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One-pot N-alkylation/Heck approach to substituted indoles

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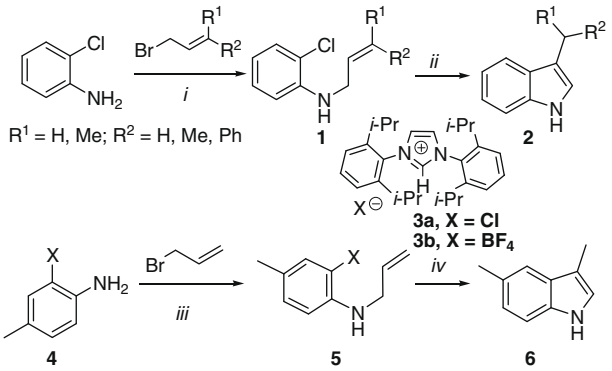
ABSTRACT

Here, we report the palladium-catalyzed one-pot N-alkylation/Heck cyclization of anilines to substituted indoles employing $Pd(OAc)_2$/XPhos. The scope and limitations of this methodology will be described.

Due to the prevalence of indole functionality in several biologically active molecules, many research efforts are focused on developing novel general, mild, and efficient methods for the regioselective preparation of substituted indoles from readily available starting materials.[1] The intramolecular Heck reaction has been widely used for the synthesis of substituted indoles.[2] In addition, indoles have been prepared utilizing one-pot cascade reactions.[3] For example, the palladium-catalyzed one-pot cascade reactions of 2-halo-anilines employing ketones[4] and aldehydes[5] have been reported. Here, we report a mild, one-pot cascade reaction affording substituted indoles from commercially available anilines and readily accessible $Pd(OAc)_2$/XPhos.

The palladium-catalyzed Heck reaction of 2-iodo- [8] and 2-bromo[7]-*N*-allylanilines has been reported. In addition, an intramolecular Heck reaction employing palladium/imidazolium **3a** catalyst system with 2-chloro-*N*-allyl-anilines **1** afforded 3-substitued indoles **2** in moderate to high yields (Scheme 1).[8] In our hands, *N*-allylation of aniline **4** in the presence of K_2CO_3 resulted in low to modest yields of the *N*-allylanilines **5**.[9] The major byproduct being *N*,*N*-diallylanilines (X = Br, 14%; X = Cl 15%). The *N*-allylanilines **5** underwent an intramolecular Heck coupling reaction in the presence of XPhos and $Pd(OAc)_2$ to give the desired substituted indole **6** in low yield (X = Br, 40%; X = Cl, 25%). A one-pot cascade reaction involving Heck cyclization of 2-bromo- and 2-iodo-*N*-allyl-aniline intermediates was recently disclosed.[10] Thus, we sought a one-pot cascade reaction to afford the desired substituted indole **6**.

We turned our attention to the one-pot *N*-allylation/Heck cascade of 2-bromo or 2-chloroanilines to access indoles. Several solvents were examined for this transformation.[11,12] For the 2-bromoaniline **4**, DME and *t*-BuOH gave 37% and 31% isolated yield of indole **6**, respectively (Table 1, entries 4 and 6). In addition a reaction temperature of 80 °C is required for the cascade sequence. A temperature of 25 °C resulted in recovered starting material (87%) along with debromination of the aniline (Table 1, entry 7). At 50 °C, 23% conversion to the *N*-allylaniline **5** was observed (Table 1, entry 8). The remaining material was unreacted starting material and debrominated aniline. Using *t*-BuOH or DME as a solvent for the cascade reaction with 2-chloroaniline **4** resulted in desired indole **6** in 62% and 67% isolated yield, respectively (Table 1, entries 13 and 14). Next, we examined different bases. For both 2-bromo and 2-chloroanilines K_3PO_4, KOAc, and $MeNCy_2$ resulted in moderate conversion to *N*-allylanilines **5,** but no Heck cyclization product was detected (Table 1, entries 9, 10, 12, 15, 16, and 18). K_2CO_3 resulted in high conversion of the 2-chloroaniline to the desired indole **6**; on the other hand, Cs_2CO_3 was found to be the best base for 2-bromoaniline conversion to the indole **6** (Table 1, entry 14 vs entry 17 and entry 4 vs entry 11). In addition, both allyl bromide and allyl chloride were excellent reagents for the cascade reaction, while allyl methyl carbonate provided a moderate conversion of the desired indole (Table 1, entries 19–21).



Scheme 1. Reagents and conditions: (i) LDA, THF, −78 °C; (ii) **3a** (1 mol %), $Pd_2(dba)_3$ (1 mol %), Cs_2CO_3 (1.5 equiv), TBAB (1 equiv), DMA, 140 °C, 24–48 h, 21–70% (iii) K_2CO_3, 60 °C, MeCN, X = Br, 12 h, 40%; X = Cl, 4 d, 25%; (iv) XPhos (10 mol %), $Pd(OAc)_2$ (5 mol %), K_3PO_4 (3 equiv), *n*-BuOH, 2.5 h, 80 °C, X = Br, 35%; X = Cl, 13%.

