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Direct palladium-catalyzed C-3 arylation of indoles

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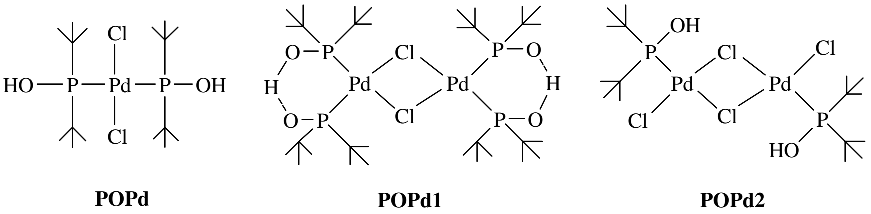
Abstract—An efficient protocol for palladium-catalyzed direct C-3 arylation of indoles containing unprotected heterocyclic nitrogen atom has been developed.

Indole derivatives are one of the most important and commonly found heterocyclic motifs in both pharmaceuticals and natural products,[1] since indole can be considered as a commonly used starting material for further alkaloid synthesis if suitable synthetic methodology can be developed from this parent skeleton.[2] The Pd-catalyzed arylation of indole is a quite hot research area in recent years. In most cases, this type of Pd-catalyzed reaction gave 2-arylated indole[3] or N-arylated indole[4] as major products. Among the arylated indole compounds, 3-phenylindole is an antimicrobial compound active towards many fungi and Gram-positive bacteria.[5] Usually 3-arylated indoles have been prepared by ring-synthesis[6] or by introducing protecting groups on heterocyclic nitrogen atom and/or reactive functionalities prior to C–C formation.[7] Herein, we report the direct C-3 arylation of indoles containing unprotected heterocyclic nitrogen atom, which demonstrates the high selectivity of palladium catalyst with phosphinous acid complexes (abbreviated as POPd), formed in situ, in the presence of a mild base.

Li and co-workers developed the air-stable palladium–phosphinous acid complexes, such as $[(t\text{-Bu})_2P(OH)]_2PdCl_2$, $[[(t\text{-Bu})_2P(OH)(t\text{-Bu})_2PO]PdCl]_2$ and $[(t\text{-Bu})_2P(OH)PdCl_2]_2$ (abbreviated as POPd, POPd1 and POPd2) (Scheme 1),[8] which were investigated and found to be the efficient catalysts for a variety of cross-coupling reactions.[9] The principal goal of this study was to explore the possibility of using the air-stable POPd catalysts, in the arylation of substituted indoles with phenyl bromides (Scheme 2) to afford *N*-aryl indoles **E** or *C*-aryl indoles **C** and **D**. We found that indoles reacted with aryl bromides to form 3-arylindole (**D**) with high degree of selectivity to 2-arylindole (**C**), without extra reagents introduced to protect free N–H of indole, and no **E** was detected.

The reaction sequences were carried out in thermal fashion, according to the standard procedure of Pd-catalyzed coupling reaction. The various conditions were tested in order to optimize the desired results. An examination of selected and inexpensive bases revealed that



Scheme 1.

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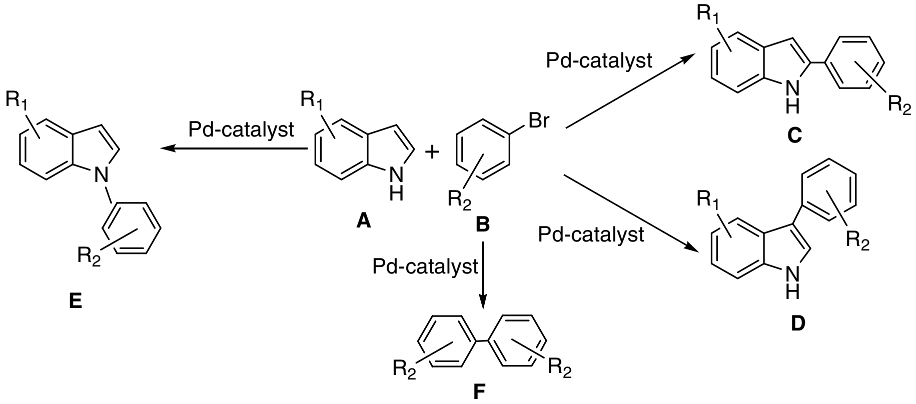


Scheme 2.

