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The regioselective Larock indole synthesis catalyzed by NHC–palladium complexes†

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The first practical and regioselective process for the synthesis of 2,3-disubstituted indoles from the reaction of *o*-iodoanilines or *o*-bromoanilines and their derivatives with symmetrical and unsymmetrical internal alkynes catalyzed by a ferrocene-functionalized N-heterocyclic carbene (NHC)–palladium complex has been developed, and the indoles were isolated in good yields with high regioselectivity.

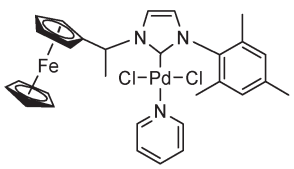
Introduction

The indoles, as very important ubiquitous heterocycles, are abundantly found in numerous natural products, pharmaceuticals, agrochemicals and functional materials.[1] For over a century, the synthesis and functionalization of indoles has been a major area of focus for synthetic organic chemists, and numerous methods for the preparation of indoles have been developed up to now.[2,3] In recent years, the palladium-catalyzed heteroannulation discovered by Larock has emerged as a versatile and practical method for the construction of indole rings.[4] This approach is extremely attractive to form complex indole targets in a single operation, as both anilines and internal alkynes can possess considerable functionality. Originally, Larock's heteroannulation was performed under 'ligandless' conditions, however, it only allowed the use of 2-iodoaniline as the reactant. To improve the Larock protocol, cheaper 2-bromo and 2-chloroanilines were applied with the use of additives and ligands.[4h,i,j] However, these methodologies suffer from drawbacks linked to the usage of a high loading catalyst, excess ligand, and unstable, expensive and toxic phosphine to maintain high activity. Furthermore, the Pd complex was not well defined and it is difficult to understand the composition of the active species and mechanistically explain the result. Consequently, it is necessary to develop air-stable, robust and well-defined Pd complexes with inexpensive ligands. Although the N-heterocyclic carbenes have been used widely in organometallic chemistry and catalysis,[5] Larock's heteroannulation based on N-heterocyclic carbene as the ligand is relatively scarce.[6] We have developed an interest in exploring the utility of N-heterocyclic carbenes in chemical catalysis.[7] In an extension of our previous work, herein we describe the first efficiently regioselective synthesis of 2,3-disubstituted indole derivatives catalyzed by the ferrocenyl NHC–Pd complex (**1**).

Results and discussion

The structure of the ferrocenyl NHC–Pd–Py complex **1** used in this study is shown in Scheme 1. The synthesis of **1** in 77% yield was achieved by the reaction of $PdCl_2$ with ferrocenyl imidazolium chloride in pyridine in the presence of K_2CO_3.[7] The complex **1** is very stable and not sensitive to air or moisture. From the previous result of screening the solvents, bases, catalyst loadings, and temperature, the indolization of diphenylacetylene with bromoaniline catalyzed by **1** can be effectively performed with 1 mol% of catalyst, with K_2CO_3 as base and tetra-*n*-butylammonium bromide (TBAB) as additive, in the solvent dioxane at 140 °C for 24 h.[6]

To probe the scope of the application of the NHC–Pd complex in the indolization reaction, more symmetrical internal aromatic alkynes were chosen to react with iodo and bromoanilines under the optimized conditions. The results are presented in Table 1. It was found that the indolization of aromatic alkynes would take place smoothly not only with the



Scheme 1 Ferrocenyl NHC–Pd–Py complex **1**.

