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Cascade Alkenyl Amination/Heck Reaction Promoted by a Bifunctional Palladium Catalyst: A Novel One-Pot Synthesis of Indoles from *o*-Haloanilines and Alkenyl Halides

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Abstract: A novel approach for the synthesis of the important indole ring is described. Indoles are obtained from *o*-bromoanilines and alkenyl halides in a Pd-catalyzed cascade process that involves an alkenyl amination followed by an intramolecular Heck reaction. The overall process represents the first example of the participation of alkenyl amination reactions in Pd-catalyzed cascade reactions. Initially, the relative reactivity of aryl and alkenyl bromides and chlorides towards Pd-catalyzed amination was investigated. Competition experiments were carried out in the presence of primary and secondary amines, and these revealed the reactivity order alkenyl bromides > aryl bromides > alkenyl chlorides > aryl chlorides, as well as very high chemoselectivity; the more reactive halide was always favored. Thereafter, optimized reaction conditions for the sequential alkenyl amination/Heck cyclization to give indoles were investigated with the model reaction of *o*-bromoaniline with α-bromostyrene. An extensive screening of ligands, bases, and reaction conditions revealed that the $[Pd_2(dba)_3]$/DavePhos, NaO*t*Bu, toluene combination at 100 °C were the optimized reaction conditions to carry out the cascade process (dba = dibenzylideneacetone, DavePhos = 2-dicyclohexylphosphino-2′-*N*,*N*-dimethylaminobiphenyl). The reaction proceeds with aryl, alkyl, and functionalized substitutents in both starting reactants. The cyclization was also studied with N-substituted *o*-bromoanilines (which would give rise to N-substituted indoles); however, in this case, indole formation occurred only with 1-substituted-2-bromoalkenes. Finally, the application of this methodology to *o*-chloroanilines required further optimization. Although the catalyst based on DavePhos failed to promote the cascade process, a catalytic combination based on $[Pd_2(dba)_3]$/X-Phos promoted the formation of the indole ring also from the less reactive chloroanilines.

Keywords: amination · enamines · Heck reaction · indoles · nitrogen heterocycles · palladium

Introduction

Palladium-catalyzed cross-coupling reactions are amongst the more powerful transformations in synthetic organic chemistry. As a result of the intense effort of many research groups over the years, a large repertoire of C–C and C–X bond-forming reactions, and highly active catalytic combinations are currently available.[1] Nevertheless, in most cases, the palladium species is used to catalyze one single reaction. However, those transformations in which the same catalytic species—a multifunctional catalyst—promotes two or more distinct reactions in a sequential manner are highly desirable.[2] Such processes make better use of the relatively expensive catalysts, eliminate the need for the isolation and purification tasks between steps, and are more atom economical, since less waste materials and solvents are produced.

In the recent years, we have been studying the palladium-catalyzed amination of alkenyl bromides[3] and chlorides.[4,5] This reaction, which is an extension of the well-developed Buchwald–Hartwig amination,[6] gives rise to enamines and imines, versatile intermediates in organic synthesis.[7] In the course of our investigation, we observed a remarkable selectivity in the amination of alkenyl bromides in the presence of aryl bromides. For instance, the competition reaction of 4-bromobiphenyl (**1**) and α-bromostyrene (**2**) affords exclusively the enamine **3** derived from the amination of the al-

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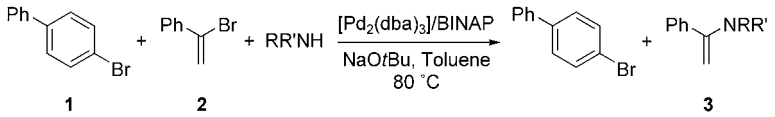
kenyl bromide; the aryl bromide is left untouched (Scheme 1).

The higher reactivity of alkenyl bromides than aryl bromides in the amination reaction is not surprising, and can be rationalized in terms of the higher tendency of alkenyl bromides to undergo oxidative addition to Pd.[8] Nevertheless, the complete chemoselectivity observed is very interesting indeed. We envisioned that this exquisite selectivity in Pd-catalyzed aminations could be exploited in sequential processes promoted by a single Pd catalyst, and involving consecutive reactions of alkenyl and aryl halides. Herein we report our efforts towards this aim.



1 2 3

Scheme 1. Selectivity in the Pd-catalyzed amination of alkenyl and aryl bromides. RR′ = morpholine, PhMeNH; dba = dibenzylideneacetone, BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl.

Abstract in Spanish: *Se describe una nueva aproximación al importante anillo de indol a partir de o-bromoanilinas y haluros de alquenilo, en un proceso en cascada catalizado por Pd, que implica la aminación del alquenilo seguida de una reacción de Heck intramolecular. El proceso en su conjunto constituye el primer ejemplo de la participación de una aminación de alquenilo en una secuencia de reacciónes en cascada catalizada por Pd. En primer lugar, se estudió la reactividad relativa de diferentes halogenuros en reacciones de aminación catalizadas por Pd. Se llevaron a cabo experimentos de competencia en presencia de aminas primarias y secundarias que revelaron el orden de reactividad siguiente: bromuros de alquenilo > bromuros de arilo > cloruros de alquenilo > cloruros de arilo, así como muy alta quimioselectividad a favor del halogenuro más reactivo. Seguidamente las condiciones apropiadas para el proceso secuencial aminación de alquenilo/reacción de Heck, se investigaron con la reacción modelo de o-bromoanilina con α-bromostireno. Tras un amplio estudio de ligandos, bases y condiciones de reacción la combinación [Pd$_2$(dba)$_3$]/DavePhos, NaOtBu, en tolueno a 100°C resulto ser la más adecuada para efectuar el proceso en cascada. La reacción transcurre con sustituyentes arilo, alquilo y funcionalizados en ambos reactivos de partida. La ciclación también fue estudiada utilizando o-bromoanilinas N-sustituidas, si bien la formación de indol solo tuvo lugar con 2-bromoalquenos monosustituidos en posición 1. Finalmente, la aplicación de esta metodología a o-cloroanilinas requirió una optimización adicional. Si bien el catalizador basado en DavePhos no fue capaz de promover el proceso en cascada, la utilización de X-Phos como ligando sí permitió obtener el anillo de indol a partir de cloroanilinas.*

