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First heterogeneously palladium-catalysed fully selective C3-arylation of free NH-indoles

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Abstract

A simple heterogeneously palladium-catalysed procedure for the selective C3-arylation of indoles is reported. Under relatively standard reaction conditions (Pd-catalyst, K_2CO_3, dioxane, reflux), using only 1 mol % $[Pd(NH_3)_4]$/NaY as the catalyst, indoles substituted or not at position 2 gave up to 92% conversion (i.e., 85% isolated yield) towards the expected C3-arylated indole.

Keywords: Indoles; Selective C3-arylation; Palladium; Heterogeneous catalysis

The substituted indole nucleus is a structural fragment found in numerous biologically active natural and synthetic compounds.[1,2] The synthesis and the functionalisation of indoles have been the subject of many researches for over 100 years,[3,4] leading to well-established syntheses.[5–8]

In the last 40 years, alternative palladium-catalysed syntheses, generally tolerant to a wide range of substituents, have appeared in the literature.[8,9] These methods include the palladium-induced cycloadditions of 2-haloanilines with alkynes and the intra- or intermolecular reactions of 2-alkynyl anilides with aryl- or alkylhalides.[10,11] Other approaches are based on Heck-type cyclisations,[12,13] reactions of alkynes with imines[14] or on intramolecular cyclisations. Heteroannulation sequences achieved through palladium-catalysed aryl amination reaction were also reported.[15,16]

Many of these methods have proven to be the most powerful and are currently applied in the target- or the diversity-oriented synthesis of multi-functional indoles, generally substituted at position 2 and/or 3 of the indole ring.[17] However, they remain limited when applied to the synthesis of 2-substituted-3-aryl-indoles, an important feature of alkaloids having antimicrobial properties against fungi and Gram positive bacteria, due to the limited choice of reagents to introduce directly the right substituent at position 3 and since unprotected indoles lead often to the formation of a mixture of N1- and C2- or C3-arylated indoles.

Alternatively, some research groups developed the palladium-catalysed direct arylation of the indole nucleus: Sames and co-workers reported a procedure for selective C2-arylation of N-substituted indoles using $\{[Pd(OAc)_2], PPh_3\}$ as the catalyst.[18] Sanford and co-workers reported a palladium-catalysed C2-arylation of indoles under mild reaction conditions (25 °C, AcOH, 15–24 h) using $[Ar_2I^+, BF_4^-]$ as the arylating agent. If Sames supported an electrophilic palladation mechanism based on a $Pd^{(0)}/Pd^{(II)}$ catalytic cycle, Sanford proposed that the palladium-catalysed C2-arylation of *N*-methyl or NH-indoles resulted from a $Pd^{(II)}/Pd^{(IV)}$ catalytic cycle.[19] Bellina and co-workers reported selective palladium- and copper-mediated C2-arylations of heterocycles including free (NH)-indoles with aryl iodides under ligandless and base-free

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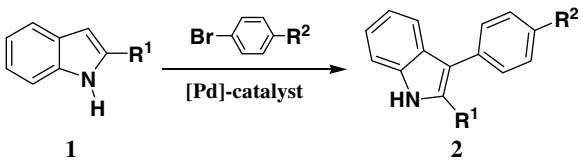
conditions.[20] Recently, Fagnou and co-workers described palladium-catalysed selective oxidative C2-arylations of N-protected indole.[21] In some cases, selective C3-arylation was achieved by using re-oxidant ($Cu(OAc)_2$ (3 equiv), 3-nitropyridine (0.1 equiv), CsOPiv (0.4 equiv)) or a large excess of palladium 'catalysts' (i.e., 300 mol %). In previous studies we reported the selective N1- versus C3-arylation of free NH-indole, those selectivities being directed through the catalytic system. However, the reported methodology was rather limited to the use of activated aryl halides.[22]

In this rather hot research area, Zhang, He and co-workers reported an interesting contribution using dinuclear palladium phosphinous acid complexes for the direct palladium-catalysed C3-arylation of the indole nucleus.[23] While they observed generally high selectivity towards the C3-arylated compound, the method suffers from two limitations: the use of 5 mol % homogeneous Pd-catalyst that is tedious to separate and recycle and the scope limitation to the indole nucleus itself as generally 2-substituted indoles did not react. Furthermore, except for some cases, the isolated yields are limited ($\leqslant$50%).