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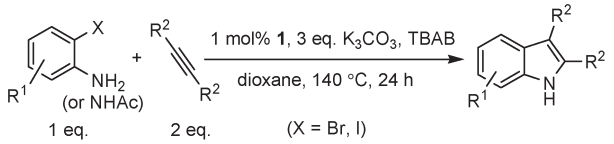
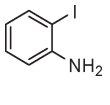
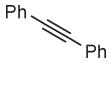
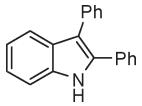
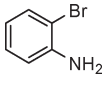
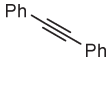
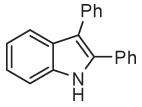
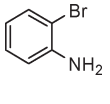
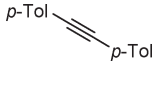
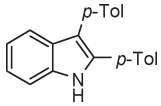
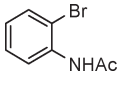
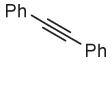
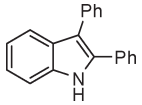
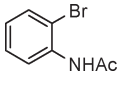
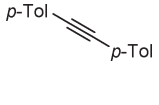
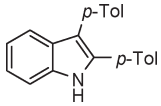
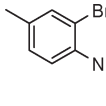
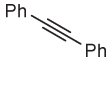
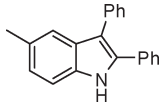
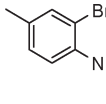
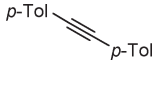
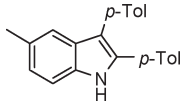
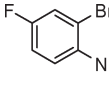
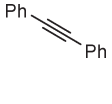
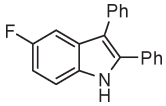
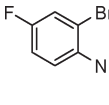
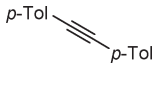
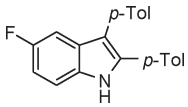
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ra42788a

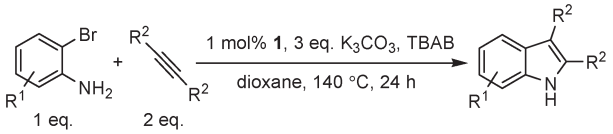
Table 1 Synthesis of 2,3-disubstituted indoles *via* NHC–Pd-catalyzed hetero-annulation of symmetrical internal aromatic alkynes

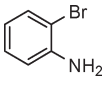
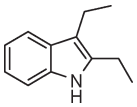
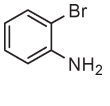
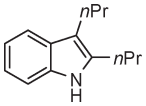
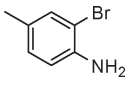
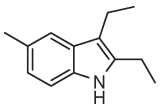
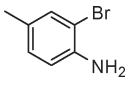
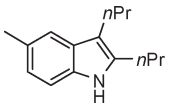
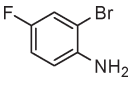
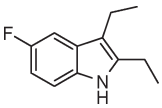
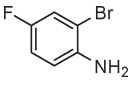


Entry[a]	Aniline	Aryl alkyne	Product	Yield (%)[b]
1				86
2				78
3				87
4				73
5				77
6				90
7				88
8				85
9				80

[a] Reaction conditions: 1 mmol of aniline, 2 mmol of alkyne, 1 mmol of TBAB and 3 mmol of K_2CO_3 in 2 mL dioxane. [b] Average isolated yield from two runs.

Table 2 Synthesis of 2,3-disubstituted indoles *via* NHC–Pd-catalyzed hetero-annulation of symmetrical internal aliphatic alkynes with 2-bromoanilines



Entry[a]	Aniline	R^2	Product	Yield (%)[b]
1		Et		81
2		*n*Pr		70
3		Et		83
4		*n*Pr		82
5		Et		79
6		*n*Pr		69

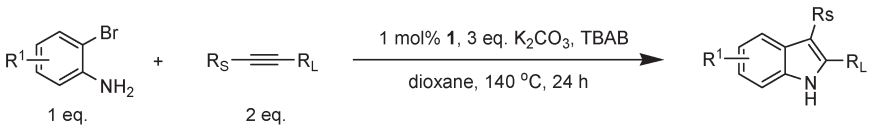
[a] Reaction conditions: 1 mmol of aniline, 2 mmol of alkyne, 1 mmol of TBAB and 3 mmol of K_2CO_3 in 2 mL dioxane. [b] Average isolated yield from two runs.

more reactive iodoanilines, but also with the less reactive bromoanilines. A better yield was generally achieved with iodoanilines, compared to bromoanilines (Table 1, entry 1 *vs.* 2). Furthermore, both electron-rich and electron-deficient bromoanilines were reacted with aromatic alkynes in good yield, however, the elelctron-rich anilines generally gave the higher yields (entries 6 and 7 *vs.* entries 8 and 9). Interestingly, 2-bromophenyl acetamide, a derivative of bromoaniline, is also a good substrate in the indolization, affording N-deacylated indoles as the final product (entries 4 and 5). Unfortunately, the ferrocenyl NHC–Pd complex is not effective with 2-chloroaniline.

