One-Pot 2-Aryl/Vinylindole Synthesis Consisting of a Ruthenium-Catalyzed Hydroamination and a Palladium-Catalyzed Heck Reaction Using 2-Chloroaniline

Lutz Ackermann,* Andreas Althammer

Department Chemie und Biochemie, Ludwig-Maximilians-Universität München, Butenandtstrasse 5-13, Haus F, 81377 München, Germany
Fax +49(89)218077425; E-mail: Lutz.Ackermann@cup.uni-muenchen.de

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Dedicated to Professor Richard F. Heck in recognition of his seminal contributions to the development of palladium-catalyzed coupling reactions

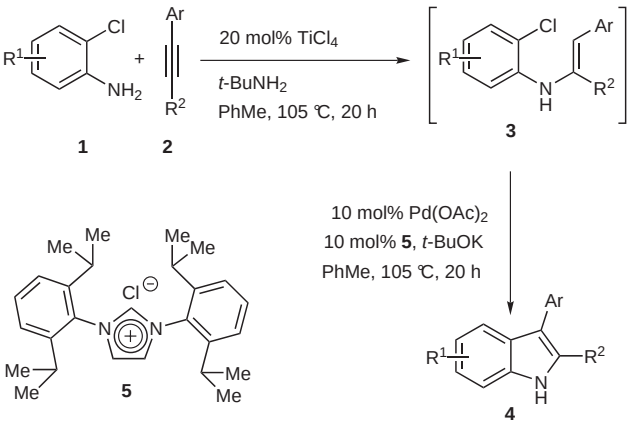
Abstract: A one-pot synthesis of 2-aryl- and 2-vinylindoles based on a ruthenium-catalyzed hydroamination and a palladium-catalyzed intramolecular Heck reaction is reported. The ruthenium-catalyzed addition reaction was applied to terminal as well as internal alkynes. Intramolecular Heck reactions of the resulting 2-chloroanilino enamines were achieved using an in situ generated palladium complex derived from an *N*-heterocyclic carbene.

Key words: aryl chlorides, Heck reaction, hydroamination, palladium, ruthenium

The palladium-catalyzed coupling between an alkene and an aryl or a vinyl halide,[1,2] often referred to as the Heck reaction, is one of the most useful and versatile methodologies for the carbon–carbon bond formation involving sp^2-hybridized carbons.[3] Intramolecular Heck reactions allowed for the development of protocols for the synthesis of diversely substituted carbo- and heterocycles.[4] Cyclization reactions of 2-haloanilino enamines proved valuable tools for the synthesis of differently substituted indole derivatives.[5] A significant extension of this approach was established through the in situ preparation of the corresponding enamines via condensation of 2-iodoanilines with, preferably cyclic, ketones.[6]

Recently, we reported on a novel one-pot indole synthesis, which relied on the in situ formation of 2-bromoanilino enamines via $TiCl_4$-catalyzed[7–9] hydroamination reactions[10] of alkynes with 2-bromoaniline.[11] Aryl chlorides are arguably the most useful single class of electrophiles due to their lower cost and the significantly wider diversity of available compounds.[12] Therefore, we developed a protocol for a one-pot indole synthesis starting from more readily available 2-chloroaniline derivatives **1** (Scheme 1).[13–15] The intramolecular Heck reactions of 2-chloroanilino enamines **3** were accomplished with the use of a palladium complex modified with *N*-heterocyclic carbene[16] precursor **5**. The regioselective titanium-catalyzed hydroamination reaction of alkyne **2** set the stage for the selective formation of 3-aryl-substituted indole derivatives **4**.[13] This regioselectivity complements Larock's annulation of alkynes by 2-haloaniline derivatives.[17,18]

As part of our program directed towards the development of protocols for efficient syntheses of selectively functionalized heterocycles,[19–24] we became interested in probing hydroamination methodologies based on late transition-metal catalysts for novel one-pot indole syntheses. Ruthenium[25–30] and platinum[31] compounds emerged as highly active catalysts for the intermolecular hydroamination[32] of alkynes.[10c] However, $Ru_3(CO)_{12}$- and $PtBr_2$-catalyzed intermolecular hydroamination reactions were predominantly[33] applied to addition reactions of terminal alkynes.[28,31] Herein, we report a one-pot synthesis of 2-aryl- and 2-vinylindoles, which relies on a regioselective $Ru_3(CO)_{12}$-catalyzed hydroamination reaction and a palladium-catalyzed intramolecular Heck reaction of the resulting 2-chloroanilino enamine.