Following our interest to develop new simple, eco-efficient and environmentally friendly procedures for the synthesis of biologically and pharmaceutically relevant molecules, including indole heterocycles, we explored the Pd-catalysed selective C3-arylation of NH-free indoles using homogeneous and heterogeneous palladium catalysts under mild reaction conditions.

Initially, the reaction was studied using the indole, the 2-methylindole and the 2-phenylindole as substrates and bromobenzene as the arylating agent under similar reaction conditions as those reported by Zhang, He and co-workers (K_2CO_3 as the base, $Pd(OAc)_2$ as the catalyst, 24 h in refluxing dioxane) (Scheme 1).

Whatever the substrate used, high conversions were achieved under these conditions: 100% for the 3-phenylindole, 90% for the 3-phenyl-2-methylindole and 95% for the 2,3-diphenylindole. These conversions are close to the best result reported by Zhang, He and co-workers for the arylation of the indole (71%), given that the $Pd(OAc)_2$ is apparently not an optimum catalyst. Under these conditions, decreasing the amount of catalyst from 5 mol % to 1 mol % affected considerably the performance of the reaction as no conversion were achieved for all substrates. This is attributed to the formation of inactive palladium black as observed during the reaction.



Scheme 1. C3-Arylation of the 2-substituted indoles.

Having these conditions (Pd-catalyst, K_2CO_3, dioxane, reflux) in hand we evaluated the activity of the heterogeneous $[Pd(NH_3)_4]^{2+}$/NaY. The heterogeneous catalyst was prepared, according to procedure previously reported, by ion exchange of a NaY zeolite using a 0.1 M aqueous solution of $[Pd(NH_3)_4]^{2+}$, $2Cl^-$. After a period of 24 h, the exchanged $[Pd(NH_3)_4]$/NaY catalyst was obtained. The absolute palladium content of the catalyst was determined by ICP-AES as 1.0 wt % Pd.[24]

The results obtained for the arylation of various indoles using bromobenzene as the arylating agent and 1 mol % $[Pd(NH_3)_4]^{2+}$/NaY as the catalyst are reported in Table 1.

As expected all substrates led to good to high conversions under the reaction conditions. The results depend mainly on the nature of the substituent at position 2 of the indole nucleus: while the 2-phenylindole and the indole gave 68% and 74% conversion, respectively, the 2-methylindole bearing the more donating substituent (CH_3) led to the lowest conversion (47%). For comparison, under the same reaction conditions, Zhang, He and co-workers achieved 71% conversion for the Indole using 5 mol % of the optimised Pd-catalyst ($[Pd(P(tBu)_2OH)_2Cl_2]$), while we achieved 74% conversion but using only 1 mol % heterogeneous Pd-catalyst.

Attempting to improve this result by using the more reactive iodobenzene as the arylating agent unexpectedly led to lack of conversion. Zhang, He and co-workers reported that in some cases, generally, when poor conversions of the indole were achieved, they observed the formation of biphenyl derivatives due to homocoupling. In our case, because we used heterogeneous catalysts, we did not observe such a compound but rather the dehalogenation product (i.e., nitrobenzene in this case) in relatively high yield (>20%).

After demonstrating the applicability of the heterogeneous $[Pd(NH_3)_4]$/NaY catalyst for the selective C3-arylation of free NH-indoles, we extended the study to various aryl bromides (Table 2).

As reported in Table 2, almost all evaluated aryl bromides led to moderate to high conversions with some differences depending on the nature of the substituent at position 2 on the indole ring. Generally, both the indole and the 2-phenylindole gave moderate to high conversions (13–92%

Table 1
Arylation of various indoles using the bromobenzene as arylating agent (Scheme 1: $R^2 = H$)[a]

Entry	R^1	Yields[b] (%)
1	H	74
2	CH_3	47
3	Ph	68

[a] Reaction conditions: 2 mmol of 2-substituted indole, 2.2 mmol of bromobenzene, 6 mmol of K_2CO_3, 1 mol % $[Pd(NH_3)_4]^{2+}$/NaY, 4 mL of dioxane, reflux, 24–48 h.