K_2CO_3 and KOH were effective (Table 1), compared to KO(*t*-Bu) and NaO(*t*-Bu). It was which indicated that the stronger base such as KO(*t*-Bu) and NaO(*t*-Bu) would remove the proton on nitrogen atom, which alerted the electronic distribution of indole aromatic ring system and resulted in no occurrence of the desired reaction.

In regard to the comparisons of catalytic effects among POPd, POPd1, POPd2 and other conventional Pd catalysts such as $Pd(OAc)_2(PPh_3)_2$, $Pd(PPh_3)_4$, $Pd(dba)_2$ and $Pd_2(dba)_3$, the reactions between indole and bromobenzene (Table 2) were conducted, using these catalysts. When dioxane was used as a solvent under the identical conditions of concentration and temperature, $Pd(dba)_2$ and $Pd_2(dba)_3$ completely failed to yield any coupled products (entries 9 and 10). However, when POPd1 was applied as the catalyst, the coupling reaction of indole and bromobenzene (entry 4) led to 3-phenylindole with good yield. In the cases of POPd, POPd2, $Pd(OAc)_2(PPh_3)_2$ and $Pd(PPh_3)_4$, the direct arylation proceeded with moderate yield (entries 1, 6–8). In terms of the POPd catalysts, when dioxane was used as the solvent, the formation of 2-phenylindole was depressed while the content of biphenyl increased. However, when toluene was used, the content of 2-phenylindole enhanced while that of biphenyl decreased (entries 1–6). It was interesting that POPd1 and POPd2 demonstrated different reactivity in toluene and dioxane (entries 3–6). Based upon these results, the POPds have been found to be superior catalysts in this kind of cross-coupling reactions. Additionally, due to the air-stability of the POPd catalysts, we believe that POPd catalysts are much more convenient to handle and thus offer an attractive alternative for the chemists interested in exploring their use in the Pd-catalyzed reactions in organic synthesis.

Table 1. Effect of various bases upon the C-3 arylation of indole[a]

Entry	Base	Yield[b] (%)
1	K_2CO_3	71.5
2	KOH	70.6
3	NaOH	36.8
4	Na_2CO_3	0
5	KO(*t*-Bu)	0
6	NaO(*t*-Bu)	0

[a] Reactions were carried out with indole (0.5 mmol), bromobenzene (0.6 mmol), 5 mol % POPd and K_2CO_3 (3 equiv) in 2 mL of dioxane under refluxing for 24 h.

[b] Isolated yields.

Table 2. Effect of various catalysts upon the coupling reaction based on the same amount of Pd[a]

Entry	Catalyst (mol %)	Base (solvent)	Yield[b] (%)	(HPLC %)		
				C[c]	**D**[d]	**F**[e]
1	POPd (5.0)	K_2CO_3 (toluene)	66.6	8.8	77.9	3.3
2	POPd (5.0)	K_2CO_3 (dioxane)	71.5	0.8	83.4	6.9
3	POPd1 (2.5)	K_2CO_3 (toluene)	54.9	7.8	68.9	2.7
4	POPd1 (2.5)	K_2CO_3 (dioxane)	85.4	1.3	87.4	6.7
5	POPd2 (2.5)	K_2CO_3 (toluene)	72.9	7.0	81.0	1.3
6	POPd2 (2.5)	K_2CO_3 (dioxane)	60.8	1.6	68.9	3.8
7	$Pd(OAc)_2(PPh_3)_2$ (5.0)	K_2CO_3 (dioxane)	74.5	1.0	80.2	14.2
8	$Pd(PPh_3)_4$ (5.0)	K_2CO_3 (dioxane)	65.2	2.0	71.5	13.5
9	$Pd(dba)_2$ (5.0)	K_2CO_3 (dioxane)	0	0	0	5.8
10	$Pd_2(dba)_3$ (2.5)	K_2CO_3 (dioxane)	0	0	0	10.4

[a] Reactions were carried out with indole (0.5 mmol), bromobenzene (0.6 mmol), catalyst and K_2CO_3 (3 equiv) in 2 mL of dioxane or toluene under refluxing for 24 h.