Results and Discussion

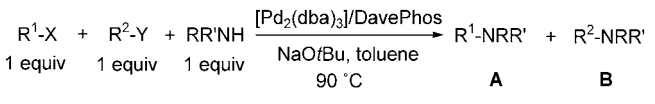
Relative reactivity of aryl and alkenyl bromides and chlorides in Pd-catalyzed amination reactions: As a continuation of our studies on the amination of alkenyl bromides, we recently reported the Pd-catalyzed amination of alkenyl chlorides.[4,9] Intrigued by the remarkable selectivity observed in the amination of alkenyl bromides versus aryl bromides, we decided to investigate a broader range of reactants that can participate in amination processes. Accordingly, we conducted similar competition experiments with different alkenyl and aryl bromides and chlorides and in the presence of three amines with different steric and electronic properties: a secondary cyclic amine such as morpholine, a secondary aromatic amine such as *N*-methylaniline, and 4-methoxybenzylamine as a typical primary amine. All the reactions were conducted with the [Pd$_2$(dba)$_3$]/DavePhos[10,24] catalytic system (dba = dibenzylideneacetone) at 90°C, which have been shown to be suitable reaction conditions for the amination of the less reactive aryl chlorides.[11]

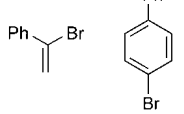
The results represented in Table 1 allowed us to establish the following relative reactivity order in the Pd-catalyzed amination reaction: alkenyl bromide > aryl bromide > alkenyl chloride > aryl chloride. It is well documented that vinyl halides are usually more reactive than the corresponding aryl halides, because vinyl halides tend to undergo oxidative addition to Pd more easily.[12,13] However, the high chemoselectivity observed is remarkable: In all the experiments carried out, the product derived from the amination of the less reactive halide of each pair was not even detected.

Synthesis of indoles by a cascade alkenyl amination/Heck cyclization: The interesting observations discussed above, prompted us to initiate research aimed at developing Pd-catalyzed cascade processes, in which several different alkenyl and aryl halides may participate in amination and other cross-coupling reactions, mainly oriented towards the synthesis of heterocycles.

As a simple model system we chose the reaction of α-bromostyrene (**2**) with *o*-bromoaniline (**4**). We anticipated that the initially formed enamine **5**, which is in tautomeric equilibrium with the more stable imine **6**, would undergo an intramolecular Heck reaction,[14] catalyzed by the same Pd system, to produce indole **7** (Scheme 2).[15,16] Although cascade processes involving a cross-coupling reaction followed by a Heck reaction are known (Suzuki–Heck,[17] Stille–Heck[18]), this strategy would represent the first example of a Pd-catalyzed sequential process involving an alkenyl amination reaction,[19] and would also provide a new approach to the synthesis of the important indole scaffold.[2–22]

Table 1. Competition experiments in Pd catalyzed amination of aryl and vinyl bromides and chlorides.[a]



Entry	R^1–X	R^2–Y	Amine	Ratio A:B[b]
1				>95:5
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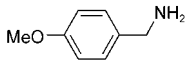
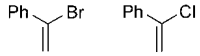
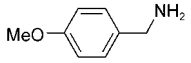
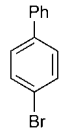
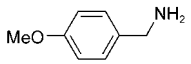
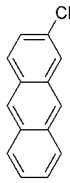
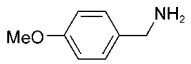
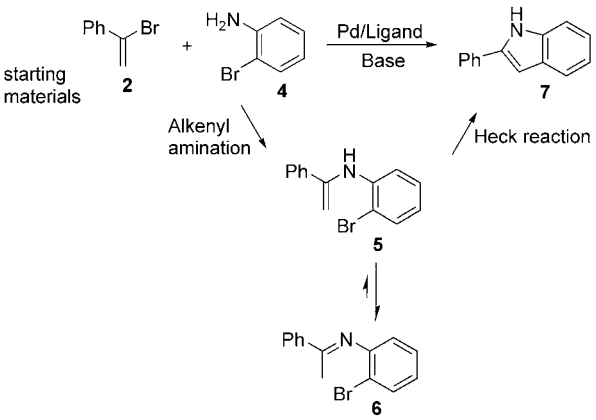
3				>95:5
4				>95:5
5				>95:5
6				>95:5
7				>95:5
8				>95:5
9				>95:5[c]
10				>95:5
11				>95:5
12				>95:5

[a] Reaction conditions: 1 equiv of R^1–X, 1 equiv of R^2-Y, 1 equiv of amine, 1.4 equiv of NaO*t*Bu, 2 mol% of $[Pd_2(dba)_3]$, 4 mol% of DavePhos, toluene (4 mL mmol^{-1}), 90 °C, 6 h. [b] Determined from the crude reaction mixture by GC and ^{1}H NMR spectroscopy. [c] 75% conversion.

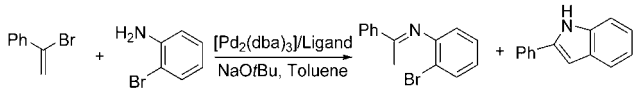
To optimize the reaction conditions for the overall transformation, we carried out a large array of experiments using catalytic combinations that had been effective in the amination of alkenyl bromides, but with larger amounts of NaO*t*Bu as base,[23] and under various reaction conditions. Representative results are depicted in Table 2.