Scheme 1 One-pot indole synthesis consisting of a titanium-catalyzed hydroamination and a palladium-catalyzed Heck reaction

On the outset of our studies we tested a variety of protocols for intermolecular hydroamination reactions for a regioselective one-pot indole synthesis. A potential addition of 2-chloroaniline (**1a**) onto either terminal alkyne **2a** or internal alkyne **2b** employing $FeCl_3(H_2O)_6$[34] was not viable (Scheme 2, Table 1, entries 1, and 2). On the contrary, the platinum-catalyzed hydroamination[31] with 2-chloroaniline (**1a**) proved applicable to the functionalization of terminal alkyne **2a** (entry 3). However, a double

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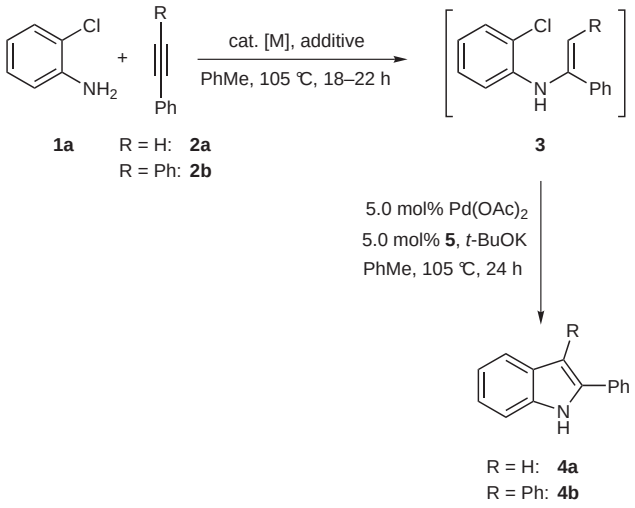
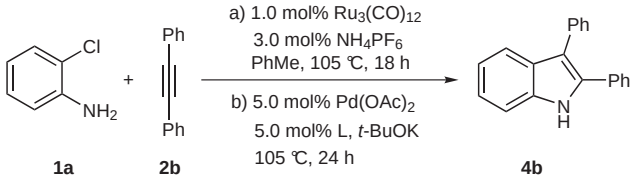
Table 1 Evaluation of Late Transition-Metal-Catalyzed Hydroamination Protocols for a One-Pot Indole Synthesis (see Scheme 2)[a]

Entry	Hydroamination reaction conditions	R	Isolated yield (%)
1	$FeCl_3 \cdot 6H_2O$ (5.0 mol%)	H (**2a**)	–[b]
2	$FeCl_3 \cdot 6H_2O$ (5.0 mol%)	Ph (**2b**)	–[b]
3	$PtCl_2$ (3.0 mol%)	H (**2a**)	–
4	$PtCl_2$ (3.0 mol%)	Ph (**2b**)	24 (**4b**)
5	$Ru_3(CO)_{12}$ (1.0 mol%), NH_4PF_6 (3.0 mol%)	H (**2a**)	60 (**4a**)
6	$Ru_3(CO)_{12}$ (1.0 mol%), NH_4PF_6 (3.0 mol%)	Ph (**2b**)	89 (**4b**)

[a] Reaction conditions: **1a** (1.0 mmol), **2** (1.5 mmol), [M], additive, PhMe (1 mL), 105 °C, 18–22 h; $Pd(OAc)_2$ (5.0 mol%), **5** (5.0 mol%), *t*-BuOK (2.0 mmol), PhMe (2 mL), 24 h.
[b] No conversion of **1a** as judged by GC-MS analysis.



Scheme 2



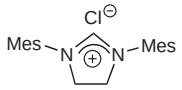
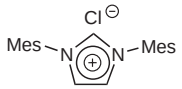
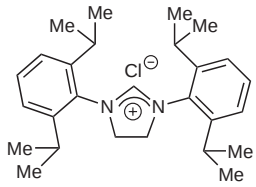
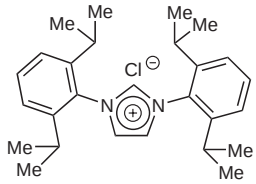
Scheme 3

alkenylation of aniline **1a** led to the formation of numerous products under the reaction conditions of the palladium-catalyzed Heck cyclization. Interestingly, we observed an unprecedented platinum-catalyzed intermolecular hydroamination of an internal alkyne (entry 4). Thus, the addition of aniline **1a** onto tolan (**2b**) provided the corresponding enamine **3**, along with its tautomeric imine, in high yield as determined by GC analysis. Unfortunately, the isolated yield of product **4b** was not satisfactory (entry 4).

