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Authors: Vignesh Arumugam, Werner Kaminsky, and Dharmaraj Nallasamy

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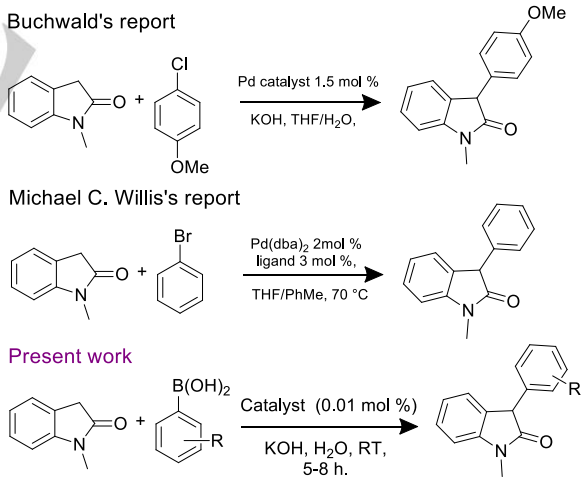
Arylation of *N*-methyl-2-oxindole with arylboronic acids in water catalyzed by Pd(II) pincer complexes with low catalyst loading

Arumugam Vignesh,[a] Werner Kaminsky[b] and Nallasamy Dharmaraj*[a]

Abstract: A couple of new Pd(II) ONO pincer complexes were efficiently utilized as homogeneous catalysts for the site-selective C3-arylation of *N*-methyl-2-oxindole with arylboronic acids at room-temperature to yield a series of 3-aryl-*N*-methyl-2-oxindoles in aqueous media. This catalytic reaction progressed well with low catalyst loading (0.01 mol %) under open-flask conditions. Of note, a column chromatography free methodology for C3-aryalated *N*-methyl-2-oxindoles in quantitative yield is reported. The catalyst showed good compatibility with wide range of substrates with recyclability up to five consecutive runs without appreciable loss of yield.

Search for novel and efficient synthetic methodologies towards rapid functionalization of indoles has triggered great deal of interest among synthetic organic and medicinal chemists.[1] Indoles are the target molecules for several research activities owing to their presence in a number of active pharmaceutical ingredients[2] and also in material science.[3] C−C Bond formation *via* carbon−hydrogen (C−H) bond activation receives top priority to construct new molecular architects.[4] A regio-selective, direct C−H functionalization methodology for arylation of indole scaffolds is favored over the conventional coupling reaction (e.g., Suzuki coupling).[5] This C−H bond activation protocol avoids the pre-functionalization of indole derivatives and thus offers a proficient synthetic route to construct arylated indoles.[6] Palladium-catalyzed α-arylation to create a new C−C bond at the α-position of a carbonyl group is an important methodology for the synthesis of several natural products and biologically active organic compounds.[7] Pd-Catalyzed α-arylation of carbonyl and related compounds was achieved with an array of nucleophiles such as ketones,[8a] aldehydes,[8b] esters,[8c] malonates,[8d] nitriles,[8e] silyl enol ethers[8f] and amides.[8g] However, owing to the high p*K*a of the amide enolates, arylation of such substrates is more challenging and hence required the use of a strong base.[9]

Generally, C-arylated indoles demonstrate great potential in pharmaceuticals;[10] especially anticancer drugs.[10c,d] Among them, C-3 arylated indoles were tested and proved as for the treatment of uterine fibroids.[11] In spite of the numerous synthetic protocols known for C-3 arylation of indoles,[12] only few of them dealt with that of *N*-methyl-2-oxindoles.[9,13] Michael C. Wills group reported[9] the α-arylation of oxindole using palladium as catalyst in combination with electron rich phosphine ligand. Later, S. L. Buchwald *et al*., published a chemo-selective C-3 arylation of oxindole catalyzed by Pd-dialkylbiarylphosphine-based catalyst system.[13a] Highly enantio-selective, Pd-catalyzed intermolecular coupling of oxindoles with aryl and vinyl bromides facilitated by a biaryl monophosphine ligand was documented by S. L. Buchwald *et al*. [13b] Further, the same research group has proclaimed palladium-catalyzed α-arylation/alkylation of oxindole by continuous-flow synthesis method. [13c] Besides, aryl halides were the most commonly utilized coupling partners for direct α-arylation of oxindoles promoted by transition-metal catalysts.[9,13] However, these strategies required the use of high catalyst loadings, elevated temperature, long reaction times and inert atmosphere. Specifically, use of arylboronic acids as coupling partners with *N*-methyl-2-oxindole remains unexplored so far. [9,13] Owing to the inherent merits of boronic acids such as less toxicity, stability to ambient conditions including humidity and the facile removal of boron containing side products, aromatic boranes are widely utilized in such coupling reactions. [14] Based on these facts, we decided to carry out arylation of *N*-methyl-2-oxindole with arylboronic acids as the coupling partner.