The reaction was studied by employing several different ligands that had been effective the amination of alkenyl bromides: P(*o*-Tol)$_3$, bidentate ligands (BINAP, Xantphos),



Scheme 2. General strategy for the cascade alkenyl amination/Heck reaction.

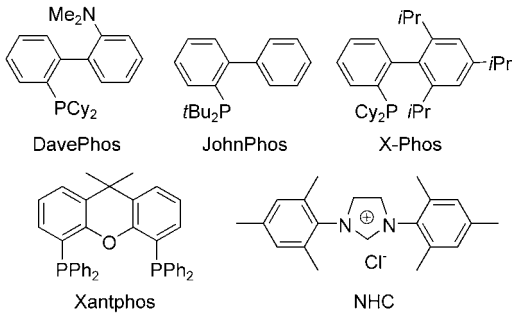
Table 2. Influence of the ligand and the reaction conditions in the cascade alkenyl amination/Heck reaction.[a]



Entry	$[Pd_2(dba)_3]$ [mol%]	Ligand	T [°C]	Conversion[b] [%] **6**/**7**
1	2	BINAP	100	100/0
2	4	BINAP	100	100/0
3	4	P(*o*-Tol)$_3$	100	100/0
4	4	DavePhos	100	0/100 (64)[c]
5	4	Xantphos	100	100/0
6	4	JohnPhos	100	100/0
7	4	X-Phos	100	0/100 (52)[c]
8	4	NHC	100	100/0
9	2	DavePhos	90	50/50
10	2	DavePhos	100	30/70
11	2	X-Phos	100	35/65
12	4	DavePhos	120	0/100 (62)[c]
13[d]	4	DavePhos	100	0/100 (50)[c]

[a] Reaction conditions: 1 equiv of **2**, 1 equiv of **4**, 3 equiv of NaO*t*Bu, 1:2 Pd/ligand ratio, toluene (4 mL mmol^{-1}), 20 h. [b] Determined from the crude reaction mixture by GC and ^{1}H NMR spectroscopy. [c] Yield of indole **7**. [d] Performed in dioxane.

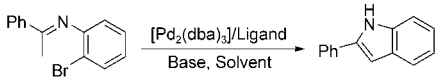
bulky electron-rich biphenyl phosphines (JohnPhos, DavePhos, X-Phos) and a *N*-heterocyclic carbene (NHC). The best results in the formation of the indole were observed



when the reactions were carried out using 4 mol% of Pd and the bulky biphenylphospane ligands DavePhos[24] and X-Phos[25] (entries 4 and 7, Table 2), although the former provided better overall yield. Catalysts based on the other ligands induced the formation of the imine **6**, but failed to promote the subsequent Heck reaction. The process also was carried out at higher temperatures and with the more polar dioxane as solvent (entries 12 and 13, Table 2) but the yield of the cascade sequence did not improve. Finally, a decrease in the Pd loading (entries 9–11, Table 2) resulted in a decrease in the overall yield.

In an attempt to improve the results of the cascade process, the second step in the sequence, the Heck reaction, was investigated independently. Thus, the Pd-catalyzed cyclization of preformed imine **6** to indole **7** was studied in the presence of DavePhos and X-Phos as supporting ligands and by employing different solvents and bases. The results are shown in Table 3. Under the reaction conditions studied,

Table 3. Optimization of the reaction conditions for the Heck cyclization.[a]



6 **7**

Entry	Ligand	Solvent	Base	Conversion to **7**[b] [%]
1	DavePhos	toluene	NaO*t*Bu	100 (64)[c]
2	DavePhos	toluene	K_3PO_4	10
3	DavePhos	toluene	Cs_2CO_3	–
4	DavePhos	toluene	$AgCO_3$	10
5	DavePhos	toluene	NaOH	10
6	DavePhos	toluene	KO*t*Bu	–
7	DavePhos	dioxane	NaO*t*Bu	100 (50)[c]
8	DavePhos	dioxane	K_3PO_4	20
9	DavePhos	dioxane	Cs_2CO_3	20
10	X-Phos	toluene	K_3PO_4	5
11	X-Phos	toluene	Cs_2CO_3	–
12	X-Phos	toluene	NaOH	5
13	X-Phos	toluene	$AgCO_3$	–

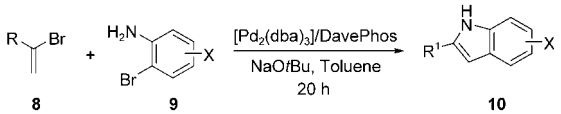
[a] Reaction conditions: 0.5 mmol **6**, 3 equiv of Base, 4 mol% of Pd, 1:2 Pd/ligand ratio, solvent (4 mL mmol^{-1}), 20 h. [b] Determined by GC. [c] Yield of indole **7**.

NaO*t*Bu provided the best results. Inorganic bases such as K_3PO_4 and $CsCO_3$ in dioxane, also promoted the Heck cyclization, although to a much lesser extent.

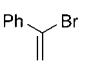
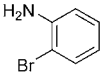
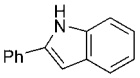
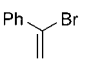
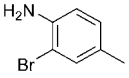
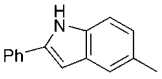
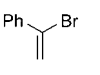
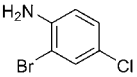
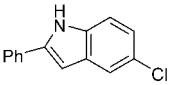
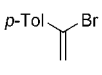
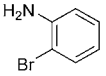
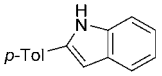
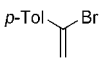
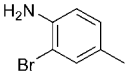
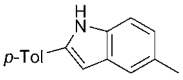
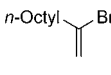
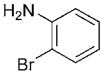
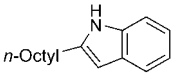
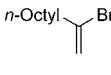
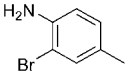
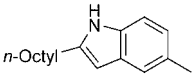
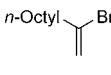
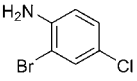
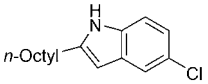
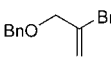
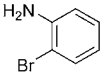
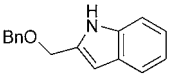
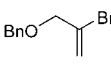
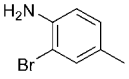
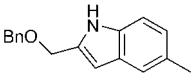
The optimized reaction conditions were then applied to a variety of alkenyl bromides **8** and bromoanilines **9** to give the corresponding 1*H*-indoles **10** in good yields (Table 4).

