Thieme Chemistry Journal Awardees – Where Are They Now? Palladium-Catalyzed N-Arylation–Hydroamination Sequence for the Synthesis of Indoles with Sterically Demanding N-Substituents

Lutz Ackermann,* René Sandmann, Mikhail V. Kondrashov

Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Goettingen, Tammannstr. 2, 37077 Goettingen, Germany
Fax +49(551)396777; E-mail: Lutz.Ackermann@chemie.uni-goettingen.de

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Abstract: A palladium-catalyzed sequence consisting of an N-arylation and an intramolecular hydroamination sets the stage for a modular synthesis of indoles bearing sterically hindered N-substituents.

Key words: amination, heteroarenes, hydroamination, indoles, palladium

Due to their remarkable range of biological activities, indoles are among the most abundant heterocyclic substructures in drug discovery. As a consequence, a continuing demand exists for generally applicable syntheses of this heteroarene.[1–5] Recently, significant progress has been accomplished, in particular, through the application of transition-metal catalysis.[6–13] Although these efforts greatly expanded the generality of catalytic indole syntheses, the preparation of derivatives bearing sterically demanding N-substituents continues to represent a significant challenge. For example, functionalizations of free (NH) indoles via substitution reactions at nitrogen are hampered by their relatively low nucleophilicities. However, a major advance was recently achieved by Willis and coworkers with an application of their elegant palladium-catalyzed N-annulation[14] to the preparation of indoles with sterically demanding N-substituents.[15] Furthermore, Schirok reported on the microwave-assisted preparation of N-*tert*-alkylated indoles through the conversion of *ortho*-(haloaryl)oxiranes with primary amines at 240 °C.[16]

Previously, we reported on palladium-[17,18] and copper-catalyzed[17] syntheses of diversely substituted indoles[19] employing *ortho*-dihaloarenes or *ortho*-alkynylhaloarenes, such as chlorides **1** (Scheme 1). This reaction sequence consisting of an intermolecular N-arylation and an intramolecular hydroamination laid the foundation for a modular access to N-substituted indoles. Considering the valuable biological activities[20] of indoles with sterically hindered N-substituents as well as the limitations associate with their syntheses,[14,16] we became interested in exploring the use of our protocol in this challenging task, the results of which we wish to report herein.

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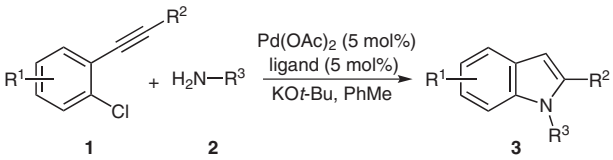
Lutz Ackermann was educated at the Christian-Albrechts-University Kiel, and obtained his Ph.D. in 2001 under the supervision of Alois Fürstner, Max-Planck-Institut für Kohlenforschung in Mülheim/Ruhr. He was a DAAD postdoctoral fellow in the laboratories of Robert G. Bergman at the University of California at Berkeley, USA, and initiated his independent career – supported by the Emmy Noether program (DFG) – in 2003 at the Ludwig-Maximilians-Universität Munich. In 2007, he became full professor at the Georg-August-Universität Göttingen. The unifying theme of his research program is represented by the development and applications of novel concepts for efficient catalytic processes. Lutz Ackermann was visiting professor at the Università degli Studi di Milano, Italy, as well as the University of Wisconsin at Madison, USA, and his recent awards include a Thieme Journal Award, an ORCHEM-prize, an ADUC-prize, and a Dozentenstipendium (FCI).

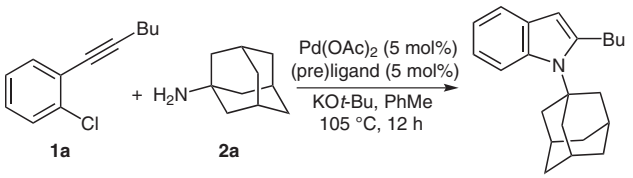


Scheme 1 Palladium-catalyzed synthesis of indoles **3**

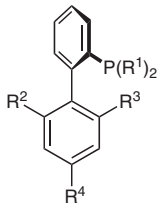
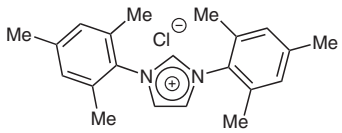
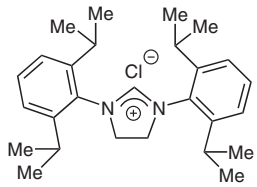
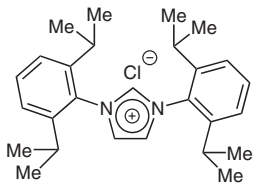
At the outset of our studies, we explored palladium complexes derived from various phosphine or N-heterocyclic carbene[21–23] ligands in the conversion of sterically hindered 1-AdNH$_2$ (**2a**, Table 1). Unfortunately, diphosphines **4** and **5** gave only rise to unsatisfactory results (entries 2 and 3). On the contrary, electron-rich monophosphines **6** and **7a–d**[24] (entries 4–8) provided improved isolated yields of desired indole **3a**. Interestingly, most efficient catalysis was achieved with N-heterocyclic carbene precursors (entries 9–11), with sterically demanding imidazolium salt **10** leading to optimal results (entry 11).

