Journal of Organometallic Chemistry 696 (2011) 195–201

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Nickel-catalyzed, base-mediated amination/hydroamination reaction sequence for a modular synthesis of indoles

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ARTICLE INFO

Article history:
Received 31 July 2010
Accepted 26 August 2010
Available online 16 October 2010

Keywords:
Amination
Base
Hydroamination
Indole
Nickel

ABSTRACT

A catalytic system consisting of [Ni(cod)$_2$] and ligand dppf enabled an efficient synthesis of differently substituted indoles through a modular reaction sequence, which consists of intermolecular aminations and intramolecular hydroaminations with *ortho*-alkynylhaloarenes.

1. Introduction

The addition of nitrogen nucleophiles onto non-activated, unsaturated carbon–carbon multiple bonds represents one of the most attractive approaches to substituted amines and imines, largely because these hydroamination reactions [1] occur with ideal atom-economy.[2] Particularly, intramolecular hydroaminations set the stage for the preparation of various N-heterocycles.[3,4] Since indoles are omnipresent in biologically active compounds and natural products, a continued strong demand exists for broadly applicable syntheses of this structural motif.[5–11] Specifically, significant progress was accomplished with intramolecular addition reactions of *ortho*-alkynylanilines.[3,12] Contrarily, we devised transition-metal-catalysts for the selective conversion of easily accessible *ortho*-alkynylhaloarenes **1** to indole derivatives **4** through a reaction cascade comprising intermolecular aminations[13–15] of aryl halides and subsequent intramolecular hydroamin(d)ations [16] of alkynes (Scheme 1). Hence, palladium[17–21] and copper[17,22] complexes were found to enable the formation of indoles bearing *inter alia* aryl-, alkyl- or alkoxycarbonyl-substituents on nitrogen.[7] In continuation of our research program on sustainable catalysis for effective heterocycle syntheses,[23] we became interested in exploring the unprecedented use of inexpensive nickel catalysts[24] for a modular indole synthesis starting from *ortho*-alkynylhaloarenes **1**, the results of which we wish to disclose herein.

2. Results and discussion

At the outset of our studies, we probed representative ligands and nickel compounds for the envisioned amination/hydroamination sequential synthesis of indole **4a** (Table 1). Notably, no conversion of starting material **1a** to desired product **4a** occurred in the absence of a stabilizing ligand, irrespective of the oxidation state of the nickel precursors (entries 1, and 2). While monodentate phosphine ligands **5**–**8** provided only unsatisfactory catalysis (entries 3–6), improved isolated yields were obtained with precursors to N-heterocyclic carbenes (NHC) **9**–**11** (entries 7–9). However, nickel complexes derived from bidentate ligands proved to be superior (entries 10–13), with dppf (**16**) being optimal (entry 14). Generally, the use of additional base KO*t*-Bu proved beneficial to ensure quantitative cyclization of intermediate **3a** to the desired indole **4a** via a base-mediated or -catalyzed (entry 15)[25] intramolecular hydroamination.

With an optimized catalytic system in hands, we probed its scope in the amination/hydroamination reaction sequence employing aniline derivatives (Table 2). Notably, differently substituted aromatic amines could be employed, bearing either electron-donating or electron-withdrawing substituents (entries 1–4). Further, the nickel catalyst was not restricted to the use of tolane derivatives. Indeed, substrates **1** displaying alkyl-substituted alkynes were converted with an efficacy being comparable to the one observed when using the corresponding aryl-substituted analogues (entries 5–7). Moreover, sterically hindered aniline derivatives **2** provided the desired indoles in high yields (entries 8, and 9), as did a nucleophile bearing a further Lewis-basic pyridyl moiety (entry 10).

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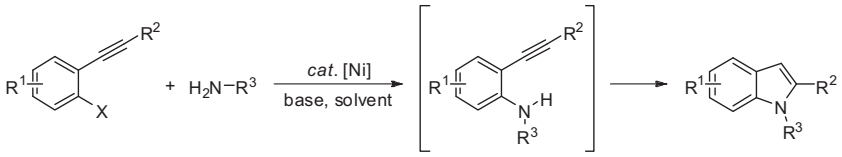
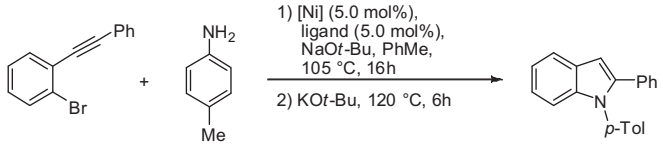
doi:10.1016/j.jorganchem.2010.08.047



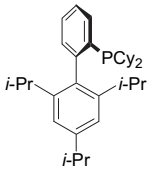
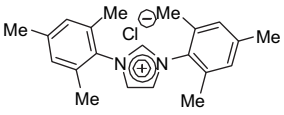
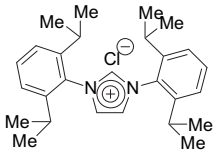
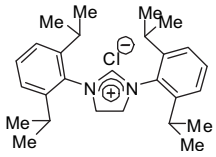
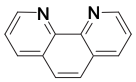
1 2 3 4

Scheme 1. Nickel-catalyzed sequential synthesis of substituted indoles **4**.