The $Ru_3(CO)_{12}$-catalyzed hydroamination[26] of terminal alkyne **2a** with aniline **1a** yielded selectively the formal Markovnikov addition product. It proved also viable to perform a subsequent intramolecular palladium-catalyzed Heck reaction of the resulting 2-chloroanilino enamine **3** in the same reaction flask, yielding indole **4a** regioselectively in good yield (entry 5). Additionally, the $Ru_3(CO)_{12}$-based hydroamination protocol allowed for heterofunctionalization of internal alkyne **2b**. Subsequent palladium-catalyzed Heck reaction led to indole **4b** in high yield of isolated product (entry 6).

With an efficient protocol for a one-pot indole synthesis using 2-chloroaniline (**1a**) in hand, we probed the influence of various stabilizing ligands on the palladium-catalyzed intramolecular Heck reaction of 2-chloroanilino enamine **3**. Under otherwise identical reaction conditions,

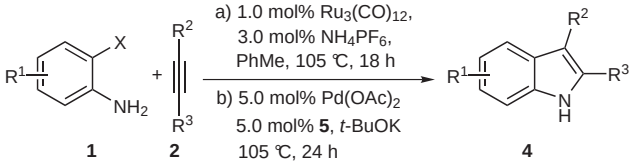
Table 2 Influence of Different Ligands on the One-Pot Indole Synthesis (see Scheme 3)[a]

Entry	Ligand L		Isolated yield of **4b** (%)
1	PPh_3	**6**	24
2		**7**	15
3		**8**	19
4		**9**	31
5		**5**	89

[a] Reaction conditions: **1a** (1.0 mmol), **2b** (1.5 mmol), $Ru_3(CO)_{12}$ (1.0 mol%), NH_4PF_6 (3.0 mol%), PhMe (1 mL), 105 °C, 18 h; $Pd(OAc)_2$ (5.0 mol%), L (5.0 mol%), *t*-BuOK (2.0 mmol), PhMe (2 mL), 24 h. Mes = 2,4,6-$Me_3C_6H_2$.[36]

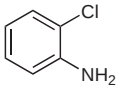
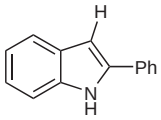
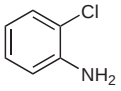
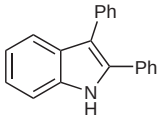
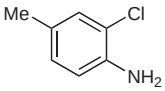
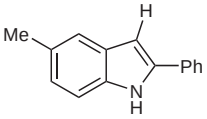
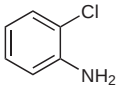
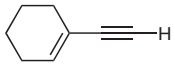
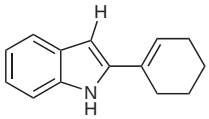
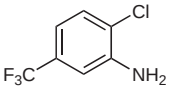
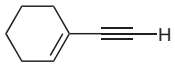
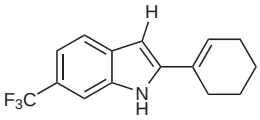
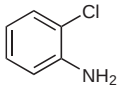
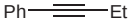
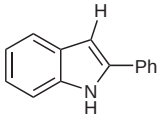
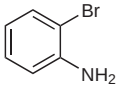
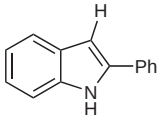
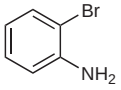
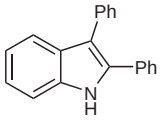
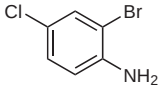
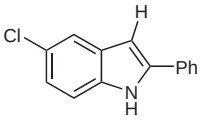
phosphine ligand **6** gave rise to lower yields of isolated product (Scheme 3, Table 2, entry 1).[35] Among different precursors for *N*-heterocyclic carbenes (entries 2–5), sterically hindered imidazolium chloride **5** led to most efficient catalysis (entry 5).