With a highly active catalytic system in hand, we probed its scope in the synthesis of indoles bearing sterically demanding N-substituents (Table 2).[25,26] *ortho*-Alkynyl-

Table 1 Evaluation of (Pre)Ligands in the Synthesis of Indole **3a**[a]



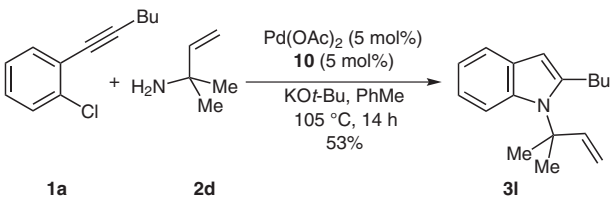
1a **2a** **3a**

Entry	(Pre)Ligand			Yield (%)
1	–		–	–
2	dppf		**4**	–
3	BINAP		**5**	(5)[b]
4	PCy_3		**6**	38
5		R^1 = *t*-Bu, R^2 = R^3 = R^4 = H	**7a**	30
6		R^1 = Cy, R^2 = NMe_2, R^3 = R^4 = H	**7b**	51
7		R^1 = Cy, R^2 = R^3 = OMe, R^4 = H	**7c**	59
8		R^1 = Cy, R^2 = R^3 = R^4 = *i*-Pr	**7d**	45
9			**8**	(9)[b]
10			**9**	39
11			**10**	62

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (5.0 mol%), (pre)ligand (5.0 mol%), KO*t*-Bu (1.5 mmol), PhMe (1.5 mL), 105 12 h; yields of isolated products.
[b] GC conversion.

chloroarenes **1** with both alkyl (Table 1, entry 11, and Table 2, entry 6) or aryl substituents (Table 2, entries 1–5, 7, and 8) at the alkyne were converted regioselectively with bulky (1-Ad)NH_2 (**2a**). Importantly, a comparable efficacy was observed with sterically demanding amine *t*-BuNH_2 (**2b**, entry 9). Furthermore, the protocol was not restricted to the use of more nucleophilic alkyl-substituted amines, but enabled also the high-yielding synthesis of indole **3k** displaying a sterically encumbered N-aryl substituent (entry 10).

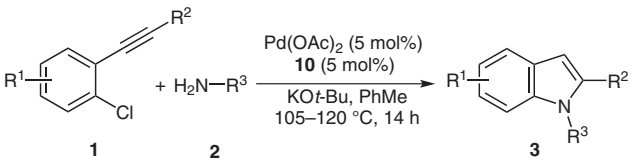
A variety of naturally occurring indole derivatives feature reverse prenyl substituents. For example, fungal natural products asterriquinones[20] exhibit valuable biological – including antitumor – activities, and are decorated with an N-reverse prenyl group. Therefore, we explored the use of amine **2d** under the optimized reaction conditions for the synthesis of this structural motif, and were pleased to observe the regioselective formation of indole **3l** (Scheme 2).



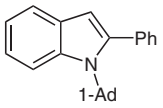
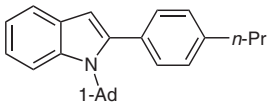
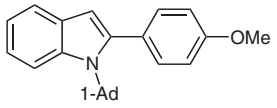
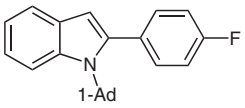
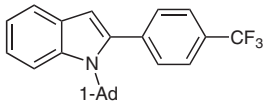
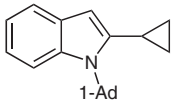
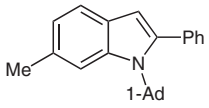
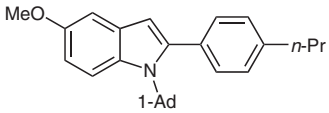
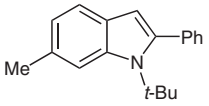
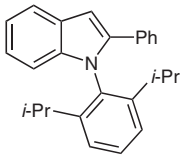
1a **2d** **3l**

Scheme 2 Synthesis of indole **3l** bearing an N-reverse prenyl group

Table 2 Scope of Palladium-Catalyzed Synthesis of Indoles with Sterically Hindered N-Substituents[a]



1 2 3

Entry	R^3	Temp (°C)	Product		Yield (%)
1	1-Ad **2a**	120		**3b**	83
2	1-Ad **2a**	120		**3c**	88
3	1-Ad **2a**	120		**3d**	79
4	1-Ad **2a**	120		**3e**	94
5	1-Ad **2a**	120		**3f**	83
6	1-Ad **2a**	105		**3g**	80
7	1-Ad **2a**	120		**3h**	94
8	1-Ad **2a**	120		**3i**	55
9	*t*-Bu **2b**	120		**3j**	90
10	2,6-(*i*-Pr)$_2$C$_6$H$_3$ **2c**	105		**3k**	94

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), $Pd(OAc)_2$ (5.0 mol%), **10** (5.0 mol%), KO*t*-Bu (1.5 mmol), PhMe (1.5 mL), 14 h; yields of isolated products.