Table 1
Effect of ligands on the nickel-catalyzed synthesis of indole **4a**.[a]



1a **2a** **4a**

Entry	[Ni]	Ligand		Yield
1	$NiCl_2$	–		<2%
2	$[Ni(cod)_2]$	–		<5%
3	$[Ni(cod)_2]$	PPh_3	**5**[b]	<2%
4	$[Ni(cod)_2]$	PCy_3	**6**[b]	<2%
5	$[Ni(cod)_2]$	$(1\text{-Ad})_2P(O)H$	**7**[b]	10%
6	$[Ni(cod)_2]$		**8**[b]	<5%
7	$[Ni(cod)_2]$		**9**[b]	12%
8	$[Ni(cod)_2]$		**10**[b]	51%
9	$[Ni(cod)_2]$		**11**[b]	47%
10	$[Ni(cod)_2]$		**12**	49%
11	$[Ni(cod)_2]$	BINAP	**13**	31%
12	$[Ni(cod)_2]$	dppp	**14**	46%
13	$[Ni(cod)_2]$	dppe	**15**	71%
14	$[Ni(cod)_2]$	dppf	**16**	88%
15	$[Ni(cod)_2]$	dppf	**16**	92%[c]

[a] Reaction conditions: **1a** (1.0 equiv.), **2a** (1.5 equiv.), [Ni] (5.0 mol%), ligand (5.0 mol%), NaO*t*-Bu (1.5 equiv), PhMe (2.0 mL), 105 °C, 16 h; b) KO*t*-Bu (3.0 equiv.), 120 °C, 6 h; isolated yields.
[b] Ligand (10 mol%).
[c] b) KO*t*-Bu (0.6 equiv.).

Moreover, the nickel catalyst derived from dppf (**16**) enabled also the preparation of indoles **4l**–**4o** when using benzyl or even more challenging *n*-alkyl amines **2** (Scheme 2).

Notably, the catalytic system was further not limited to aryl bromides as electrophiles, but also proved amenable to an efficient amination/hydroamination sequence with aryl iodide **1d** as starting material (Scheme 3). As was observed for the corresponding bromoarenes **1a**–**1c**, the intermolecular amination as well as the intramolecular hydroamination occurred readily with both aniline derivatives and alkyl amines, thereby yielding the corresponding indoles **4b** and **4n**, respectively.

Finally, we exploited the excellent chemoselectivity of the dppf (**16**) derived catalyst for the synthesis of indoles **4p**–**4r** highlighting 6-chloro-substituents, a valuable asset for further catalyzed functionalizations (Scheme 4).

3. Conclusion

We have devised a nickel catalyst for a sequential indole synthesis consisting of intermolecular aminations of aryl halides and subsequent intramolecular hydroaminations. Thus, an *in-situ* generated complex derived from ligand dppf allowed for efficient transformations of *ortho*-alkynylhaloarenes with aryl as well as alkyl-substituted amines, and enabled the chemoselective synthesis of chloro-substituted indoles.

4. Experimental section

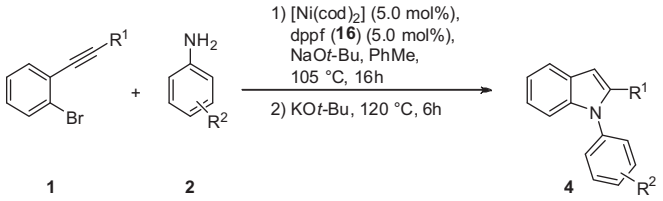
4.1. General remarks

Catalytic reactions were carried out under a N_2 atmosphere using pre-dried glassware. *ortho*-Alkynylbromoarenes **1** were prepared as previously described [17–22]. Other starting materials were obtained from commercial sources, and were used without further purification. Yields refer to isolated compounds, estimated to be > 95% pure as determined by ^1H NMR and GC. Flash chromatography: Macherey–Nagel silica gel 60 (70–230 mesh). NMR: Spectra were recorded on Varian Mercury 300, Unity 300 or Inova 500 instruments in the solvent indicated; chemical shifts (δ) are given in ppm.