To determine the scope of this system with other kinds of alkynes, we also investigated the reaction of symmetrical internal aliphatic alkynes with bromoanilines (Table 2). The results showed that both electron-rich and electron-poor bromoanilines reacted with aliphatic alkynes in good yield (69–83%).

This methodology has also been extended to use unsymmetrical internal alkynes in the indole synthesis, which represents an even more challenging task (Table 3). Good yields were achieved in all the examples (73–90%) and good regioselectivities were observed in most of the tested reactions.

Table 3 Synthesis of 2,3-disubstituted indoles *via* NHC–Pd-catalyzed heteroannulation of unsymmetrical internal alkynes



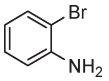
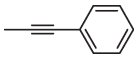
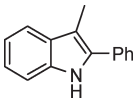
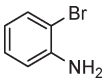
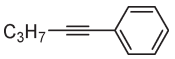
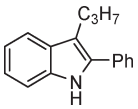
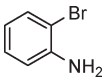
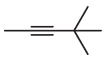
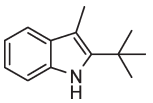
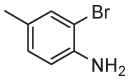
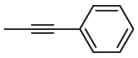
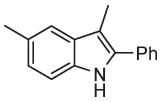
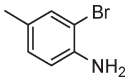
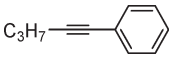
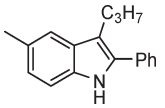
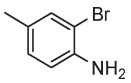
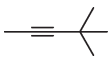
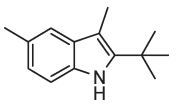
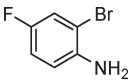
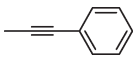
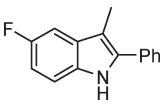
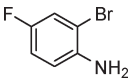
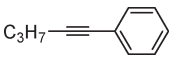
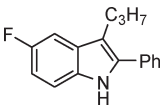
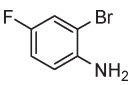
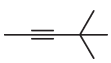
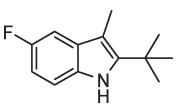
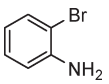
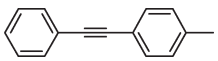
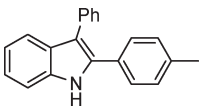
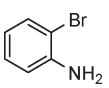
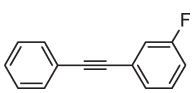
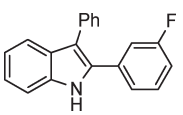
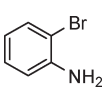
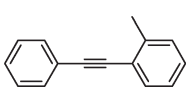
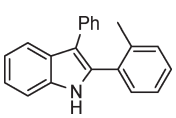
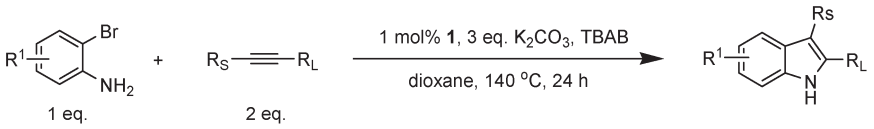
Entry[a]	Aniline	Aryl alkyne	Major isomer	Yield[b] (ratio)[c]
1				86% (>99 : 1)
2				78% (89 : 11)
3				87% (>99 : 1)
4				73% (96 : 4)
5				77% (86 : 14)
6				90% (>99 : 1)
7				88% (>99 : 1)
8				85% (84 : 16)
9				80% (>99 : 1)
10				82% (55 : 45)
11				75% (56 : 40)
12				79% (92 : 8)