[b] Yields were determined by GC based on the area of the product compared to that of an internal standard (diethylene glycol di-*n*-butyl ether) ($\Delta_{rel} = \pm 5\%$).

Table 2
Arylation of indoles (Scheme 1)[a,b]

Entry	R^1	R^2	Yields[c,d] (%)
1	H	H	74 (70)
2		CN	13
3		NO_2	18
4		OCH_3	42 (40)
5		CH_3	14
6		Cl	81 (75)
7	CH_3	H	47
8		CN	0
9		NO_2	86 (80)
10		OCH_3	0
11		CH_3	0
12		Cl	47
13	Ph	H	68 (62)
14		CN	19
15		NO_2	34
16		OCH_3	0
17		CH_3	0
18		Cl	92 (85)

[a] Reaction conditions: 2 mmol of 2-substituted indole, 2.2 mmol of bromobenzene, 6 mmol of K_2CO_3, 1 mol % $[Pd(NH_3)_4]^{2+}$/NaY, 4 mL of dioxane, reflux, 24–48 h.
[b] All compounds were identified by GC–MS (Shimadzu GC–MS QP2010S).
[c] Yields were determined by GC based on the area of the product compared to that of an internal standard (diethylene glycol di-*n*-butyl ether) ($\Delta_{rel} = \pm 5\%$).
[d] Isolated yields are reported in brackets.

conversions) depending mainly on the nature of the substituent on the arylhalide: except some specific cases electron-donating substituent gave the highest conversions, while electron-withdrawing substituent gave low conversions. This should be, however, moderated by the reactivity of aryl halide towards the oxidative addition. This explanation is in agreement with the generally accepted mechanism for the indole arylation through an electrophilic substitution (ES) mechanism (Fig. 2), the rate being almost related to the electron density at the metallic centre.

Remarkably, when using the Indole as the substrate, only the arylation towards the 3-substituted indole nucleus was observed.[25] In the case of C2-arylation a singlet signal would be expected at ca. 6.4 ppm for both compounds. N1-arylation or C2-arylation that was often described in the literature for this substrate was never observed under our reaction conditions.[18–20]

The case of the 2-methylindole is probably the most instructive. According to the ES mechanism, some authors reported that the generally observed lower reactivity of the 2-methylindole can be explained by the presence of the 2-methyl group adjacent to the reactive C-3 position of the indole nucleus that causes steric hindrance and prevents the 'free' approach of electrophile. Such an explanation did not appear to be fully satisfactory when regarding the high reactivity observed when using the 4-bromonitrobenzene as the arylating agent.

In order to account for these results, we suggest that two concurrent mechanisms could occur: the electrophilic substitution (ES) versus a SNAr mechanism (SNAr).

For the first mechanism (ES) to occur the initial step is the formation of Pd(II)-complexes [ArPdX] resulting from the oxidative addition of the aryl halide on in situ generated Pd(0)-species from the palladium precursors. Following this step, indole coordination occurs at the metallic centre to give finally the expected arylated compound (Fig. 2). In this mechanism, due to the relative hindrance around the palladium centre, steric hindrance at the indole C2 position would be a limitation to the reaction, as mentioned above. It is generally admitted that the Indole reacts following this mechanism.

In the second mechanism (SNAr), the indole nucleus would directly coordinate the Pd(II)-precursors to give by intramolecular CH-activation a pallada-indole derivative enhancing thus strongly the nucleophilicity of the indole nucleus. This derivative reacts then with the arylhalide by the well-documented SNAr mechanism to give then the expected arylated indole (Fig. 1). Such a mechanism is

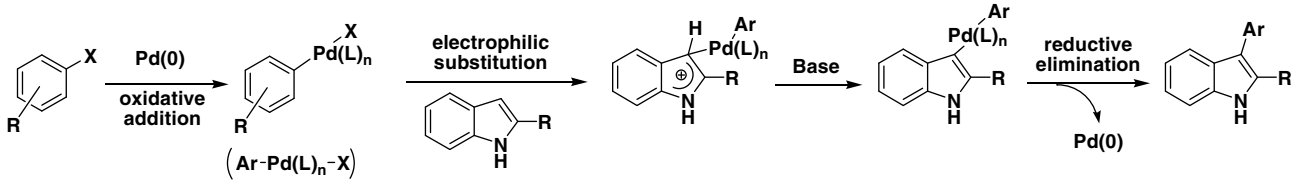


Fig. 1.