4.1.1. Representative procedure: nickel-catalyzed synthesis of *4a* (Table 1, entry 14)

To a solution of $[Ni(cod)_2]$ (6.9 mg, 0.025 mmol, 5.0 mol%), dppf (13.9 mg, 0.025 mmol, 5.0 mol%) and NaO*t*-Bu (96 mg, 0.750 mmol) in PhMe (2.0 mL) were added **1a** (129 mg, 0.500 mmol) and **2a** (80 mg, 0.750 mmol) at ambient temperature. The resulting mixture was stirred for 16 h at 105 °C. At ambient temperature, KO*t*-Bu (168 mg, 1.500 mmol) was added, and the resulting mixture was stirred for 6 h at 120 °C. EtOAc (5 mL) and H_2O (5 mL) were added to the cold suspension. The separated aqueous phase was extracted with EtOAc (3 × 10 mL), the combined organic phases were washed with H_2O (10 mL) and brine (10 mL). Drying with Na_2SO_4 and purification by column chromatography on silica gel (*n*-hexane/EtOAc, 500/1) yielded **4a** (125 mg, 88%) as a white solid

Table 2
Scope of nickel-catalyzed hydroamination-based indole synthesis with aniline derivatives **2**.[a]

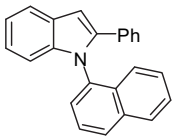
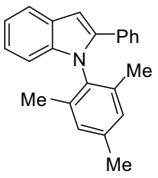
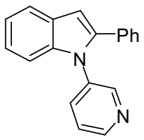


1 **2** **4**

Entry	R^1	**1**	R^2	**4**	Isolated Yield
1	Ph	**1a**	H	**4b**	86%
2	Ph	**1a**	4-MeO	**4c**	98%
3	4-$MeOC_6H_4$	**1b**	4-MeO	**4d**	89%
4	Ph	**1a**	3-CF_3	**4e**	72%
5	*n*-Hex	**1c**	H	**4f**	78%
6	*n*-Hex	**1c**	4-Me	**4g**	81%
7	*n*-Hex	**1c**	4-MeO	**4h**	75%

(*continued on next page*)

Table 2 (*continued*)

Entry	R^1	1	R^2	4		Isolated Yield
8	Ph	**1a**	1-Naphthyl		**4i**	78%
9	Ph	**1a**	Mes		**4j**	81%
10	Ph	**1a**	3-py		**4k**	74%

[a] Reaction conditions: **1** (1.0 equiv.), **2** (1.5 equiv.), [Ni(cod)$_2$] (5.0 mol%), **16** (5.0 mol%), NaO*t*-Bu (1.5 equiv), PhMe (2.0 mL), 105 °C, 16 h; b) KO*t*-Bu (3.0 equiv.), 120 °C, 6 h; isolated yields.

(m.p. 97–98 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (dd, J = 5.7, 3.3 Hz, 1H), 7.44–7.03 (m, 12H), 6.81 (s, 1H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.8, 139.1, 137.0, 135.9, 132.6, 129.9, 128.9, 128.2, 128.1, 127.8, 127.2, 122.2, 120.5, 120.4, 110.7, 103.4, 21.1. IR (KBr): 3054, 3033, 2920, 1514, 1451, 1356, 1322, 1208, 1108, 1022, 741, 696 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 283 (100) [M$^+$], 267 (14), 165 (13), 133 (9). HR-MS (EI) *m*/*z* calcd for $C_{21}H_{17}N$ 283.1361, found 283.1359. The spectral data are in accordance with those reported in literature[17].