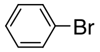
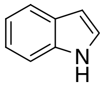
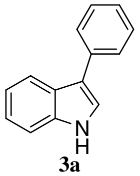
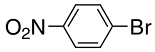
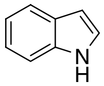
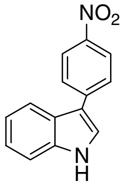
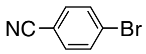
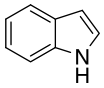
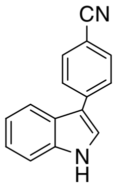
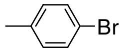
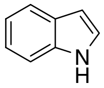
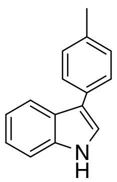
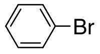
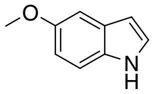
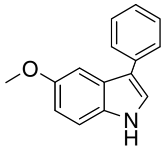
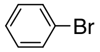
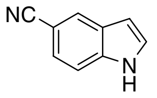
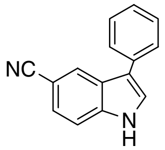
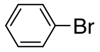
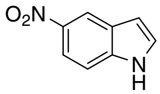
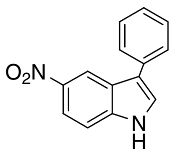
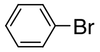
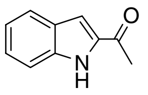
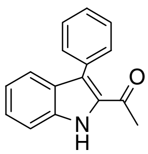
[b] Isolated yields of 3-phenylindole.

[c] **C**: 2-phenylindole.

[d] **D**: 3-phenylindole.

[e] **F**: biphenyl.

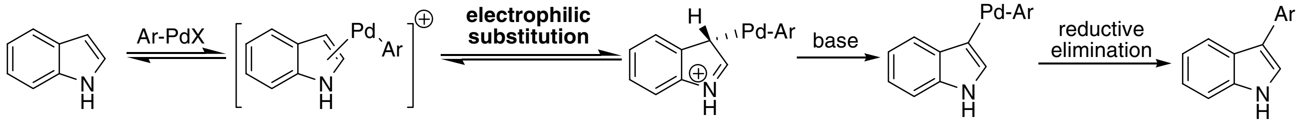
Table 3. Palladium-catalyzed coupling reaction of indole with substituted bromobenzenes[a]

Entry	Halide	Coupling partner	Target product	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	71.5
2	 **1b**	 **2a**	 **3b**	48.0
3	 **1c**	 **2a**	 **3c**	52.6
4	 **1d**	 **2a**	 **3d**	53.9
5	 **1a**	 **2b**	 **3e**	79.9
6	 **1a**	 **2c**	 **3f**	12.0[c]
7	 **1a**	 **2d**	 **3g**	—
8	 **1a**	 **2e**	 **3h**	—

[a] Reactions were carried out using a mixture of (substituted) indole (0.5 mmol), substituted bromobenzene (0.6 mmol), 5 mol % POPd and K_2CO_3 (3 equiv) in 2 mL of dioxane under refluxing for 24 h.

[b] Isolated yields.

[c] HPLC yield.



Scheme 3.

The reactions of various substituted indoles with substituted bromobenzenes were also explored and the results are shown in Table 3.[10] It was found that either electron-withdrawing substituted bromobenzenes (entries 2 and 3) or electron-donating substituted bromobenzenes (entry 4) depressed the arylation. When methoxyl group was introduced at 5-position of indole, the reaction occurred in good yield (entry 5), while cyano and nitro group were introduced at the same position, the reaction was seriously retarded (entries 6 and 7). When 2-acetylindole reacted with bromobenzene, no arylated product was found possibly due to the steric effect (entry 8). According to our findings, we proposed a possible reaction mechanism in the C-3 arylation of indoles (Scheme 3).

In conclusion, we have demonstrated that cross-coupling of indoles with various aryl bromides proceeded in moderate to good yields when the palladium–phosphinous acid complex POPd was used as the catalyst. The direct arylation of an indole core would eliminate the need to protect indole nitrogen atom or establish a reactive functionality (cf., halogenation or stoichiometric metalation) prior to C–C coupling, and would enable the direct elaboration and expansion of the core motif. The further application of this catalyst for the synthesis of substituted indoles, mechanism study and scope and limitation of this kind of reaction are currently under investigation in our group.

