodoaniline and aldehydes[a]

S. no.	*ortho* iodoaniline (1)	Aldehyde (2)	Product (3)	Yield[b] (%)
a				72
b				80
c				69
d				70
e				64
f				66
g				75

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