*4.1.2. 1,2-Diphenyl-1H-indole (**4b**).[17]*

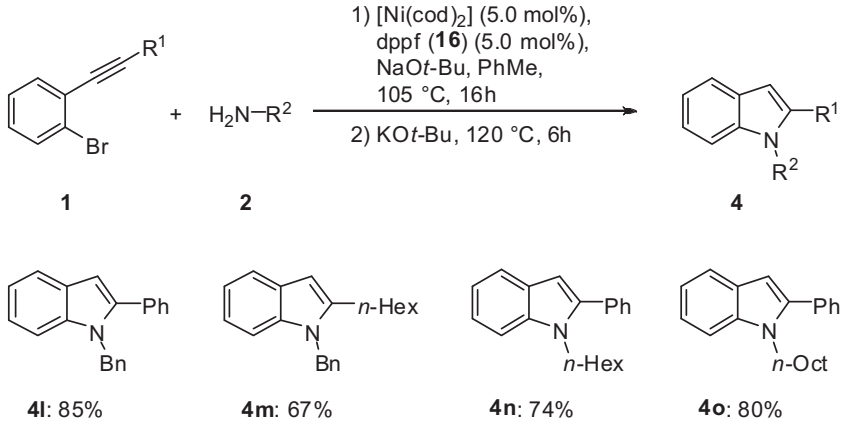
Following the general procedure, indole **4b** (115 mg, 86%) was obtained as a white solid (m.p. 83–84 °C) after purification by column chromatography (*n*-hexane/EtOAc 500:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (m, 1H), 7.48–7.14 (m, 13H), 6.85 (d, J = 0.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.7, 139.0, 138.5, 132.5, 129.2, 129.0, 128.3, 128.1, 128.0, 127.3, 127.2, 122.3, 120.7, 120.5, 110.6, 103.7. IR (KBr): 3056, 1597, 1495, 1451, 1377, 1352, 1321, 795, 755, 697 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 269 (100) [M$^+$], 268 (35), 165 (26), 133 (27), 127 (12). HR-MS (ESI) *m*/*z* calcd for [$C_{20}H_{15}N$ + H]$^+$ 270.1277, found 270.1275.

*4.1.3. 1-(p-Anisyl)-2-phenyl-1H-indole (**4c**).[17]*

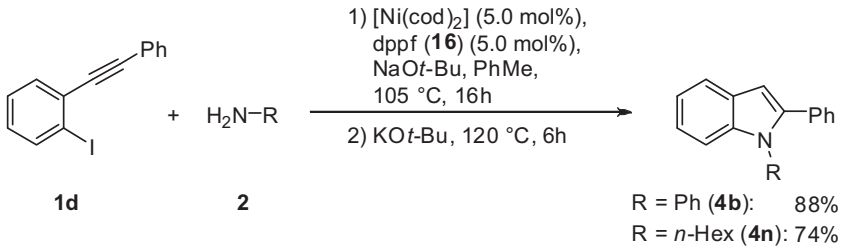
Following the general procedure, indole **4c** (146 mg, 98%) was obtained as a white solid (m.p. 143–144 °C) after purification by column chromatography (*n*-hexane/EtOAc 500:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (m, 1H), 7.42–7.12 (m, 10H), 6.97 (d, J = 8.9 Hz, 2H), 6.85 (s, 1H), 3.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.5, 140.8, 139.3, 132.6, 131.3, 129.1, 128.8, 128.1, 128.1, 127.2, 122.1, 120.5, 120.4, 114.4, 110.6, 103.1, 55.4. IR (KBr): 3054, 2956, 2835, 1612, 1512, 1460, 1294, 1175, 1031, 842, 754, 694 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 299 (100) [M$^+$], 284 (26), 256 (10), 254 (16). HR-MS (EI) *m*/*z* calcd for $C_{21}H_{17}NO$ 299.1310, found 299.1313.

*4.1.4. 1,2-Di-p-anisyl-1H-indole (**4d**)*

Following the general procedure, indole **4d** (147 mg, 89%) was obtained as a yellow solid (m.p. 136–137 °C) after purification by column chromatography (*n*-hexane/EtOAc, 100/1). ^{1}H NMR



Scheme 2. Nickel-catalyzed indole synthesis with alkyl amines **2**.



Scheme 3. Nickel-catalyzed indole synthesis with aryl iodide **1d**.

(300 MHz, $CDCl_3$): δ 7.68 (m, 1H), 7.23–7.13 (m, 7H), 6.93 (dt, $J = 9.8$, 3.4 Hz, 2H), 6.80 (dt, $J = 9.8$, 3.1 Hz, 2H), 6.73 (d, $J = 0.7$ Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.9, 158.5, 140.8, 139.2, 131.4, 130.1, 129.2, 128.2, 125.1, 121.8, 120.4, 120.2, 114.4, 113.6, 110.5, 102.2, 55.4, 55.2. IR (KBr): 3000, 2933, 2838, 1608, 1541, 1513, 1456, 1361, 1249, 1116, 1031, 834, 740, 646 cm^{-1}. MS (EI) *m/z* (relative intensity) 329 (100) [M$^+$], 314 (36), 298 (2), 283 (5), 271 (5), 254 (15), 242 (16), 215 (3), 190 (2). HR-MS (ESI) *m/z* calcd for $[C_{22}H_{19}NO_2+H]^+$ 330.1489, found 330.1489.

