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# Selective arylation of 2-substituted indoles towards 1,2- and 2,3-functional indoles directed through the catalytic system

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**Abstract**

A simple palladium catalysed procedure for the synthesis of 1,2- and 2,3-disubstituted indoles is reported. It was found that the selectivity of the reaction, i.e. the N1- *versus* the C3-arylation of 2-functional indoles was mainly directed by electronic factors. Fine tuning of the reaction conditions and the right choice of the substrates allowed a full selective N1-(ArI, [Pd(OAc)$_2$], PPh$_3$) or C3 (ArBr, [Pd(OAc)$_2$], AgBF$_4$) arylation. Using only 1 mol% Pd-catalyst gave up to 92% isolated yield of expected compound.

*Keywords:* Palladium; Substituted indoles; *N*-Arylation; *C*-Arylation

## 1. Introduction

The indole nucleus are important substructures found in numerous natural or synthetic alkaloids [1,2]. The diversity of the structures encountered, as well as their biological and pharmaceutical relevance, have motivated research aimed at the development of new economical, efficient and selective synthetic strategies, particularly for the synthesis of substituted indole rings [3,4]. In addition to classical methodologies like the Fisher indole synthesis from aryl hydrazone, [5,6] the Batcho–Limgruber synthesis from *o*-nitrotoluenes and dimethylformamide acetals, [7] the Gassman synthesis from *N*-haloanilines [8,9] or the Madelung cyclisation of *N*-acyl-*o*-toluidines, [10–12] two important metal-catalysed strategies are employed for the preparation of indoles: the most commonly used involves the construction of the pyrrole ring through a palladium catalysed annulation of *o*-alkynylacetanilide, [13–17] a strategy that was efficiently extended to the preparation of 2,3-disubstituted indoles mainly by Cacchi and co-workers; [18–26] the alternative route to produce 2,3-disusbtituted indoles, initially reported by Larock and co-workers, [27–30] was thoroughly developed by several research groups and involves the palladium catalysed annulation of internal alkynes with *o*-iodoanilines (Fig. 1). [16,17,31–33] Recently, Ackermann and co-workers reported a one-pot synthesis of 2,3-disubstituted indoles from 2-chloroaniline consisting of regioselective Ti-catalysed hydroamination and Pd-catalysed 5-*endo* Heck cyclisation [34]. The regioselectivity observed is complementary to the Larock procedure.

A variety of indole derivatives could be prepared in good to excellent yields by these methods; however, few reports concern the post-functionalisation of indole nucleus, and particularly the selective N1- or C3-arylation of 2-susbtituted indoles. During the course of our studies in developing new efficient and selective palladium catalysed one-pot synthesis of functional indoles from simple *o*-iodoanilines and alkynes *via* the Sonogashira coupling reaction, we discover the dual N1- *versus* C3-reactivity of 2-susbtituted indoles [35]. We decided to develop further this area as it could be implemented in a one-pot synthesis of 1,2- or 2,3-functional indoles, and described in this communication the selective arylation of 2-susbtituted indoles at the N1- or C3-position directed through the catalytic system.

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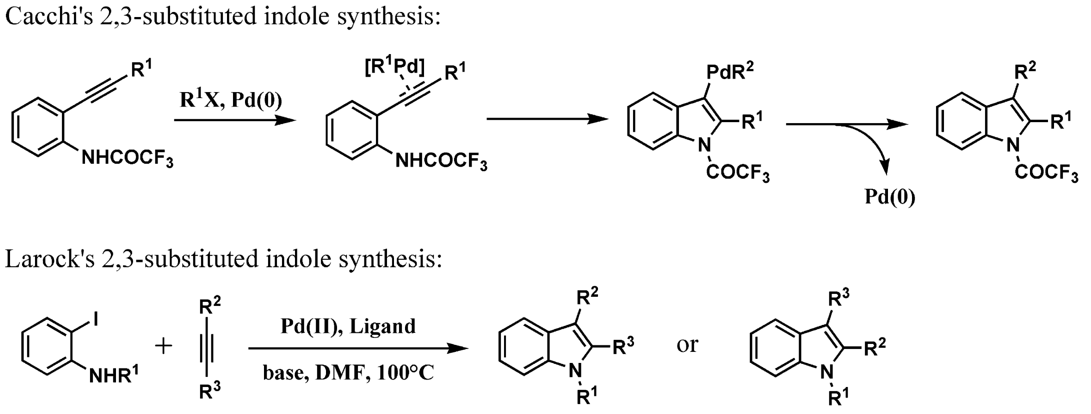

Fig. 1. Towards the synthesis of 2,3-disubstituted indoles.

## 2. Experimental

All manipulations were conducted under a strict inert atmosphere using Schlenk techniques, including the transfer of the catalysts to the reaction vessel. All glassware was base- and acid-washed and oven dried.

All chemicals (organic reagents and solvents) were used as received after being deaerated by an argon flow.