Table 3 (*Continued*)

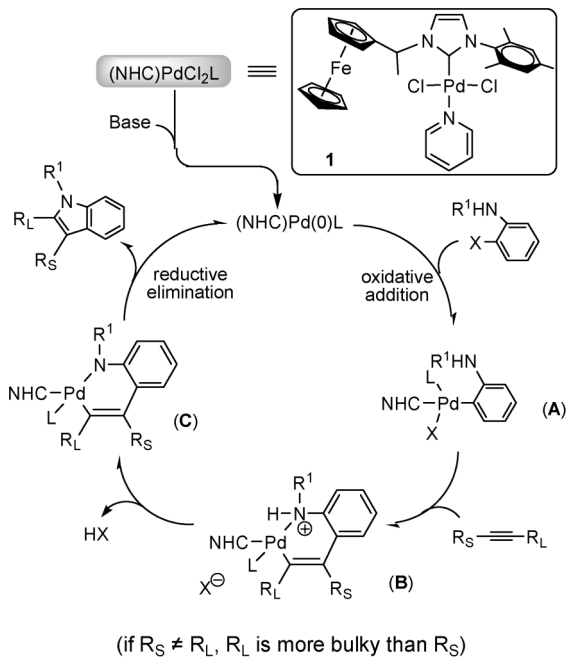


Entry[a]	Aniline	Aryl alkyne	Major isomer	Yield[b] (ratio)[c]

[a] Reaction conditions: 1 mmol of aniline, 1 mmol of TBAB, 2 mmol of alkyne and 3 mmol of K_2CO_3 in 2 mL dioxane. [b] Average isolated yield from two runs. [c] The ratios were determined by GC and ^{1}H NMR.

The regioselectivities of the products were largely dependent on the difference in size between the two substituents on the alkynes, and the more sterically hindered group (R_L) of the alkyne occupies the 2-position of the indole ring.

On the basis of our results and other studies on Pd-catalyzed reactions, we propose that the indolization reaction proceeds through the following steps, as shown in Scheme 2. Firstly, oxidative addition of the C–X bond to Pd(0), which is generated *in situ* from the ferrocenyl NHC–Pd(II) complex (**1**), produces a Pd(II)–aryl complex **A**; and then coordination and regioselective insertion of the Pd(II) complex into the alkyne gives intermediate **B**. The insertion of the Pd(II)–aryl bond into the alkyne occurs such that the bulky group in the alkyne is preferentially set near the smaller Pd(II) side, as the aryl group in the Pd(II)–aryl bond is geometrically more bulky than Pd(II), which is consistent with the regioselectivities observed in the NHC–Pd-catalyzed indolization reactions. Deprotonation of **B** by base gives complex **C**. Finally, the indole product is formed *via* the reductive elimination of **C**, regenerating the Pd(0) catalyst. The role of TBAB may be to stabilize the charged Pd(II) intermediate **B** and transition states.



Scheme 2 Possible mechanism.

Experimental section

General considerations

Complex **1** was synthesized according to our previous procedure.[6] All the other reagents were commercially available and were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer at room temperature and referenced to the residual signals of the solvent. The coupling constants (*J*) are given in Hz. HRMS was recorded on a Fisher LTQ-Orbitrap XL combined-type mass spectrometer.

General procedure for the synthesis of 2,3-disubstituted indole derivatives

Aniline (1 mmol), alkyne (2 mmol), Pd catalyst **1** (1 mol%), TBAB (1 mmol), and K_2CO_3 (3 mmol) were dissolved in dioxane (2 mL) in a 5 mL vial in air and heated at 140 °C for 24 h. After the reaction was completed, the mixture was diluted with ethyl acetate (10 mL), filtered through a pad of Celite, and washed multiple times with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired product.

Characterization data for indoles

2,3-Diphenyl-1*H*-indole. (Table 1, entry 1): yield: 86%; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.45–7.14 (m, 13H).