*4.1.5. 2-Phenyl-1-{m-(trifluoromethyl)phenyl}-1H-indole (**4e**)*

Following the general procedure, indole **4e** (115 mg, 72%) was obtained as a white solid (m.p. 91–92 °C) after purification by column chromatography (*n*-hexane/EtOAc 500:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (m, 1H), 7.67–7.47 (m, 3H), 7.39 (d, $J = 7.9$ Hz, 1H), 7.34–7.16 (m, 8H), 6.83 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.6, 139.1, 138.6, 132.0, 131.8 ($^2J_{C,F} = 34$ Hz), 131.2, 129.8, 129.0, 128.5, 128.3, 127.6, 124.7 ($^3J_{C,F} = 4$ Hz), 123.7 ($^3J_{C,F} = 4$ Hz), 122.8, 121.5 ($^1J_{C,F} = 251$ Hz), 121.2, 120.8, 110.2, 104.6. IR (KBr): 3059, 1597, 1496, 1456, 1375, 1326, 1129, 799, 752, 698 cm^{-1}. MS (EI) *m/z* (relative intensity) 337 (100) [M$^+$], 336 (19), 267 (14), 165 (26), 133 (23). HR-MS (ESI) *m/z* calcd for $[C_{21}H_{14}NF_3+H]^+$ 338.1151, found 338.1152.

*4.1.6. 2-n-Hexyl-1-phenyl-1H-indole (**4f**).[17]*

Following the general procedure, indole **4f** (108 mg, 78%) was obtained as a yellow oil after purification by column chromatography (*n*-hexane/EtOAc 500:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71–7.47 (m, 4H), 7.42 (t, $J = 4.2$ Hz, 2H), 7.23–7.11 (m, 3H), 6.50 (s, 1H), 2.76–2.58 (t, $J = 7.6$ Hz, 2H), 1.71–1.58 (m, 2H), 1.40–1.20 (m, 6H), 0.93 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.0, 138.3, 138.1, 129.4, 128.3, 128.1, 127.8, 121.0, 119.9, 119.6, 109.9, 100.1, 31.5, 28.9, 28.6, 27.1, 22.5, 14.0. IR (KBr): 3056, 2927, 2857, 1596, 1498, 1459, 1392, 1211, 1016, 778, 762, 699 cm^{-1}. MS (EI) *m/z* (relative intensity) 277 (44) [M$^+$], 220 (46), 207 (100), 191 (6), 178 (7), 165 (3), 152 (2), 128 (6). HR-MS (EI) *m/z* calcd for $C_{20}H_{23}N$ 277.1830, found 277.1831.

*4.1.7. 2-n-Hexyl-1-p-tolyl-1H-indole (**4g**).[17]*

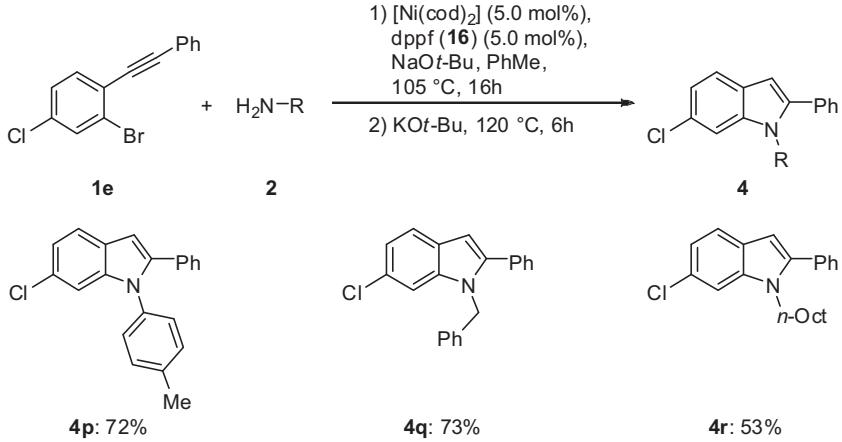
Following the general procedure, indole **4g** (117 mg, 81%) was obtained as a yellow oil after purification by column chromatography (*n*-hexane/EtOAc 500:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (m, 1H), 7.38 (d, $J = 8.5$ Hz, 2H), 7.29 (m, 2H), 7.20–7.10 (m, 3H), 6.48 (s, 1H), 2.70 (t, $J = 7.8$ Hz, 2H), 2.52 (s, 3H), 1.71–1.60 (m, 2H), 1.32 (m, 6H), 0.94 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1, 138.4, 137.6, 135.4, 130.0, 128.1, 128.0, 120.8, 119.8, 119.5, 110.0, 99.8, 31.5, 28.9, 28.6, 27.0, 22.5, 21.2, 14.0. IR (KBr): 3054, 2954, 2926, 2858, 1608, 1514, 1459, 1394, 1211, 1017, 817, 741 cm^{-1}. MS (EI) *m/z* (relative intensity) 291 (46) [M$^+$], 234 (29), 221 (100), 220 (66), 205 (34), 204 (44). HR-MS (EI) *m/z* calcd for $C_{21}H_{25}N$ 291.1987, found 291.1978.