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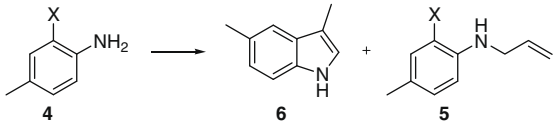
Table 1
One-pot *N*-allylation/Heck reaction conditions



Entry	X	Reagent	Base (3 equiv)	Solvent	Temperature (°C)	Time (h)	Conversion to **6**[a,b] (%)	Conversion to **5**[b] (%)
1	Br	Allyl bromide	K_2CO_3	Toluene	80	20	5[c]	
2	Br	Allyl bromide	K_2CO_3	DCE	80	20	9[c]	
3	Br	Allyl bromide	K_2CO_3	Dioxane	80	20	6[c]	
4	Br	Allyl bromide	K_2CO_3	DME	80	20	37[c]	
5	Br	Allyl bromide	K_2CO_3	NMP	80	20	8[c]	
6	Br	Allyl bromide	K_2CO_3	*t*-BuOH	80	18	31[c]	
7	Br	Allyl bromide	K_2CO_3	DME	50	24	0	23
8	Br	Allyl bromide	K_2CO_3	DME	25	24	0	0
9	Br	Allyl bromide	K_3PO_4	DME	80	24	0	50
10	Br	Allyl bromide	KOAc	DME	80	24	0	84
11	Br	Allyl bromide	Cs_2CO_3	DME	80	24	50	50
12	Br	Allyl bromide	$MeNCy_2$	DME	80	24	0	38
13	Cl	Allyl bromide	K_2CO_3	*t*-BuOH	80	24	62[c]	
14	Cl	Allyl bromide	K_2CO_3	DME	80	24	67[c]	14[c]
15	Cl	Allyl bromide	K_3PO_4	DME	80	24	0	50
16	Cl	Allyl bromide	KOAc	DME	80	24	0	64
17	Cl	Allyl bromide	Cs_2CO_3	DME	80	24	10	0
18	Cl	Allyl bromide	$MeNCy_2$	DME	80	24	0	38
19	Cl	Allyl bromide	K_2CO_3	DME	80	48	>95	0
20	Cl	Allyl methyl carbonate	K_2CO_3	DME	80	48	43	23
21	Cl	Allyl chloride	K_2CO_3	DME	80	48	>95	0

[a] Reactions were carried out at 1 mmol substrate with reagent (1 equiv), XPhos (10 mol %), $Pd(OAc)_2$ (5 mol %), base (3 equiv), in 5 mL of solvent.
[b] Conversion was determined using ^1H NMR.
[c] Isolated yield.

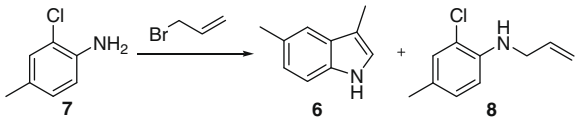
Next, we sought to establish that both XPhos and $Pd(OAc)_2$ are required for the catalytic system (Table 2). Reaction with only $Pd(OAc)_2$ resulted in 50% conversion to *N*-allylaniline **8** and unreacted starting material **7**. Similarly, reaction with only XPhos provided unreacted **7** and 40% conversion to *N*-allylaniline **8**. However, in the presence of both XPhos and $Pd(OAc)_2$ the desired indole **6** was obtained in 67% isolated yield. Thus, XPhos and $Pd(OAc)_2$ are required for the Heck cyclization step of the one-pot cascade sequence.

Next, we examined the palladium/imidazolium **3** catalyst system in order to determine whether it could also facilitate this one-pot transformation. Treatment of 2-chloroaniline **7** with allyl bromide, 1 mol % NHC-ligand **3b**, and 1 mol % $Pd_2(dba)_3$ resulted in 77% conversion to *N*-allylaniline **8** with <10% conversion to the desired indole **6** (Scheme 2).

It has been reported that the reaction rate of intramolecular Heck cyclization can be accelerated under microwave heating conditions.[13] Thus, we examined microwave heating conditions in order to increase the reaction rate and reduce the reaction time. Heating the reaction under microwave conditions for 10 min at 80 °C provided only unreacted starting material **7** (Scheme 2, conditions (ii)). Continued heating for an additional 20 min at 150 °C resulted in *N*-allylaniline **8** formation with the rest of the material being unreacted starting material **7** (22% conversion). Additional heating under microwave conditions for 20 min at 200 °C increased the production of **8** (50% conversion). None of the desired indole **6** was observed under these microwave heating conditions.