Scheme 1. Reported and present protocol for the C-3 arylation of *N*-methyl-2-oxindole.

In our quest towards designing new palladium complexes as homogeneous catalysts for cross coupling reactions, [15] herein we present the synthesis and structural characterization of two new palladium(II) complexes incorporating an ONO pincer type ligand for the C3-arylation of *N*-methyl-2-oxindole with arylboronic acids. The highlight of the present methodology merits attention as it doesn't require high catalyst loading, elevated temperatures, external oxidants, additives, phase transfer reagents and stringent reaction

[a] Inorganic & Nanomaterials Research Laboratory, Department of Chemistry, Bharathiar University, Coimbatore 641 046, India. E-mail: dharmaraj@buc.edu.in; Home page: http://ndharmaraj.wixsite.com/inrl Fax: +91 4222422387; Tel: +91 4222428316

[b] Department of Chemistry, University of Washington, Seattle, Washington 98195, USA

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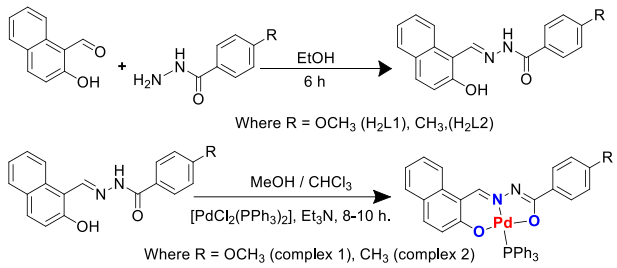
conditions. To the best of our insight, this is the first report on the utility of pincer type palladium(II) complexes **1** and **2** as catalysts for the arylation of N-methyl-2-oxindole.

Complexes **1** and **2** were obtained by the reaction of $[PdCl_2(PPh_3)_2]$ with substituted aroyl hydrazones (H_2L1–H_2L2) *via* metal introduction route as outlined in Scheme **2** (*vide infra*). The ONO donor atoms present in the chosen hydrazones are suitable to form pincer type palladium complexes.



Scheme 2. Synthetic route of ligands and their palladium(II) complexes.

Single-crystal XRD studies of complexes **1** and **2** revealed that the pincer type ligands (H_2L1– H_2L2) were chelated to the palladium ion in a binegative tridentate manner. The naphtholate oxygen, azomethine nitrogen and the deprotonated imidol oxygen atoms and formed respectively a five membered and six membered chelate rings with the palladium ion, while the fourth coordination site was occupied by a triphenylphosphine molecule. The geometry around the Pd(II) center in complexes **1** and **2** is described as distorted square-planar. ORTEP representations of complexes **1**and **2** are shown in Figure 1 and 2. The observed bond lengths and bond angles are in good agreement with reported data on related palladium(II) complexes. [16] Details on the data collection, structure refinements, bond angles, bond lengths were gathered in Tables S1– S3 in Supporting Information.

To test the ability of the complexes **1** and **2** as homogeneous catalysts for C-C bond formation, we began our investigation by employing *N*-methyl-2-oxindole (3a) and phenylboronic acid (4a) as model substrates. As expected, the reaction was successful and gave the desired product 5a in presence of complex **2** as catalyst in EtOH at room-temperature. With this result in hand, we worked out to find the optimum reaction conditions. In this connection, we tested the reaction using several inorganic and organic bases, among those KOH was found to be the most effective base. Nevertheless, the desired product 5a was not at all obtained in the absence of base. Similarly, screening of several solvents as reaction medium revealed that H_2O proved to be the best one and thus gave the product 5a in 82 % yield. Further, up on using the palladium complex **1** as a catalyst for the reaction, the isolated yield of 5a was increased to 90 % (Table 1, entry 21). In addition, the catalytic potential of complexes **1** and **2** were compared with Pd salts like $[PdCl_2]$ and $[PdCl_2(PPh_3)_2]$. Herein, only less yield of the expected product was realized. (Table 1, entries 22 & 23) . Overall, an excellent output from the present study was obtained by involving *N*-methyl-2-oxindole (4 mmol), arylboronic acid (4 mmol), KOH (5 mmol), H_2O (5 mL) and complex **1** as catalyst (0.01 mol %) at room-temperature.