*4.1.8. 1-(p-Anisyl)-2-n-hexyl-1H-indole (**4h**).[22]*

Following the general procedure, indole **4h** (113 mg, 75%) was obtained as a yellow oil after purification by column chromatography (*n*-hexane/EtOAc 500:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (m, 1H), 7.33–7.23 (m, 2H), 7.19–6.99 (m, 5H), 6.43 (s, 1H), 3.91 (s, 3H), 2.67–2.57 (t, $J = 7.4$ Hz, 2H), 1.69–1.55 (m, 2H), 1.28 (s, 6H), 0.90 (t, $J = 5.9$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 142.3, 138.6, 130.7, 129.4, 128.0, 120.8, 119.7, 119.5, 114.5, 109.9, 99.6, 55.5, 31.5, 28.9, 28.6, 27.0, 22.5, 14.1. IR (KBr): 3050, 2928, 2857, 1580, 1547, 1460, 1294, 1211, 1036, 831, 778, 742 cm^{-1}. MS (EI) *m/z* (relative intensity) 307 (51) [M$^+$], 250 (31), 237 (100), 205 (29), 192 (11), 43 (15). HR-MS (EI) *m/z* calcd for $C_{21}H_{25}NO$ 307.1936, found 307.1936.

*4.1.9. 1-Naphthyl-2-phenyl-1H-indole (**4i**)*

Following the general procedure, indole **4i** (124 mg, 78%) was obtained as a yellow solid (m.p. 73–74 °C) after purification by column chromatography (*n*-hexane/EtOAc 500:1). ^{1}H NMR



Scheme 4. Nickel-catalyzed sequential synthesis of chloro-substituted indoles **4p**–**4r**.

(300 MHz, $CDCl_3$): δ 7.98–7.88 (m, 2H), 7.74 (m, 1H), 7.55–7.42 (m, 3H), 7.42–7.30 (m, 2H), 7.26–7.04 (m, 7H), 6.94 (d, J = 0.8 Hz, 1H), 6.82 (dd, J = 8.2, 0.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1, 140.2, 135.3, 134.3, 132.5, 131.3, 128.6, 128.3, 128.2, 128.2, 128.1, 127.3, 127.2, 127.1, 126.5, 125.5, 123.6, 122.2, 120.6, 120.5, 111.2, 103.2. IR (KBr): 3053, 1599, 1509, 1460, 1403, 1317, 1215, 1017, 796, 747, 695 cm^{-1}. MS (EI) m/z (relative intensity) 319 (100) [M$^+$], 302 (4), 289 (3), 241 (8), 215 (5), 190 (2). HR-MS (EI) m/z calcd for $C_{24}H_{17}N$ 319.1361, found 319.1364.

4.1.10. 1-Mesityl-2-phenyl-1H-indole (**4j**).[17]

Following the general procedure, indole **4j** (124 mg, 81%) was obtained as a yellow oil after purification by column chromatography (*n*-hexane/EtOAc 500:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (dd, J = 6.2, 2.8 Hz, 1H), 7.43–7.18 (m, 7H), 7.03 (s, 2H), 7.00–6.90 (m, 2H), 2.42 (s, 3H), 1.93 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.5, 138.0, 137.9, 136.9, 133.9, 132.8, 129.2, 128.2, 128.2, 127.4, 127.2, 122.1, 120.4, 120.2, 110.5, 102.0, 21.1, 17.7. IR (KBr): 3054, 3027, 2919, 1604, 1486, 1371, 1209, 1030, 854, 793, 741, 696 cm^{-1}. MS (EI) m/z (relative intensity) 311 (100) [M$^+$], 310 (17), 296 (20), 237 (13). HR-MS (ESI) m/z calcd for $[C_{23}H_{21}N + H]^+$ 312.1747, found 312.1741.