Acknowledgements

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10. *Representative experimental procedure*: A mixture of indole (58.6 mg, 0.500 mmol, 1.0 equiv), bromobenzene (94.2 mg, 0.600 mmol, 1.2 equiv), potassium carbonate (207.3 mg, 1.500 mmol, 3.0 equiv) and POPd (12.5 mg, 0.025 mmol, 5 mol %) was stirred and re-fluxed in 2 mL of dioxane for 24 h. The reaction mixture was allowed to cool to room temperature, quenched with water and extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvent was removed under vacuum. The residue was purified by chromatography on silica gel eluting with hexane/EtOAc (15:1, v:v) to give white crystals **3a** (69.1 mg, 71.5%). Mp 86.0–87.0 °C. (hexane) (lit.[11] 85.5–86 °C). ^1H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.97 (d, 1H, $J = 8.1$ Hz), 7.70 (d, 2H, $J = 7.8$ Hz), 7.47 (q, 3H), 7.40 (d, 1H, $J = 2.4$ Hz), 7.32 (t, 1H, $J = 7.6$ Hz), 7.28 (t, 1H, $J = 7.7$ Hz), 7.22 (t, 1H, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 135.6, 128.8, 127.5, 126.0, 125.8, 122.5, 121.8, 120.4, 119.9, 118.4, 111.4; MS (m/z) 193.9 [$M+H^+$]. Compound **3b**: Light brown solid (48.0%), mp 142.5–144.2 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.31 (d, 2H, $J = 8.9$ Hz), 7.97 (d, 1H, $J = 8.0$ Hz), 7.84 (d, 2H, $J = 8.8$ Hz), 7.55 (s, 1H), 7.50 (d, 1H, $J = 8.1$ Hz), 7.31 (m,

2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.62, 142.79, 136.90, 127.10, 125.15, 124.33, 123.60, 123.19, 121.32, 119.54, 116.44, 111.85; MS (*m*/*z*) 239.1 [M+H$^+$]. Compound **3c**: Yellow solid (52.6%), mp 165.3–166.5 °C. ^{1}H NMR (500 MHz, CD_3COCD_3) δ 10.92 (s, 1H), 7.98 (d, 1H, $J = 7.95$ Hz), 7.96 (d, 1H, $J = 1.73$ Hz), 7.86 (s, 1H), 7.80 (d, 2H, $J = 8.13$ Hz), 7.54 (d, 1H, $J = 8.03$ Hz), 7.20 (m, 2H); ^{13}C NMR (125 MHz, CD_3COCD_3) δ 141.31, 137.59, 132.53, 126.97, 125.12, 124.82, 124.66, 122.20, 120.47, 119.14, 112.17, 112.12, 108.11; MS (*m*/*z*) 219.0 [M+H$^+$]. Compound **3d**: Light yellow crystal (53.9%), mp 86.2–87.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.94 (d, 1H, $J = 8.1$ Hz), 7.59 (d, 2H, $J = 8.2$ Hz), 7.44 (d, 1H, $J = 8.2$ Hz), 7.36 (d, 1H, $J = 2.4$ Hz), 7.25 (m, 3H), 7.16 (t, 1H, $J = 8.2$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.66, 135.61, 132.59, 129.45, 127.43, 125.89, 122.35, 121.43, 120.21, 119.88, 118.40, 111.32, 21.16; MS (*m*/*z*) 208.0 [M+H$^+$]. Compound **3e**: Yellow sticky liquid (79.9%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.67 (d, 2H, $J = 7.5$ Hz), 7.48 (t, 2H, $J = 7.8$ Hz), 7.40 (s, 1H), 7.33 (m, 3H), 6.94 (d, 1H, $J = 8.9$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.79, 135.72, 131.85, 128.81, 127.41, 126.21, 125.93, 122.59, 118.24, 112.73, 112.09, 101.70, 56.02; MS (*m*/*z*) 224.0 [M+H$^+$].

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