Bromoalkenes with aryl, alkyl, and functionalized substitutents were effective substrates for the tandem process. Noteworthy, the cyclization with alkyl-substituted bromoalkenes occurred with total regioselectivity; only the indole originating from the cyclization at the terminal position is isolated (entries f–j, Table 4). As expected from our preliminary results on the differential reactivity of halides in amination reactions, the reaction is compatible with the presence of a chloride substituent on the aromatic system (entries c, h, Table 4), an interesting feature that may allow the introduction of further substitution in the resulting indole.

Table 4. Reaction of alkenyl bromides **8** with *o*-bromoanilines **9**. Synthesis of 1*H*-indoles **10**.[a]



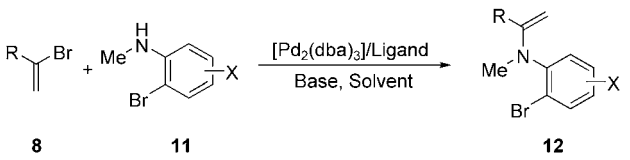
8 **9** **10**

Entry[b]	Bromide **8**	Amine **9**	Indole **10**	Yield[c] %
a				64
b				62
c				55
d				62
e				61
f				63
g				60
h				53
i				61
j				59

[a] Reaction conditions: 1 equiv of **8**, 1 equiv of **9**, 3 equiv of NaO*t*Bu, 4 mol% of Pd, 8 mol% of DavePhos, toluene (4 mL mmol^{-1}), 100 °C, 20 h. [b] Entry labels correspond to those of the product **10**. [c] Yields after flash chromatography.

Noteworthy are the relatively mild conditions and low catalyst loading required for the sequential transformation. Previously reported intramolecular Heck cyclizations of enamines usually require at least 10 mol% of Pd.[11,12] However, in these examples, the reactions proceed with only 4 mol% of a Pd catalyst that plays two different roles: to promote both the amination reaction and the subsequent Heck cyclization.

To test the scope of this novel method for the synthesis of indoles, we next examined the reactions of N-substituted *o*-bromoanilines **11** (Scheme 3). However, when alkenyl bromides **8** were treated with *o*-bromo-*N*-methylanilines **11** under several different reaction conditions, the intermediate enamine **12** was the only product isolated together with unreacted materials, and indole formation was not observed. Apparently, the increased steric hindrance prevented the



8 11 12

Scheme 3. General reaction between alkenyl bromides **8** and N-substituted *o*-bromoanilines **11**.

progress of the reaction. Nevertheless, it was possible to achieve the amination/Heck tandem process when the less sterically hindered *trans*-1,2-disubstituted bromoalkenes **13** were employed. The results are represented in Table 5. Again, the reaction is compatible with aryl, alkyl, and functionalyzed bromoalkenes and tolerates several substitutents on the nitrogen atom of the aniline.

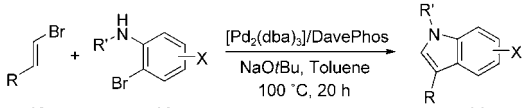
Finally, we wanted to investigate if the less reactive *o*-chloroanilines **15** were appropriate substrates for the sequential reaction. As represented in Table 6, the reaction of *o*-chloroaniline (**15**) with α-bromostyrene **2** with the optimized catalytic system developed for the reactions with *o*-bromoanilines **9**—[$Pd_2(dba)_3$], DavePhos, NaO*t*Bu—afforded exclusively the intermediate imine **16** (entry 1, Table 6), even at higher temperatures (entries 2 and 3), higher loadings of Pd and ligand (entry 4), different solvents (entry 5), and bases (entries 6 and 7). However, the indole formation could be achieved efficiently by using X-Phos as supporting ligand, and NaO*t*Bu as a base, at 110 °C (entry 10). These reaction conditions were used with different alkenyl bromides **8** to give the indoles **10** in good yields (Table 7).

It is worth noting the high sensitivity of the reaction to the structure of the supporting ligand. DavePhos was the best ligand for the cascade process with *o*-bromoanilines but failed completely in the second step with chloroanilines. On the other hand, X-Phos provided better results for *o*-chloroanilines than for the more reactive bromo analogues, showing that very fine tuning of the catalytic systems is recommended for this type of transformation.

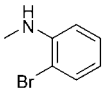
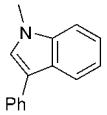
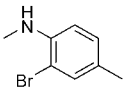
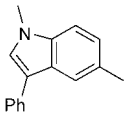
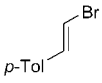
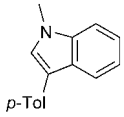
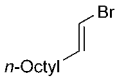
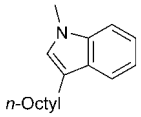
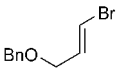
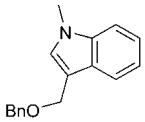
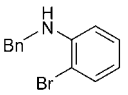
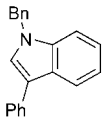
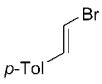
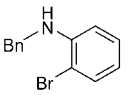
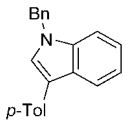
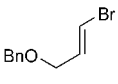
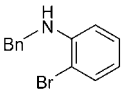
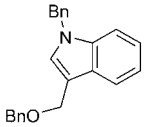
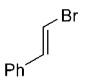
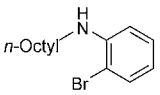
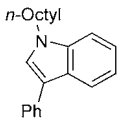
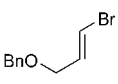
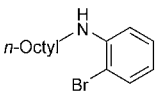
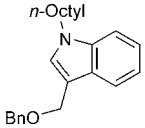
Summary

In summary, we have reported the interesting high chemoselectivity of the Pd-catalyzed amination of aryl and alkenyl halides. More interestingly, the potential application of this differential reactivity has been demonstrated by the first examples of cascade processes involving a Pd-catalyzed alkenyl amination, followed by an intramolecular Heck reaction. The overall transformation represents a new approach for the synthesis of substituted indoles in a single step, from very simple starting materials. Moreover, the incorporation of C–N bond-forming reactions, and in particular alkenyl amination reactions, in sequential processes promoted by multifunctional Pd catalysts, represents a general strategy that may be of great use in the synthesis of more complex heterocycles.