Liquid NMR spectra were recorded on a BRUKER AC-250 spectrometer. All chemical shifts were measured relative to residual $^1$H or $^{13}$C NMR resonances in the deuterated solvents: $CDCl_3$, $\delta$ 7.25 ppm for $^1$H, 77 ppm for $^{13}$C. Flash chromatography was performed at a pressure slightly greater than atmospheric pressure using silica (Merck Silica Gel 60, 230–400 mesh). Thin layer chromatography was performed on Fluka Silica Gel 60 $F_{254}$.

GC analyses were performed on a HP 4890 chromatograph equipped with a FID detector, a HP 6890 autosampler and a HP-5 column (cross-linked 5% phenyl-methylsiloxane, 30 m × 0.25 mm id × 0.25 μm film thickness). Nitrogen is used as carrier gas. The mass spectra were obtained on a HP 6890 gas chromatograph equipped with a HP 5973 mass detector and a HP-5 MS column (cross-linked 5% phenyl-methylsiloxane, 30 m × 0.25 mm id × 0.25 μm film thickness). Helium is used as carrier gas. The experimental error was estimated to be $\Delta_{rel} = \pm 5\%$.

### 2.1. Catalytic tests

The catalytic reactions were carried out in a three-necked flask, or alternatively in pressure sealed tubes, under argon. The qualitative and quantitative analysis of the reactants and the products was made by Gas Chromatography. Conversion and yields were determined by GC based on the relative area of GC-signals referred to an internal standard (diethylene glycol di-*n*-butyl ether) calibrated to the corresponding pure compound. All catalysts were handled and transferred under argon.

#### 2.1.1. General procedure

2 mmol of 2-substituted indole, 2.2 mmol of aryl halide, 2.2 mmol of NaOAc (180 mg), 1 mol% $[Pd(OAc)_2]$ (4.5 mg) and, when used, 2 mol% additive were introduced in a three-necked flask or a pressure sealed tube under argon. Then 8 mL of NMP (previously deaerated) was added and the mixture was further deaerated by an argon flow for 5 min. The reactor was placed in a preheated oil bath at 140 °C for 24–96 h. The reaction was conducted under vigorous stirring and then the reaction mixture was cooled to room temperature.

The reaction mixture was then diluted with 150 mL of water and the resulting mixture was extracted with 3 × 20 mL of ethyl acetate. The combined organic layers were washed three times with 15 mL $H_2O$, one time with 15 mL brine, dried over $MgSO_4$ and evaporated. The residue was then purified by flash chromatography on silica gel. Substituted indoles were characterised through $^1$H NMR, $^{13}$C NMR and GC–MS.

#### 2.1.2. Characterisations

*2.1.2.1. 3-(4-Nitrophenyl)-2-phenylindole* [20,22,36]. Two millimoles of 2-phenylindole (386 mg), 2.2 mmol of 4-bromonitrobenzene (442 mg), 2.2 mmol of NaOAc (180 mg), 1 mol% $[Pd(OAc)_2]$ (4.5 mg), 2 mol% $AgBF_4$-(3.9 mg). Eluant: $CH_2Cl_2$. $R_f = 0.68$ as an orange powder. Purity: >95%. mp: 158–160 °C. $^1$H NMR ($CDCl_3$, 250 MHz): 7.06 (d, $^3J_{H–H} = 9.2$ Hz, 1H, $C_6H_4$); 7.19 (m, 1H, $C_6H_4$); 7.29 (m, 2H, $C_6H_5$); 7.37 (m, 1H, $C_6H_4$); 7.48 (d, $^3J_{H–H} = 8.8$ Hz, 1H, $C_6H_5$); 7.58 (d, $^3J_{H–H} = 9.1$ Hz, 1H, $C_6H_4$); 7.64 (m, 1H, $C_6H_5$); 7.67 (d, $^3J_{H–H} = 8.8$ Hz, 1H, $C_6H_4$); 7.99 (d, $^3J_{H–H} = 9.1$ Hz, 1H, $C_6H_5$); 8.10 (d, $^3J_{H–H} = 8.8$ Hz, 1H, $C_6H_4$); 8.19 (d, $^3J_{H–H} = 9.2$ Hz, 1H, $C_6H_4$); 8.25 (d, $^3J_{H–H} = 8.8$ Hz, 1H, $C_6H_4$); 8.43 (br s, 1H, N–*H*). $^{13}$C NMR ($CDCl_3$, 62.9 MHz): 111.02 (*o*-C–C $C_6H_4$); 118.68 (*o*-C–N $C_6H_4$); 118.92 (*o*-C–$NO_2$ $C_6H_4NO_2$); 120.85 (*p*-C–N $C_6H_4$); 122.90 (*m*-C–N $C_6H_4$); 124.00 (*o*-C–$NO_2$ $C_6H_4NO_2$); 124.63 (*o*-$C_6H_5$); 125.88 (*m*-$C_6H_5$); 127.97 (*m*-$C_6H_5$); 128.19 (*p*-$C_6H_5$); 128.68 (*o*-$C_6H_5$); 129.64 ($C_q$-C–C $C_6H_4$); 129.93 (*m*-C–$NO_2$ $C_6H_4NO_2$); 131.51 ($C_q$ $C_6H_5$); 132.26 (*m*-C–$NO_2$