2,3-Di-*p*-tolyl-1*H*-indole. (Table 1, entry 3): yield: 87%; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 5H), 7.11–7.22 (m, 6H), 2.38 (s, 3H), 2.34 (s, 3H).

5-Methyl-2,3-diphenyl-1*H*-indole. (Table 1, entry 6): yield: 90%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (s, 1H), 7.49–7.30 (m, 12H), 7.11–7.09 (m, 1H), 2.43 (s, 3H).

5-Methyl-2,3-di-*p*-tolyl-1*H*-indole. (Table 1, entry 7): yield: 88%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 4.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.24–7.17 (m, 6H), 2.38 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): 138.6, 138.2, 137.6, 136.9, 134.1, 133.6, 131.4, 130.9, 129.7,

129.2, 129.1, 129.0, 128.8, 126.3, 120.6, 21.6, 21.4, 21.2. HRMS (ESI): *m*/*z* calcd: 311.1590 $[M - H]^-$, found: 310.1583.

5-Fluoro-2,3-diphenyl-1*H*-indole. (Table 1, entry 8): yield: 85%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (s, 1H), 7.44–7.30 (m, 12H), 7.03–6.98 (m, 1H).

5-Fluoro-2,3-di-*p*-tolyl-1*H*-indole. (Table 1, entry 9): yield: 80%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (s, 1H), 7.31 (t, *J* = 8.0 Hz, 6H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.99–6.94 (m, 1H), 2.40 (s, 3H), 2.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 158.5 (d, *J* = 936.0 Hz; CF), 137.8, 135.9 (d, *J* = 36.0 Hz; C), 132.3, 131.7, 130.9, 129.7, 129.6, 129.4, 129.3, 128.8, 127.9, 114.7 (d, *J* = 16.0 Hz; C), 111.4 (d, *J* = 36.0 Hz; C), 110.6 (d, *J* = 100.0 Hz; C), 104.5 (d, *J* = 96.0 Hz; C), 21.3, 19.2. HRMS (ESI): *m*/*z* calcd: 315.3834 $[M - H]^-$, found: 314.3844.

2,3-Diethyl-1*H*-indole. (Table 2, entry 1): yield: 81%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (br, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.0 Hz, 1H), 7.10–7.06 (m, 2H), 2.72 (m, 4H), 1.24 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): 135.2, 135.1, 128.4, 120.8, 118.2, 118.0, 113.1, 110.2, 19.3, 17.3, 15.8, 14.5.

2,3-Dipropyl-1*H*-indole. (Table 2, entry 2): yield: 70%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (br, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.15 (m, 1H), 6.98–7.02 (m, 2H) 2.59 (m, 4H), 1.58 (m, 4H), 0.88 (m, 6H). ^{13}CNMR ($CDCl_3$, 100 MHz): 135.4, 135.3, 132.7, 129.0, 128.5, 120.9, 119.0, 118.5, 115.9, 112.3, 110.3, 28.3, 26.4, 24.2, 23.3, 14.4, 14.1, 11.2.

2,3-Diethyl-5-methyl-1*H*-indole. (Table 2, entry 3): yield: 83%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (s, 1H), 7.35 (m, 1H), 6.98 (m, 2H), 2.48 (s, 3H), 1.64 (m, 4H), 0.96 (m, 6H). HRMS (ESI): *m*/*z* calcd: 186.1277 $[M + H]^+$, found: 186.1256.

5-Methyl-2,3-dipropyl-1*H*-indole. (Table 2, entry 4): yield: 82%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (s, 1H), 7.31 (s, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 2.71–2.63 (m, 4H), 2.46 (s, 3H), 1.71–1.63 (m, 4H), 1.00–0.95 (m, 6H).