Table 5. Reaction of alkenyl bromides **13** with *o*-bromoanilines **12**. Synthesis of indoles **14**.[a]



13 11 14

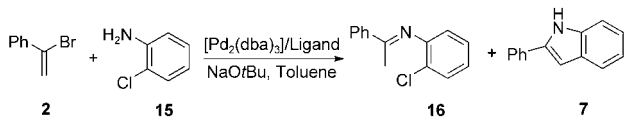
Entry[b]	Bromide **13**	Aniline **11**	Indole **14**	Yield[c] [%]
a				70
b				72
c				69
d				64
e				63
f				61
g				64
h				49
i				68
j				52

[a] Reaction conditions: 1 equiv of **13**, 1 equiv of **11**, 3 equiv of NaO*t*Bu, 4 mol% of Pd, 8 mol% of DavePhos, toluene (4 mL mmol^{-1}), 100 °C, 20 h. [b] Entry labels correspond to those of the product **14**. [c] Yields after flash chromatography.

Experimental Section

General considerations: All reactions were carried out under a nitrogen atmosphere in a RR98030 12 place Carousel Reaction Station from Radleys Discovery Technologies, equipped with gas-tight threaded caps with

Table 6. Optimization of the reaction conditions with *o*-chloroanilines **15**.[a]

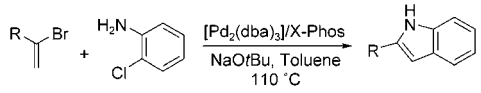


2 **15** **16** **7**

Entry	$[Pd_2(dba)_3]$ [mol %]	Ligand	Base	T [°C]	Conversion[b] [%] **16**/**7**
1	4	DavePhos	NaO*t*Bu	100	100/0
2	4	DavePhos	NaO*t*Bu	110	100/0
3	4	DavePhos	NaO*t*Bu	120	100/0
4	5	DavePhos	NaO*t*Bu	100	100/0
5[c]	4	DavePhos	NaO*t*Bu	100	100/0
6	4	DavePhos	KO*t*Bu	100	100/0
7	4	DavePhos	LHMDS	100	100/0
8	4	NHC	NaO*t*Bu	100	100/0
9	4	NHC	LHMDS	100	100/0
10	4	X-Phos	NaO*t*Bu	110	0/100 (65)[d]
11	4	X-Phos	NaO*t*Bu	100	0/100 (50)[d]
12	4	X-Phos	KO*t*Bu	110	100/0

[a] Reaction conditions: 1 equiv of **2**, 1 equiv of **15**, 3 equiv of Base, 1:2 Pd/ligand ratio, toluene (4 mL mmol^{-1}), 20 h. [b] Determined from the crude reaction mixture by GC and ^{1}H NMR spectroscopy. [c] Performed in dioxane. [d] Yield of indole **7**.

Table 7. Reaction of alkenyl bromides **8** with *o*-chloroanilines **16**. Synthesis of 1*H*-indoles **10**.[a]



8 **16** **10**

Entry[b]	Bromide **8**	Amine **16**	Indole **10**	Yield[c] [%]
a	Ph, Br	H_2N, Cl	H, N, Ph	65
b	*p*-Tol, Br	H_2N, Cl	H, N, *p*-Tol	58
c	*n*-Octyl, Br	H_2N, Cl	H, N, *n*-Octyl	60
d	BnO, Br	H_2N, Cl	H, N, BnO	55

[a] Reaction conditions: 1 equiv of **8**, 1 equiv of **16**, 3 equiv of NaO*t*Bu, 4 mol % of Pd, 8 mol % of X-Phos, toluene (4 mL mmol^{-1}), 110 °C, 20 h. [b] Entry labels correspond to those of the product **10**. [c] Yields after flash chromatography.

a valve, cooling reflux head system, and digital temperature controller. Toluene and hexane solvents were refluxed and freshly distilled from sodium/benzophenone under nitrogen. NMR spectra were recorded at 300 or 200 MHz for ^{1}H and 75 or 50.3 MHz for ^{13}C, with tetramethylsilane as internal standard for ^{1}H and the residual solvent signals as standard for ^{13}C. Chemical shifts are given in ppm. Mass spectra were obtained by EI (70 eV). $Pd(OAc)_2$ and $[Pd_2(dba)_3]$ were purchased from Strem Chemical Co. and used without further purification. All phosphine ligands used are commercially available from Strem or Aldrich and were used without further purification. NaO*t*Bu was purchased from Aldrich, stored in a flask purged with nitrogen and weighed in the air. Non-commercial alkenyl bromides were prepared according to literature procedures: 2-bromodec-1-ene,[26] 2-bromo-3-benzyloxy-1-propene,[27] 1-(1-bromovinyl)-4-methylbenzene,[26] 1-bromodec-1-ene,[28] 1-bromo-3-benzyloxy-1-propene,[29] 1-(2-bromovinyl)-4-methylbenzene.[29] Non-commercial N-substituted *o*-bromoanilines **12** were prepared by a two-step reductive amination sequence: condensation of the unsubstituted bromoanilines with the appropriate aldehydes in the presence of methyl orthoformate followed by reduction of the corresponding imines with $NaBH_4$ in methanol.