4.1.11. 2-Phenyl-1-(3-pyridyl)- 1H-indole (**4k**)

Following the general procedure, indole **4k** (98 mg, 74%) was obtained as a white oil after purification by column chromatography (*n*-hexane/EtOAc 500:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.70–8.55 (m, 2H), 7.73 (m, 1H), 7.55 (m, 1H), 7.41–7.18 (m, 9H), 6.87 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.9, 148.0, 140.6, 138.7, 135.2, 135.1, 131.8, 129.0, 128.5, 128.4, 127.6, 123.7, 122.8, 121.2, 120.7, 110.0, 104.7. IR (KBr): 3053, 1482, 1426, 1326, 1208, 1024, 798, 749, 703 cm^{-1}. MS (EI) m/z (relative intensity) 270 (100) [M$^+$], 241 (8), 216 (3), 190 (4), 165 (12), 134 (11). HR-MS (EI) m/z calcd for $C_{19}H_{14}N_2$ 270.1157, found 270.1161.

4.1.12. 1-Benzyl-2-phenyl-1H-indole (**4l**).[17]

Following the general procedure, indole **4l** (120 mg, 85%) was obtained as a white solid (m.p. 95–96 °C) after purification by column chromatography (*n*-hexane/EtOAc 500:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (dd, J = 5.9, 0.8 Hz, 1H), 7.36–7.14 (m, 11H), 7.07–7.02 (m, 2H), 6.66 (s, 1H), 5.37 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.8, 138.2, 138.0, 132.7, 129.2, 128.7, 128.5, 128.3, 128.0, 127.1, 126.0, 121.9, 120.5, 120.1, 110.5, 102.3, 47.7. IR (KBr): 3056, 3029, 2917, 1603, 1488, 1454, 1348, 1312, 1163, 730, 698, 670 cm^{-1}. MS (EI) m/z (relative intensity) 283 (50) [M$^+$], 165 (12), 91 (100), 65 (9). HR-MS (ESI) m/z calcd for $[C_{21}H_{17}N + H]^+$ 284.1434, found 284.1434.

4.1.13. 1-Benzyl-2-n-hexyl-1H-indole (**4m**).[21c]

Following the general procedure, indole **4m** (95 mg, 67%) was obtained as a white solid (m.p. 68–69 °C) after purification by column chromatography (*n*-hexane/EtOAc 500:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (m, 1H), 7.36–7.06 (m, 6H), 6.98 (d, J = 8.1 Hz, 2H), 6.38 (s, 1H), 5.34 (s, 2H), 2.69 (t, J = 7.8 Hz, 2H), 1.82–1.61 (m, 2H), 1.48–1.19 (m, 6H), 1.02–0.81 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.4, 138.0, 137.1, 128.7, 128.2, 127.2, 125.9, 120.7, 120.0, 119.4, 109.3, 99.3, 46.3, 31.6, 29.0, 28.4, 26.7, 22.5, 14.1. IR (KBr): 3031, 2953, 2921, 2851, 1650, 1541, 1453, 1352, 1309, 1250, 773, 733, 697 cm^{-1}. MS (EI) m/z (relative intensity) 291 (70) [M$^+$], 234 (32), 221 (94), 130 (23), 91 (100), 65 (14). HR-MS (EI) m/z calcd for $C_{21}H_{25}N$ 291.1987, found 291.1978.

4.1.14. 1-n-Hexyl-2-phenyl-1H-indole (**4n**).[17]

Following the general procedure, indole **4n** (102 mg, 74%) was obtained as a yellow oil after purification by column chromatography (*n*-hexane/EtOAc 500:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, J = 7.6 Hz, 1H), 7.62–7.43 (m, 6H), 7.32 (m, 1H), 7.26–7.19 (m, 1H), 6.62 (s, 1H), 4.29–4.15 (m, 2H), 1.86–1.70 (m, 2H), 1.30–1.22 (m, 6H), 0.91 (t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.3, 137.3, 133.3, 129.4, 128.4, 128.2, 127.8, 121.4, 120.5, 119.7, 110.0, 102.0, 43.9, 31.2, 29.9, 26.4, 22.4, 13.9. IR (KBr): 3056, 2954, 2859, 1646, 1462, 1350, 1313, 1166, 744, 699 cm^{-1}. MS (EI) m/z (relative intensity) 277 (44) [M$^+$], 221 (11), 206 (100), 204 (15), 178 (12), 165 (19). HR-MS (ESI) m/z calcd for $[C_{20}H_{23}N + H]^+$ 278.1903, found 278.1900.