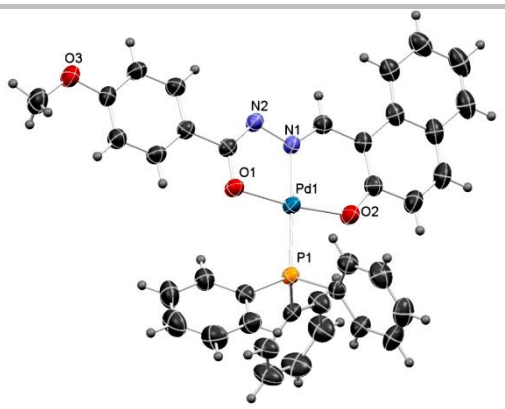


Figure 1. ORTEP diagram of complex **1** with thermal ellipsoids at the 50% probability level.

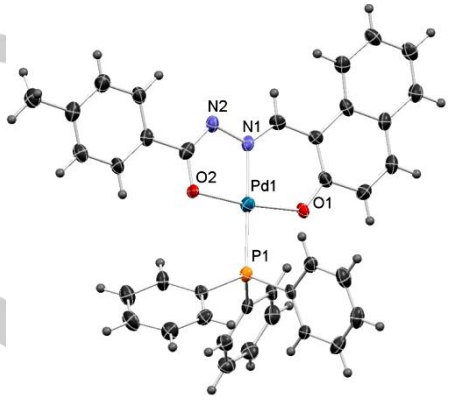
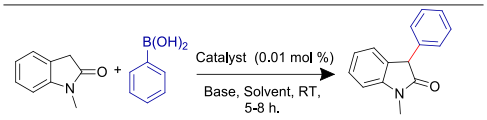


Figure 2. ORTEP diagram of complex **2** with thermal ellipsoids at the 50% probability level.

After having realized fruitful results in the model reaction discussed above, we explored the generality of our novel catalytic system towards a range of arylboronic acids. To our delight, arylboronic acids bearing both electron-rich and electron- deficient groups afforded the desired products 5a–5r in good yields as shown in Table 2. Arylboronic acids with methyl and methoxy groups at the *ortho*-position gave the respective C3-arylated products 5b and 5e in 88% and 87% yields. Further, boronic acids having electron-donating groups such as $-CH_3$, CH_3O-, $(CH_3)_3$–C-, $–N(CH_3)_2$ and -OH were well tolerated to afford the respective products in significant quantities Table 2, compounds 5c, 5f, 5i, and 5n). It is worth to mention here that the boronic acids substituted with moderately deactiving chloro, bromo, acetyl and formyl functionalities also nicely underwent α-arylation reaction that might be of significant use for further synthetic transformations (Table 2, compounds 5l, 5m, 5o, 5p, and 5q). Reaction of *N*-methy-2-oxoindole with disubstituted arylboronic acids (2,6-dimethoxy and 2,3-dimethyl phenylboronic acids) proceeded smoothly and furnished the desired products with excellent site-selectivity (Table 2, compounds 5d & 5g). In addition, biphenyl and naphthyl boronic acids also yielded 3-arylated indole derivatives in 73 and 70% isolated yields. Succesfully, phenylboronic acids possessing a strong deactivating $–CF_3$ group at the *para* position also well tolerated and yielded the expected product in 66%. Of note, during the entirity of reactions carried out with a arylboronic

acids, formation of any homo-coupled or other by-products was never observed.

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	Base	Solvent	Yield (%)[b]
1	Complex 2	No base	EtOH	NR
2	Complex 2	Cs_2CO_3	EtOH	12
3	Complex 2	KOH	EtOH	76
4	Complex 2	K_2CO_3	EtOH	71
5	Complex 2	NaOH	EtOH	66
6	Complex 2	Na_2CO_3	EtOH	60
7	Complex 2	CH_3COONa	EtOH	46
8	Complex 2	Et_3N	EtOH	37
9	Complex 2	Pyridine	EtOH	32
10	Complex 2	KOH	THF	52
11	Complex 2	KOH	EtOAc	49
12	Complex 2	KOH	DMF	56
13	Complex 2	KOH	CH_3CN	44
14	Complex 2	KOH	DMSO	51
15	Complex 2	KOH	MeOH	76
16	Complex 2	KOH	H_2O	82
17	Complex 2	KOH	Toluene	55
18	Complex 2	KOH	Benzene	53
19	Complex 2	KOH	$CHCl_3$	45
20	Complex 2	KOH	DCM	32
21	Complex 1	KOH	H_2O	90
22	$[PdCl_2]$	KOH	H_2O	28
23	$[PdCl_2(PPh_3)_2]$	KOH	H_2O	32