General procedure for the study of the relative reactivity of aryl and alkenyl bromides and chlorides in Pd-catalyzed amination reactions: A reaction tube under a nitrogen atmosphere was charged with the ligand DavePhos (15.5 mg, 0.04 mmol, 4 mol %), tris(dibenzylideneacetone)dipalladium(**0**) (9.15 mg, 0.001 mmol, 2 mol %), sodium *tert*-butoxide (134 mg, 1.4 equiv), and toluene (4 mL). After 1 min, the two halides (1 mmol each) and the amine (1 mmol) were added under nitrogen and the tube was placed in the carousel block and heated to 90 °C with stirring for 6 h. The mixture was allowed to cool to room temperature, taken up in hexanes (15 mL), and filtered through Celite. The solvents were evaporated under reduced pressure.

General procedure for the synthesis of 1*H*-indoles 10 by palladium-catalyzed cascade reactions of alkenyl bromides 8 with *o*-bromoanilines 9: A reaction tube under a nitrogen atmosphere was charged with DavePhos (31 mg, 0.08 mmol, 8 mol %), tris(dibenzylideneacetone)dipalladium(**0**) (18.3 mg, 0.002 mmol, 4 mol %), sodium *tert*-butoxide (288 mg, 3 mmol, 3 equiv), and toluene (4 mL). After 1 min, the alkenyl bromide **8** (1 mmol) and the bromoaniline **9** (1 mmol) were added under nitrogen and the tube was placed in the carousel block and heated to 100 °C with stirring for 20 h. The mixture was allowed to cool to room temperature, taken up in hexanes (15 mL), and filtered through Celite. The solvents were evaporated under reduced pressure. Purification by flash chromatography (SiO_2, Hex/EtOAc, 20:1) afforded indoles **10**.

Spectroscopic data of known indoles **10a** and **10b**,[30] **10c**,[31] **10d**,[32] **10e**,[33] **10f**,[34] **14a**,[35] and **14f**[36] were in complete agreement with literature values.

2-Phenyl-1*H*-indole 10a: The general procedure gave **10a** in 64 % yield.

5-Methyl-2-phenyl-1*H*-indole 10b: The general procedure gave **10b** in 62 % yield.

5-Chloro-2-phenyl-1*H*-indole 10c: The general procedure gave **10c** in 55 % yield.

2-*p*-Tolyl-1*H*-indole 10d: The general procedure gave **10d** in 62 % yield.

5-Methyl-2-*p*-tolyl-1*H*-indole 10e: The general procedure gave **10e** in 61 % yield.

2-Octyl-1*H*-indole 10f: The general procedure gave **10f** in 63 % yield.

5-Methyl-2-octyl-1*H*-indole 10g: The general procedure gave **10g** in 60 % yield as an orange syrup. R_f: 0.40 (SiO_2, Hex/AcOEt, 9/1); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.96$ (t, $^3J = 6.2$ Hz, 3H), 1.38–1.28 (m, 10H), 1.77–1.72 (m, 2H), 2.49 (s, 3H), 2.74 (t, $^3J = 7.6$ Hz, 2H), 6.20 (s, 1H), 6.99 (d, $^3J = 7.9$ Hz, 1H), 7.19 (d, $^3J = 7.9$ Hz, 1H), 7.37 (s, 1H), 7.82 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 13.9$ (CH_3), 21.3 (CH_3), 22.5 (CH_2), 28.1 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 31.7 (CH_2), 98.7 (CH), 109.8 (CH), 119.3 (CH), 122.2 (CH), 128.4 (C), 129.1 (C), 134.0 (C), 140.0 ppm (C); HRMS calcd for $C_{17}H_{25}N$: 243.19815; found: 243.19804.

5-Chloro-2-octyl-1*H*-indole 10h: The general procedure gave **10h** in 53 % yield as an orange syrup. R_f: 0.40 (SiO_2, Hex/AcOEt, 9/1); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.91$ (t, $^3J = 6.2$ Hz, 3H), 1.35–1.28 (m, 10H), 1.74–1.70 (m, 2H), 2.74 (t, $^3J = 7.6$ Hz, 2H), 6.20 (s, 1H), 7.07 (d, $^3J = 8.5$ Hz, 1H), 7.20 (d, $^3J = 8.5$ Hz, 1H), 7.50 (s, 1H), 7.98 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 14.0$ (CH_3), 22.5 (CH_2), 28.1 (CH_2), 28.9 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 31.7 (CH_2), 99.1 (CH), 111.1 (CH), 119.0 (CH), 120.9 (CH), 125.0 (C), 129.8 (C), 134.0 (C), 141.6 ppm (C); HRMS calcd for $C_{16}H_{22}ClN$: 263.14352; found: 263.14348.

2-Benzyloxymethyl-1*H*-indole 10i: The general procedure gave **10i** in 61 % yield as an orange syrup. R_f: 0.14 (SiO_2, Hex/AcOEt, 9/1); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 4.63$ (s, 2H), 4.79 (s, 2H), 6.55 (s, 1H), 7.31–7.19 (m, 2H), 7.45–7.38 (m, 6H), 7.71 (d, $^3J = 7.7$ Hz, 1H), 8.62 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 64.9$ (CH_2), 71.5 (CH_2), 101.8 (CH),

110.8 (CH), 119.6 (CH), 120.4 (CH), 121.9 (CH), 127.7 (CH), 127.9 (2CH), 128.0 (C), 128.3 (2CH), 134.8 (C), 136.4 (C), 137.6 ppm (C); HRMS calcd for $C_{16}H_{15}NO$: 237.11481; found: 237.11503.