4.1.15. 1-n-Octyl-2-phenyl-1H-indole (**4o**).[17]

Following the general procedure, indole **4o** (120 mg, 80%) was obtained as a yellow solid after purification by column chromatography (*n*-hexane/EtOAc 500:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J = 7.8 Hz, 1H), 7.59–7.36 (m, 6H), 7.26 (m, 1H), 7.15 (m, 1H), 6.55 (s, 1H), 4.16 (t, J = 7.7 Hz, 2H), 1.77–1.65 (m, 2H), 1.34–1.09 (m, 10H), 0.89 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.3, 137.3, 133.3, 129.4, 128.4, 128.2, 127.9, 121.4, 120.5, 119.7, 110.0, 102.0, 43.9, 31.7, 29.9, 29.1, 29.0, 26.7, 22.6, 14.1. IR (KBr): 3030, 2926, 2855, 1606, 1462, 1350, 1163, 1016, 786, 743, 700 cm^{-1}. MS (EI) m/z (relative intensity) 305 (43) [M$^+$], 207 (16), 206 (100), 193 (13), 178 (12), 165 (9). HR-MS (ESI) m/z calcd for $[C_{22}H_{27}N + H]^+$ 306.2216, found 306.2218.

4.1.16. 6-Chloro-2-phenyl-1-p-tolyl-1H-indole (**4p**)

Following the general procedure, indole **4p** (113 mg, 72%) was obtained as a white solid (m.p. 112–113 °C) after purification by column chromatography (*n*-hexane/EtOAc 500:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, J = 8.4 Hz, 1H), 7.30–7.19 (m, 8H), 7.16–7.05 (m, 3H), 6.75 (s, 1H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.5, 139.5, 137.5, 135.3, 132.1, 130.1, 128.8, 128.2, 128.0, 127.6, 127.5, 126.7, 121.2, 121.2, 110.7, 103.2, 21.2. IR (KBr): 3057, 3034, 1604, 1514, 1457, 1378, 1071, 927, 759, 732, 695 cm^{-1}. MS (EI) m/z (relative intensity) 317 (100) [M$^+$], 281 (23), 267 (14), 239 (3), 179 (6), 165 (8). HR-MS (EI) m/z calcd for $C_{21}H_{16}ClN$ 317.0971, found 317.0968.

4.1.17. 1-Benzyl-6-chloro-2-phenyl-1H-indole (**4q**)

Following the general procedure, indole **4q** (115 mg, 73%) was obtained as a white solid (m.p. 130–131 °C) after purification by column chromatography (*n*-hexane/EtOAc 500:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, J = 8.4 Hz, 1H), 7.44–7.35 (m, 12H), 6.61 (s, 1H), 5.31 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.6, 138.4, 137.6, 132.2, 129.2, 128.9, 128.6, 128.3, 127.7, 127.3, 126.9, 125.9, 121.4, 120.9, 110.5, 102.4, 47.8. IR (KBr): 3060, 3030, 1605, 1460, 1384, 1073, 916, 760, 732, 698 cm^{-1}. MS (EI) m/z (relative intensity) 317 (80) [M$^+$], 226 (8), 199 (12), 91 (100), 65 (15), 43 (13). HR-MS (EI) m/z calcd for $C_{21}H_{16}ClN$ 317.0971, found 317.0971.

4.1.18. 6-Chloro-1-n-octyl-2-phenyl-1H-indole (**4r**)

Following the general procedure, indole **4r** (91 mg, 53%) was obtained as a yellow oil after purification by column chromatography (*n*-hexane/EtOAc 500:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.34 (m, 7H), 7.10 (d, J = 8.4 Hz, 1H), 6.48 (s, 1H), 4.09 (t, J = 7.5 Hz, 2H), 1.69–1.63 (m, 2H), 1.32–1.10 (m, 10H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1, 137.8, 132.8, 129.4, 128.5, 128.1, 127.3, 126.7, 121.3, 120.3, 110.0, 102.1, 44.1, 31.7, 29.8, 29.0, 28.9, 26.6, 22.6, 14.1. IR (KBr): 3062, 2926, 2856, 1607, 1463, 1341, 1302, 1068, 919, 810, 759, 699 cm^{-1}. MS (EI) m/z (relative intensity) 339 (81) [M$^+$], 254 (11), 242 (38), 240 (100), 227 (23), 205 (88). HR-MS (ESI) m/z calcd for $[C_{22}H_{26}ClN + H]^+$ 340.1827, found 340.1814.

Acknowledgements

Support by the DFG, and the Chinese Scholarship Council (fellowship to WS) is gratefully acknowledged.

Appendix. Supplementary material

Supplementary data related to this article can be found online at doi:10.1016/j.jorganchem.2010.08.047.

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