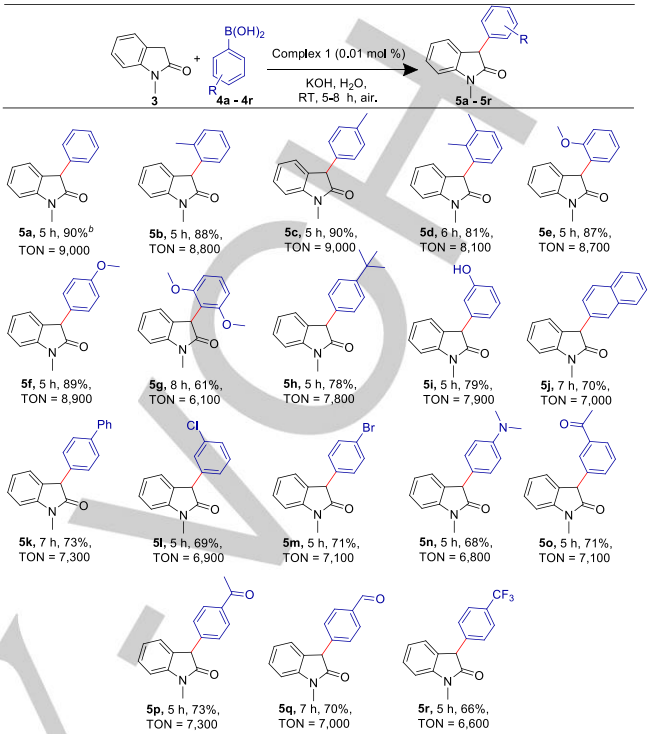
[a] = Reaction conditions: N-methyl-2-oxindole (4 mmol), phenylboronic acid (4 mmol), base (5 mmol), solvent (5 mL) and catalyst (0.01 mol %) stirred at room temperature for 5-8 h. [b] = Isolated yieldy. NR = No reaction.

To extend the present methodology for large scale production, we investigated the gram scale synthesis of 1-methyl-3-phenyl-1,3-dihydro-indol-2-one (5a) as a representative example wherein 85 % yield was realised. Reusability of the selected catalyst **1** was assessed under parallel reaction conditions. The first cycle afforded 90% of the corresponding coupled product followed by 88% in the next run. However, third and fourth cycles gave 81% and 76% of the coupled product. In the fifth cycle, only 68% of the product was realized (Figure 3).

With an aim to get some significant insights into the mechanism of the titled reaction, the following controlled experiments were carried out. At first, a trial reaction conducted without the palladium catalyst was completely unsuccessful with total recovery of the substrates intact. This fact demonstrated that the presence of the palladium catalyst is inevitable to effect the expected reaction. Next, we focused our attention to know whether any catalyst poisoning occurred during the catalysis by adding mercury to the reaction medium, wherein no influence was noticed and thus proved the active catalyst is likely to be a homogeneous species and not metallic palladium nanoparticles.

Based on the controlled experiments and literature reports,[15,17] a plausible mechanism to explain the catalytic process was proposed in Scheme 3. Initially, an active species, $Pd^{(0)}L$ **(I)** was formed through a two-electron reduction of the palladium(II) complex by transmetalation of arylboronic acids[17a] followed by an oxidative addition of deprotonated *N*-methyl-2-oxindole in the enol form to $Pd^{(0)}L$ to form intermediate II.

Table 2. Scope of arylboronic acids under optimized reaction conditions.[a]



[a] = Reaction conditions: *N*-methyl-2-oxindole (4 mmol), arylboronic acid (4 mmol) KOH (5 mmol), H_2O and catalyst (0.01 mol %) stirred at room-temperature for 5-8 h in an open-flask. TON = Turnover number = ratio of moles of product formed to moles of catalyst used. [b] = Isolated yield.