Subsequently, the scope of the one-pot indole synthesis was evaluated (Scheme 4, Table 3). Importantly, the



Scheme 4

Table 3 Scope of the One-Pot Synthesis of Substituted Indole Derivatives (Scheme 4)[a]

Entry	Aniline		Alkyne		Indole		Isolated yield (%)
1		**1a**		**2a**		**4a**	<5[b]
2							60
3		**1a**		**2b**		**4b**	<5[b]
4							89
5							60[c]
6		**1b**		**2a**		**4c**	75[d]
7		**1a**		**2c**		**4d**	49[e]
8		**1c**		**2c**		**4e**	35[e]
9		**1a**		**2d**		**4f**	–
10		**1d**		**2a**		**4a**	78
11		**1d**		**2b**		**4b**	73
12		**1e**		**2a**		**4g**	87

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.5 mmol), $Ru_3(CO)_{12}$ (1.0 mol%), NH_4PF_6 (3.0 mol%), PhMe (1 mL), 105 °C, 18 h; $Pd(OAc)_2$ (5.0 mol%), **5** (5.0 mol%), *t*-BuOK (2.0 mmol), PhMe (2 mL), 24 h.
[b] Aniline **1** (1.0 mmol), **2** (1.5 mmol), $Pd(OAc)_2$ (5.0 mol%), **5** (5.0 mol%), *t*-BuOK (2.0 mmol), PhMe (3 mL), 24 h.
[c] $Pd(OAc)_2$ (1.0 mol%), **5** (1.0 mol%).
[d] $Pd(OAc)_2$ (10.0 mol%), **5** (10.0 mol%).
[e] $Ru_3(CO)_{12}$ (3.0 mol%), NH_4PF_6 (9.0 mol%), $Pd(OAc)_2$ (10.0 mol%), **5** (10.0 mol%).

loading of palladium catalyst for the intramolecular Heck reaction could be significantly reduced (entry 5). The methodology was also applicable to the synthesis of regioselectively substituted 2-aryl- (entry 6) and 2-vinylindoles (entries 7 and 8). Hydroamination of internal alkyne **2d** with 2-chloroaniline (**1a**) was not accomplished with $Ru_3(CO)_{12}$ as catalysts (entry 9). However, 2-bromoaniline (**1d**) gave rise to the corresponding indole derivatives **4a** and **4b** in high yields of isolated product (entries 10 and 11). It is noteworthy that not only terminal alkyne **2a**, but also internal alkyne **2b** was efficiently converted. Finally, dihaloaniline **1e** was chemoselectively transformed into chloro-substituted indole **4g** (entry 12). This chemoselectivity will allow for further functionalization reactions of the resulting indole derivatives.

In summary, we report on a one-pot synthesis of 2-aryl- and 2-vinylindoles consisting of a $Ru_3(CO)_{12}$-catalyzed hydroamination and an intramolecular palladium-catalyzed Heck reaction employing 2-chloroaniline. Protocols for $Ru_3(CO)_{12}$- and $PtCl_2$-catalyzed hydroamination reactions were found applicable to addition reactions of an internal alkyne. A bulky imidazolium salt preligand enabled most efficient intramolecular palladium-catalyzed Heck reactions of aryl chlorides.

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(36) **Representative Procedure: Synthesis of 2,3-Diphenylindole (4b)**
2-Chloroaniline (**1a**; 133 mg, 1.04 mmol), and tolan (**2b**; 267 mg, 1.50 mmol) were added to a solution of $Ru_3(CO)_{12}$ (6.4 mg, 0.01 mmol, 1 mol%) and NH_4PF_6 (4.9 mg, 0.03 mmol, 3 mol%) in toluene (1 mL) and the resulting mixture was stirred for 18 h at 105 °C. Thereafter, *t*-BuOK (224 mg, 2.00 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol%), **5** (21.3 mg, 0.05 mmol, 5 mol%), and toluene (2 mL) were added and the mixture was stirred at 105 °C for 24 h. Et_2O (50 mL)

and brine (50 mL) were added to the cold suspension. The separated aqueous phase was washed with Et_2O (2 × 50 mL). Drying with $MgSO_4$ and purification by column chromatography (silica gel; *n*-pentane–Et_2O, 10:1 to 6:1) yielded 2,3-diphenylindole (**4b**; 248 mg, 89%) as a yellow solid; mp 129.8–130.0 °C. ^{1}H NMR (400 MHz): δ = 8.23 (s, 1 H), 7.71 (d, *J* = 8.6 Hz, 1 H), 7.49–7.14 (m, 13 H). ^{13}C NMR (100 MHz): δ = 135.8, 135.0, 134.0, 132.7, 130.1, 128.7, 128.6, 128.5, 128.1, 127.7, 126.2, 122.7, 120.4, 119.7, 115.0, 110.8. IR (ATR): 3396, 3052, 1600, 1533, 1455, 1439, 1371, 1328, 1249, 1152, 1070, 1011, 965, 919, 828, 763, 740, 693 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{20}H_{15}N$: 269.1204; found: 269.1202.