2-Benzyloxymethyl-5-methyl-1*H*-indol 10j: The general procedure gave **10j** in 59% yield as an orange syrup. R_f: 0.15 (SiO_2, Hex/AcOEt, 9/1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.53 (s, 3H), 4.59 (s, 2H), 4.75 (s, 2H), 6.44 (s, 1H), 7.09 (d, ^3J = 8.2 Hz, 1H), 7.27 (d, ^3J = 8.2 Hz, 1H), 7.46–7.41 (m, 6H), 8.40 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.3 (CH_3), 65.0 (CH_2), 71.5 (CH_2), 101.5 (CH), 110.5 (CH), 120.1 (CH), 123.5 (CH), 127.7 (CH), 127.9 (2CH), 128.1 (C), 128.4 (2CH), 128.8 (C), 134.6 (C), 134.9 (C), 137.6 ppm (C); HRMS calcd for $C_{17}H_{17}NO$: 251.13046; found: 251.13063.

General procedure for the synthesis of 1*R*-indoles 14 by palladium-catalyzed cascade reactions of alkenyl bromides 13 with *o*-bromoanilines 11: A reaction tube under a nitrogen atmosphere was charged with DavePhos (31 mg, 0.08 mmol, 8 mol%), tris(dibenzylideneacetone)dipalladium(0) (18.3 mg, 0.002 mmol, 4 mol%), sodium *tert*-butoxide (288 mg, 3 mmol, 3 equiv), and toluene (4 mL). After 1 min, the alkenyl bromide **8** (1 mmol) and the bromoaniline **11** (1 mmol) were added under nitrogen and the tube was placed in the carousel block and heated to 100°C with stirring for 20 h. The mixture was allowed to cool to room temperature, taken up in hexanes (15 mL), and filtered through Celite. The solvents were evaporated under reduced pressure. Purification by flash chromatography (SiO_2, Hex/EtOAc, 20:1) afforded indoles **14**.

1-Methyl-3-phenyl-1*H*-indole 14a: The general procedure gave **14a** in 70% yield.

1,5-Dimethyl-3-phenyl-1*H*-indole 14b: The general procedure gave **14b** in 72% yield as an orange syrup. R_f: 0.33 (SiO_2, Hex/AcOEt 9/1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.56 (s, 3H), 3.84 (s, 3H), 7.18 (dd, ^3J = 1.4 y 8.2 Hz, 1H), 7.23 (s, 1H), 7.35–7.30 (m, 2H), 7.50 (t, ^3J = 7.7 Hz, 2H), 7.72 (dd, ^3J = 1.4 y 8.2 Hz, 2H), 7.81 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.5 (CH_3), 32.8 (CH_3), 109.1 (CH), 115.9 (C), 119.4 (CH), 123.4 (CH), 125.4 (CH), 126.2 (C), 126.5 (CH), 127.2 (2CH), 128.6 (2CH), 129.1 (C), 135.7 (C), 135.8 ppm (C); HMRS calcd for $C_{16}H_{15}N$: 221.11990; found: 221.11979.

1-Methyl-3-*p*-tolyl-1*H*-indole 14c: The general procedure gave **14c** in 69% yield as an orange syrup. R_f: 0.32 (SiO_2, Hex/AcOEt 9/1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.50 (s, 3H), 3.88 (s, 3H), 7.46–7.26 (m, 6H), 7.65 (d, ^3J = 7.3 Hz, 2H), 8.04 ppm (d, ^3J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.1 (CH_3), 32.7 (CH_3), 109.4 (CH), 116.5 (C), 119.6 (CH), 119.8 (CH), 121.8 (CH), 126.2 (CH), 127.1 (2CH), 128.9 (C), 129.3 (2CH), 132.6 (C), 135.7 (C), 137.3 ppm (C); HRMS calcd for $C_{16}H_{15}N$: 221.11990; found: 221.11959.

1-Methyl-3-octyl-1*H*-indole 14d: The general procedure gave **14d** in 64% yield as an orange syrup. R_f: 0.40 (SiO_2, Hex/AcOEt 9/1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.94 (t, ^3J = 6.2 Hz, 3H), 1.40–1.25 (m, 14H), 2.94 (s, 3H), 6.69–6.60 (m, 3H), 7.29–7.24 (m, 1H), 7.48 ppm (d, ^3J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.0 (CH_3), 22.6 (CH_2), 29.5–29.3 ($5CH_2$), 30.4 (CH_3), 31.8 (CH_2), 109.4 (C), 110.6 (CH), 117.5 (CH), 128.4 (2CH), 128.5 (C), 132.1 (CH), 145.8 ppm (C); HRMS calcd for $C_{17}H_{25}N$: 243.19815; found: 243.19850.

3-Benzyloxymethyl-1-methyl-1*H*-indole 14e: The general procedure gave **14e** in 63% yield as an orange syrup. R_f: 0.22 (SiO2, Hex/AcOEt 9/1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.81 (s, 3H), 4.66 (s, 2H), 4.84 (s, 2H), 7.13 (s, 1H), 7.24 (t, ^3J = 6.8 Hz, 1H), 7.45–7.31 (m, 7H), 7.80 ppm (d, ^3J = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 32.6 (CH_3), 63.7 (CH_2), 71.3 (CH_2), 109.1 (CH), 111.4 (C), 119.2 (2CH), 121.7 (CH), 127.3 (CH), 127.5 (C), 127.7 (2CH), 128.2 (2CH), 128.4 (CH), 137.1 (C), 138.6 ppm (C); HRMS calcd for $C_{17}H_{17}NO$: 251.13046; found: 251.13057.

1-Benzyl-3-phenyl-1*H*-indole 14f: The general procedure gave **14f** in 61% yield.