2,3-Diethyl-5-fluoro-1*H*-indole. (Table 2, entry 5): yield: 79%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (s, 1H), 7.19 (d, *J* = 4.0 Hz, 1H), 7.17 (d, *J* = 4.0 Hz, 1H), 6.88–6.83 (m, 1H), 2.78–2.65 (m, 4H), 1.31–1.20 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): 157.7 (d, *J* = 924.0 Hz), 138.1, 131.6, 128.9 (d, *J* = 36.0 Hz), 113.4 (d, *J* = 20.0 Hz), 110.7 (d, *J* = 40.0 Hz), 108.8 (d, *J* = 102.0 Hz), 103.2 (d, *J* = 96.0 Hz), 19.4, 17.3, 15.5, 14.3. HRMS (ESI): *m*/*z* calcd: 191.1027 $[M - H]^-$, found: 190.1031.

5-Fluoro-2,3-dipropyl-1*H*-indole. (Table 2, entry 6): yield: 69%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (s, 1H), 7.18–7.15 (m, 2H), 6.88–6.83 (m, 1H), 2.70 (t, *J* = 8.0 Hz, 2H), 2.64 (t, *J* = 8.0 Hz, 2H), 1.72–1.61 (m, 4H), 1.02–0.95 (m, 6H).

3-Methyl-2-phenyl-1*H*-indole. (Table 3, entry 1): yield: 86%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (s, 1H), 7.56–7.61 (m, 2H), 7.42–7.49 (m, 3H), 7.31–7.37 (m, 2H), 7.12–7.24 (m, 2H), 2.46 (s, 3H).

2-Phenyl-3-propyl-1*H*-indole. (Table 3, entry 2): yield: 78%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (s, 1H), 7.64 (d, *J* = 4.0 Hz, 1H), 7.44–7.50 (m, 4H), 7.29–7.36 (m, 2H), 7.09–7.19 (m, 2H), 2.84 (t, *J* = 8.0 Hz, 2H), 1.70–1.76 (m, 2H), 0.97 (t, *J* = 8.0 Hz, 3H).

2-(*tert*-Butyl)-3-methyl-1*H*-indole. (Table 3, entry 3): yield: 87%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (s, 1H), 7.39–7.43 (m, 1H), 7.11–7.23 (m, 2H), 6.98–7.05 (m, 1H), 2.32 (s, 3H), 1.38 (s, 9H).

3,5-Dimethyl-2-phenyl-1*H*-indole. (Table 3, entry 4, major product): yield: 73%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.38 (s, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.27 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 2.48 (s, 3H), 2.44 (s, 3H).

2,5-Dimethyl-3-phenyl-1*H*-indole. (Table 3, entry 4, minor product): colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (s, 1H), 7.50–7.45 (m, 5H), 7.31 (t, *J* = 8.0 Hz, 1H) , 7.23 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 2.50 (s, 3H), 2.43 (s, 3H).

5-Methyl-2-phenyl-3-propyl-1*H*-indole. (Table 3, entry 5): yield: 77%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.41–7.47 (m, 3H), 7.33–7.36 (m, 1H), 7.21–7.26 (m, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 2.83 (t, *J* = 8.0 Hz, 2H), 2.47 (s, 3H), 1.70–1.80 (m, 2H), 0.99 (t, *J* = 8.0 Hz, 3H).

2-(*tert*-Butyl)-3,5-dimethyl-1*H*-indole. (Table 3, entry 6): yield: 90%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.95 (s, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.06–7.09 (m, 2H), 2.30 (s, 3H), 1.63 (s, 3H), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): 135.9, 131.8, 130.3, 125.1, 122.3, 120.7, 120.1, 110.5, 29.3, 27.6, 21.3, 20.8. HRMS (ESI): *m*/*z* calcd: 201.3074 $[M - H]^-$, found: 200.3018.