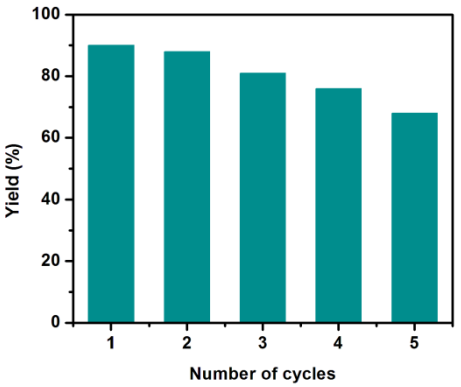
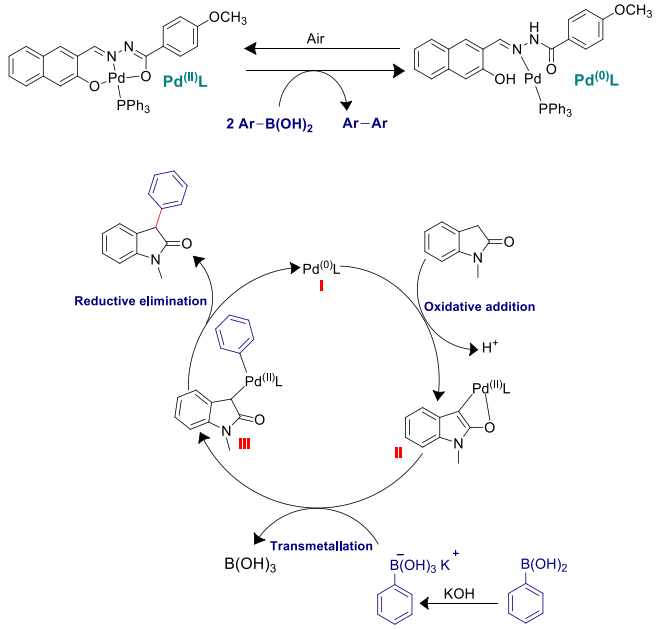


Figure 3. Recyclability of catalyst **1.**

Transmetalation of intermediate **II** with phenylboronic acid gave intermediate **III** which on further reductive elimination afforded the coupled product,[17b] 3-phenyl-2-oxindole with the regeneration of the active species $Pd^{(0)}L$ **(I)**. At the end of the cycle, the catalyst $Pd^{(II)}L$ was regenerated by the oxidation of intermediate **I** by O_2.[17 c,d] The same reaction performed under nitrogen atmosphere also afforded the expected product.



Scheme 3. Possible mechanism for the α-arylation of *N*-methyl-2-oxindoles.

In this communication, we report a novel as well as green methodology for the α-arylation of *N*-methyl-2-oxindole with arylboronic acids catalyzed by palladium(II) complex in aqueous media under open-flask conditions at room-temperature. From the large scale synthesis point of view, this method was successfully extended to gram-scale synthesis and the applied palladium catalyst showed potential re-usability up to five cycles. The present research work comprising with characteristic merits such as column chromatography free separation of the products, low catalyst loading, non-involvement of any external oxidant, additive and phase transfer agents could be well considered as a complementary and practical protocol for a site-selective, mild oxidative coupling reaction for the synthesis of 3-arylated-*N*-methyl-2-oxindoles in good yields with tolerance to wide range of functionalities. Extension of the scope of this methodology to various substituted *N*-methyl-2-oxindoles is under progress.

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Keywords: Nitrogen heterocycles • C-H activation • Arylboronic acid • Pd(II) complex • Open-flask condition

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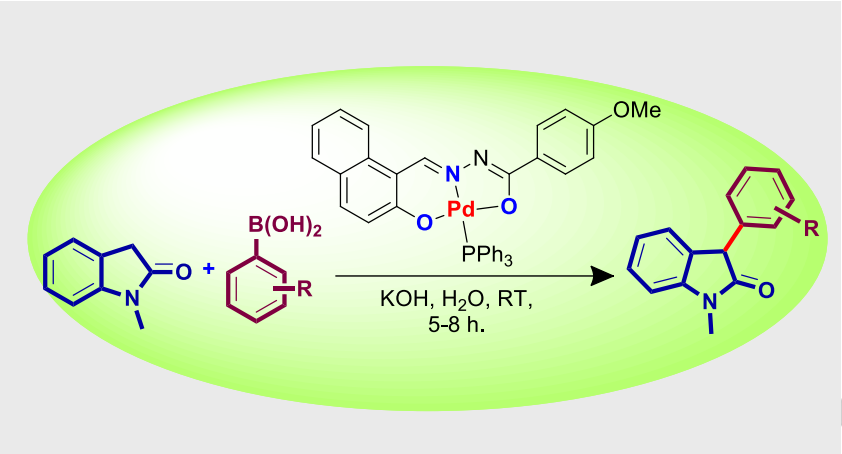

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