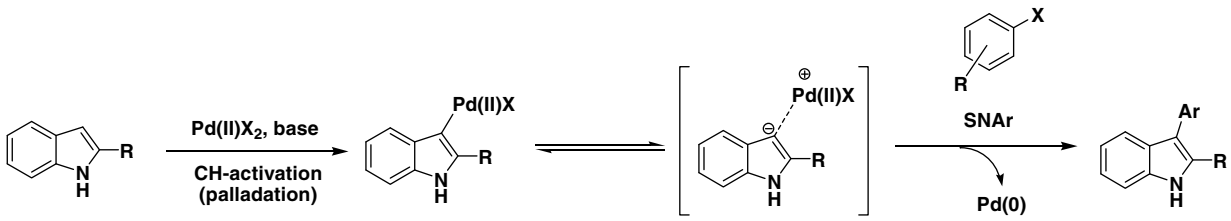


Fig. 2. Proposed mechanisms for C3-arylation of 2-susbtituted indoles.

supported by previous studies on the selective vinylation of the indole nucleus, a reaction that occurs exclusively through intramolecular CH-activation, for which we remarked the exceptional high reactivity of the 2-methylindole (2-Me $\gg$ 2-H $>$ 2-Ph).[26] In addition, such a mechanism would occur only when activated aryl halides, like 4-bromonitrobenzene, are used.

In summary, according to these suggestions, the way the arylation of the indole nucleus would occur depends mainly on the reactivity of the indole nucleus towards the Pd(II)-precursors initiating therefore the SNAr mechanism; when too slow, the in situ reduction of the Pd(II)-precursors to Pd(0)-species occurs initiating then the ES mechanism. In that case the overall reactivity would depend on the rate of coordination of the indole nucleus onto the Pd(II)-centre (which depends on the steric hindrance and the electron density on both the indole ring and the metallic centre).

In conclusion, we reported in this communication an efficient heterogeneously Pd-catalysed procedure for the fully C3-selective arylation of various 2-susbtituted indoles. Depending on the nature of the substituents on the indole ring and on the aryl bromides, two 'concurrent' mechanisms were proposed to account for the results observed. Generally, indoles bearing donor groups led to lower conversions. Whatever, all evaluated substrates gave moderate to high yields of target compounds (15–92% conversion, 40–85% isolated yields on some selected compounds) that can compete with the best procedures reported to date using homogeneous non-recyclable catalysts.

Current investigations focus on improving the activity of the heterogeneous catalyst and on implementing this step in a one-pot synthesis of pharmaceutically relevant indoles.

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25. The selectivity of the reaction was attributed through ^{1}H NMR analysis from isolated compounds. For example, proton NMR data are provided for compounds **2** with $R^1 = H$ and $R^2 = Cl$: ^{1}H NMR (250 MHz, $CDCl_3$); δ ppm: 8.17 (s, 1H), 7.81 (d, $^3J = 7.6$ Hz, 1H), 7.52 (d, $^3J = 8.5$ Hz, 2H), 7.33 (dd, $^3J = 8.0$ Hz, 16.3, 4H), 7.24–7.08 (m, 3H); and $R^1 = H$ and $R^2 = OMe$: ^{1}H NMR (250 MHz, $CDCl_3$); δ ppm: 8.09 (s, 1H), 7.82 (d, $^3J = 7.7$ Hz, 1H), 7.51 (d, $^3J = 8.7$ Hz, 2H), 7.34 (d, $^3J = 7.5$ Hz, 1H), 7.24–7.06 (m, 4H), 6.93 (d, $^3J = 8.7$ Hz, 2H), 3.79 (s, 3H).[27] In the case of C2-arylation a singlet signal would be expected at ca. 6.4 ppm for both compounds.
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