5-Fluoro-3-methyl-2-phenyl-1*H*-indole. (Table 3, entry 7): yield: 88%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.35–7.38 (m, 1H), 7.21–7.29 (m, 2H), 6.91–6.96 (m, 1H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 161.7 (d, *J* = 244.0 Hz), 132.1, 131.1, 128.8, 128.6 (d, *J* = 15.0 Hz), 128.3 (d, *J* = 38.0 Hz), 127.7 (d, *J* = 15.0 Hz), 127.4, 117.6 (d, *J* = 23.0 Hz), 115.9 (d, *J* = 23.0 Hz), 110.9 (d, *J* = 65.0 Hz), 103.8 (d, *J* = 23.0 Hz), 19.9. HRMS (ESI): *m*/*z* calcd: 225.2609 $[M - H]^-$, found: 224.3617.

5-Fluoro-2-phenyl-3-propyl-1*H*-indole. (Table 3, entry 8, major product): yield: 85%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.28–7.50 (m, 5H), 6.95 (d, *J* = 8.0 Hz, 1H), 2.81 (t, *J* = 8.0 Hz, 2H), 1.70–1.76 (m, 2H), 0.99 (t, *J* = 8.0 Hz, 3H).

5-Fluoro-3-phenyl-2-propyl-1*H*-indole. (Table 3, entry 8, minor product): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.28–7.50 (m, 5H), 6.95 (d, *J* = 8.0 Hz, 1H), 3.02 (t, *J* = 8.0 Hz, 2H), 2.00–2.06 (m, 2H), 1.05 (t, *J* = 8.0 Hz, 3H).

2-(*tert*-Butyl)-5-fluoro-3-methyl-1*H*-indole. (Table 3, entry 9): yield: 80%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (s, 1H), 7.32–7.36 (m, 1H), 7.16–7.19 (m, 1H), 7.11–7.14 (m, 1H), 2.35 (s, 3H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): 158.9, 143.7, 130.1, 121.3 (d, *J* = 9.0 Hz), 116.1 (d, *J* = 23.0 Hz), 110.7 (d, *J* = 9.0 Hz), 108.9 (d, *J* = 26.0 Hz), 102.7 (d, *J* = 23.0 Hz), 37.4, 32.8, 20.7. HRMS (ESI): *m*/*z* calcd: 205.2712 $[M - H]^-$, found: 204.2691.

3-Phenyl-2-(*p*-tolyl)-1*H*-indole. (Table 3, entry 10, major product): yield: 82%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.12–7.43 (m, 13H), 2.37 (s, 3H).

2-Phenyl-3-(*p*-tolyl)-1*H*-indole. (Table 3, entry 10, minor product): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (s, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.12–7.43 (m, 13H), 2.35 (s, 3H).

2-(3-Fluorophenyl)-3-phenyl-1*H*-indole. (Table 3, entry 11, major product): yield: 75%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (s, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.10–7.42 (m, 11H), 6.97 (t, J = 8.0 Hz, 1H).

3-(3-Fluorophenyl)-2-phenyl-1*H*-indole. (Table 3, entry 11, minor product): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (s, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.10–7.42 (m, 11H), 6.97 (t, J = 8.0 Hz, 1H).

3-Phenyl-2-(*o*-tolyl)-1*H*-indole. (Table 3, entry 12): yield: 79%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.25–7.33 (m, 11H), 7.06–7.12 (m, 1H), 2.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 137.7, 135.8, 134.5, 133.8, 132.9, 131.5, 130.2, 129.6, 128.7, 127.4, 127.2, 126.7, 125.8, 122.6, 120.1, 120.0, 114.8, 110.7, 29.7. HRMS (ESI): m/z calcd: 283.1277 $[M - H]^-$, found: 282.1294.

Conclusions

A well-defined ferrocenyl functionalized NHC–palladium complex was found to be an efficient catalyst for Larock heteroannulation. The process is practical and economical for the synthesis of 2,3-disubstituted indoles from the reactions of *o*-iodoanilines or *o*-bromoanilines and their derivatives with various internal alkynes, and the indoles were isolated in good yields (*ca.* 69–90%) with high regioselectivity. The reactions occur in a broad scope and with a high tolerance of functional groups. NHC–palladium complexes could be excellent candidates to replace expensive palladium–phosphine complexes for Larock indole catalysis.

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