In summary, we have reported on a modular synthesis of indoles bearing sterically hindered N-substituents. Thus, a palladium-catalyzed sequence consisting of an intermolecular N-arylation and an intramolecular hydroamination enabled a regioselective N-annulation, which was found to be applicable to the preparation of an N-reverse prenyl-substituted indole as well.

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(25) **Representative Procedure – Synthesis of 3a (Table 1, Entry 11)**
To a suspension of **2a** (91.0 mg, 0.60 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol%), **10** (10.6 mg, 0.025 mmol, 5.0 mol%), and KO*t*-Bu (168.0 mg, 1.50 mmol) in dry toluene (1.5 mL) was added **1a** (96.0 mg, 0.50 mmol), and the mixture was stirred for 12 h at 105 °C. After the reaction mixture was cooled to ambient temperature, H_2O (25 mL) was added. The aqueous layer was extracted with Et_2O (3 × 30 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The remaining residue was purified by column chromatography on SiO_2 (*n*-hexane) to yield **3a** (95.0 mg, 62%) as a white solid (mp 143–145 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.1 Hz, 1 H), 7.51–7.48 (m, 1 H), 7.08–6.98 (m, 2 H), 6.29 (s, 1 H), 3.01 (t, *J* = 7.2 Hz, 2 H), 2.59 (d, *J* = 3.0 Hz, 6 H), 2.27 (s, 3 H), 1.81–1.68 (m, 8 H), 1.49–1.39 (m, 2 H), 0.98 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (125 MHz, APT, $CDCl_3$): δ = 142.8 (C_q), 136.4 (C_q), 129.2 (C_q), 119.8 (CH), 119.3 (CH), 118.4 (CH), 115.2 (CH), 103.0 (CH), 61.0 (C_q), 42.3 (CH_2), 36.4 (CH_2), 33.2 (CH_2), 32.0 (CH_2), 30.3 (CH), 22.9 (CH_2), 14.2 (CH_3). IR (KBr): 3429, 2918, 2855, 2361, 2337, 1653, 1457, 777, 746, 731 cm^{-1}. MS (EI): *m/z* (%) = 307 (22) [M$^+$], 265 (6), 135 (100), 107 (5). ESI-HRMS: *m/z* calcd for $C_{22}H_{30}N$: 308.2373; found: 308.2374.
(26) **Analytical Data**
Indole **3j**: mp 136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.34 (m, 7 H), 6.98–6.95 (m, 1 H), 6.27 (s, 1 H), 2.54 (s, 3 H), 1.61 (s, 9 H). ^{13}C NMR (75 MHz, APT, $CDCl_3$): δ = 141.2 (C_q), 138.3 (C_q), 137.7 (C_q), 130.1 (2 × CH), 127.3 (CH), 126.8 (2 × C_q), 121.0 (CH), 120.1 (CH), 115.1 (CH), 106.0 (CH), 58.7 (C_q), 32.0 (CH_3), 22.3 (CH_3). IR (KBr): 3421, 3003, 2968, 2918, 2356, 1653, 1540, 1443, 1332, 1206, 1104, 1028, 814, 705, 607 cm^{-1}. MS (EI): *m/z* (%) = 263 (22) [M$^+$], 235 (4), 220 (4), 207 (100), 178 (5), 152 (2). ESI-HRMS: *m/z* calcd for $C_{19}H_{21}NNa$: 286.1566; found: 286.1567.
Indole **3l**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.61 (m, 1 H), 7.50–7.46 (m, 1 H), 7.04–6.99 (m, 2 H), 6.38–6.28 (m, 2 H), 5.16–5.10 (m, 2 H), 2.90 (t, *J* = 7.2 Hz, 2 H), 1.87–1.68 (m, 8 H), 1.49–1.39 (m, 2 H), 0.97 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, APT, $CDCl_3$): δ = 147.4 (CH_2), 143.2 (C_q), 137.3 (C_q), 128.9 (C_q), 119.8 (CH), 119.5 (CH), 118.8 (CH), 114.5 (CH), 111.4 (CH), 102.4 (CH), 62.0 (C_q), 32.2 (CH_2), 30.8 (CH_2), 29.5 (CH_3), 22.8 (CH_2), 14.0 (CH_3). IR (KBr): 3048, 2959, 2932, 2872, 1456, 1379, 1291, 1265, 1184, 918, 778, 738, 704 cm^{-1}. MS (EI): *m/z* (%) = 241 (60) [M$^+$], 190 (9), 173 (29), 131 (100), 115 (2). ESI-HRMS: *m/z* calcd for $C_{17}H_{24}N$: 242.1903; found: 242.1906.