1-Benzyl-3-*p*-tolyl-1*H*-indole 14g: The general procedure gave **14g** in 64% yield as a yellow solid. m.p.: 83–85. R_f: 0.45 (SiO_2, Hex/AcOEt 9/1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.34 (s, 3H), 5.40 (s, 2H), 7.45–7.26 (m, 11H), 7.75 (d, ^3J = 8.2 Hz, 2H), 8.13–8.11 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.1 (CH_3), 49.9 (CH_2), 109.8 (CH), 117.1 (C), 119.8 (CH), 119.9 (CH), 121.9 (CH), 125.5 (CH), 126.3 (C), 126.7 (2CH), 127.1 (2CH), 127.5 (C), 128.6 (2CH), 129.3 (2CH), 132.4 (C), 135.3 (C), 136.9 (C), 137.1 ppm (C); HRMS calcd for $C_{22}H_{19}N$: 297.15120; found: 297.15151.

1-Benzyl-3-benzyloxymethyl-1*H*-indole 14h: The general procedure gave **14h** in 49% yield as an orange syrup. R_f: 0.21 (SiO_2, Hex/AcOEt 9/1); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.66 (s, 2H), 4.84 (s, 2H), 5.34 (s, 2H), 7.18–7.30 (m, 4H), 7.45–7.32 (m, 10H), 7.83–7.79 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 50.4 MHz): δ = 49.8 (CH_2), 63.9 (CH_2), 71.4 (CH_2), 109.6 (CH), 112.2 (C), 119.4 (CH), 119.5 (CH), 121.9 (CH), 126.7 (2CH), 127.4 (CH), 127.5 (CH), 127.7 (CH), 127.8 (2CH), 127.9 (C), 128.2 (2CH), 128.6 (2CH), 136.8 (C), 137.2 (C), 138.5 ppm (C); HRMS calcd for $C_{23}H_{21}NO$: 327.16171; found: 327.16194.

1-Octyl-3-phenyl-1*H*-indole 14i: The general procedure gave **14i** in 68% yield as an orange syrup. R_f: 0.56 (SiO_2, Hex/AcOEt 9/1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.06 (t, ^3J = 5.9 Hz, 3H), 1.54–1.43 (m, 10H), 2.03–1.98 (m, 2H), 4.25 (t, ^3J = 7.1 Hz, 2H), 7.42–7.35 (m, 4H), 7.62–7.52 (m, 3H), 7.96–7.83 (m, 2H), 8.14 ppm (t, ^3J = 5.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 13.9 (CH_3), 22.5 (CH_2), 26.9 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 30.1 (CH_2), 31.7 (CH_2), 46.3 (CH_2), 109.6 (CH), 116.4 (C), 119.6 (CH), 119.8 (CH), 121.6 (CH), 125.4 (CH), 125.5 (CH), 126.1 (C), 127.2 (2CH), 128.6 (2CH), 135.7 (C), 136.6 ppm (C); HRMS calcd for $C_{22}H_{27}N$: 305.21380; found: 305.21412.

3-Benzyloxymethyl-1-octyl-1*H*-indol 14j: The general procedure gave **14j** in 52% yield as an orange syrup. R_f: 0.35 (SiO_2, Hex/AcOEt 9/1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.91 (t, ^3J = 5.9 Hz, 3H), 1.34–1.29 (m, 10H), 1.88–1.84 (m, 2H), 4.11 (t, ^3J = 7.1 Hz, 2H), 4.61 (s, 2H), 4.79 (s, 2H), 7.40–7.14 (m, 9H), 7.73 ppm (d, ^3J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 13.9 (CH_3), 22.5 (CH_2), 26.9 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 30.1 (CH_2), 31.7 (CH_2), 46.2 (CH_2), 63.9 (CH_2), 71.3 (CH_2), 109.3 (CH), 111.4 (C), 119.2 (CH), 119.4 (CH), 121.5 (CH), 127.4 (CH), 127.5 (CH), 127.7 (C), 127.8 (2CH), 128.2 (2CH), 136.5 (C), 138.6 ppm (C); HRMS calcd for $C_{24}H_{31}NO$: 349.24001; found: 349.24007.

General procedure for the synthesis of 1*H*-indoles 10 by palladium-catalyzed cascade reactions of alkenyl bromides 8 with *o*-chloroanilines 15: A reaction tube under nitrogen atmosphere was charged with X-Phos (38.1 mg, 0.08 mmol), tris(dibenzylideneacetone)dipalladium(0) (18.3 mg, 0.002 mmol, 4 mol%), sodium *tert*-butoxide (288 mg, 3 mmol, 3 equiv), and toluene (4 mL). After 1 min, the alkenyl bromide **8** (1 mmol) and the chloroaniline **15** (1 mmol) were added under nitrogen and the tube was placed in the carousel block and heated to 110°C with stirring for 20 h. The mixture was allowed to cool to room temperature, taken up in hexanes (15 mL), and filtered through Celite. The solvents were evaporated under reduced pressure. Purification by flash chromatography (SiO_2, Hex/EtOAc, 20:1) afforded indoles **10**.

2-Phenyl-1*H*-indole 10a: The general procedure gave **10a** in 65% yield.

2-*p*-Tolyl-1*H*-indole 10d: The general procedure gave **10d** in 58% yield.

2-Octyl-1*H*-indole 10f: The general procedure gave **10f** in 60% yield.

2-Benzyloxymethyl-1*H*-indole 10i: The general procedure gave **10i** in 55% yield.

Acknowledgements

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[1] For some recent reviews see: a) J. Tsuji *Palladium Reagents and Catalysts*, Wiley, Chichester, **2004**; b) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, A. de Meijere), Wiley-VCH, Weinheim, **2004**; c) G. Stara, T. H. Riermeier, M. Beller in *Transition Metals for Organic Synthesis, Vol. 1*, 2nd ed. (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**, pp. 208; d) V. V. Grushin, H. Alper, *Top. Organomet. Chem.* **1999**, *3*, 193. e) *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E. Negishi), Wiley-Interscience, New York, **2002**; f) "Cross-Coupling Reactions:

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