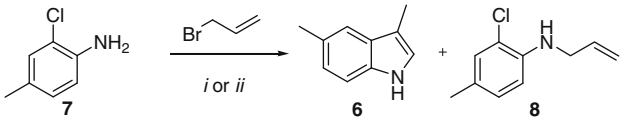
Next, we turned our attention to extending this one-pot cascade reaction to other 2-halo substituted anilines (Table 3). 2-Fluoro-4-methylaniline underwent *N*-allylation under the reaction conditions, but no indole product was formed (Table 3, entry 1). In a similar manner, 2-fluoroaniline also provided the *N*-allyl-analog, but none of the desired indole was observed (Table 3, entry 2). In contrast, 2-chloro-4-methylaniline and 2-choloraniline afforded the respective indoles in 67% and 68% isolated yield (Table 2, entry 1 and Table 3, entry 3). When 2-iodo-4-trifluoromethylaniline was treated under the reaction conditions only the *N*-allylaniline was isolated (Table 3, entry 4). On the other hand, reaction with 2-chloro-4-trifluoromethylaniline provided the desired indole in 67% yield (Table 3, entry 5). Thus, 2-fluoro and 2-iodoanilines do

Table 2
Catalyst system requirements



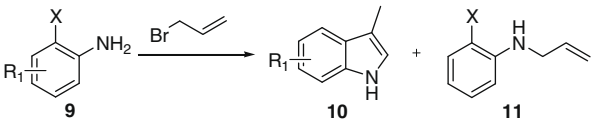
Entry	XPhos (mol %)	$Pd(OAc)_2$ (mol %)	Conversion to **6**[a,b] (%)	Conversion to **8**[b] (%)
1	10	5	67[c]	14[c]
2	0	5	0	50
3	10	0	0	40

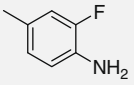
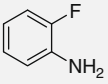
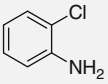
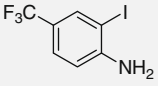
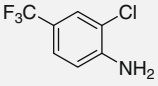
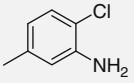
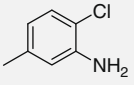
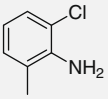
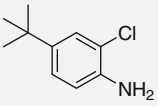
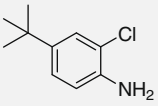
[a] Reactions were carried out at 1 mmol substrate in 5 mL DME with allylbromide (1 equiv), K_2CO_3 (3 equiv), at 80 °C for 24 h.
[b] Conversion was determined using ^1H NMR.
[c] Isolated yield.



Scheme 2. Reagents and conditions: (i) **3b** (1 mol %), $Pd_2(dba)_3$ (1 mol %), Cs_2CO_3 (1.5 equiv), TBAB (1 equiv), DMA, 140 °C, 20 h. (ii) XPhos (10 mol %), $Pd(OAc)_2$ (5 mol %), K_2CO_3 (3 equiv), DME, μW.

Table 3
Substitution scope of the cascade reaction



Entry	Aniline	Time (h)	Conversion to **10**[a,b] (%)	Conversion to **11**[b] (%)
1		48	0	65[c]
2		48	0	49[c]
3		48	68[c]	
4		48	0	38[c]
5		28	67[c]	
6		24	14	77
7		48	57[c]	
8		48	46[c]	
9		20	0	99
10		48	67[c]	

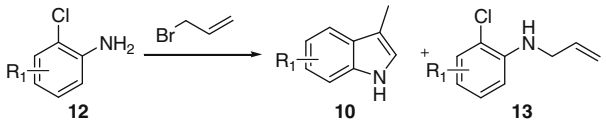
[a] Reactions were carried out at 1 mmol substrate in 5 mL DME with allylbromide (1 equiv), XPhos (10 mol %), $Pd(OAc)_2$ (5 mol %), K_2CO_3 (3 equiv), at 80 °C.
[b] Conversion was determined using ^1H NMR.
[c] Isolated yield.

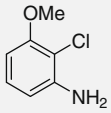
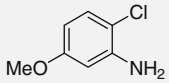
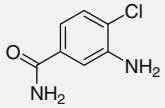
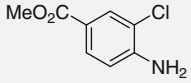
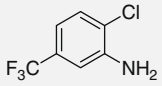
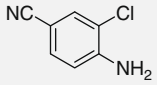
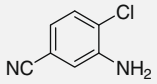
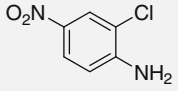
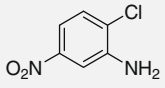
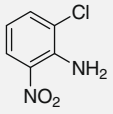
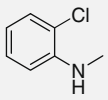
not provide access to indoles under these cascade reaction conditions.

Having established the optimal reaction conditions, we examined the scope of this cascade reaction. Since 2-chloroanilines are generally more readily available and less expensive than the corresponding 2-bromoanilines we sought to examine whether substitution on 2-chloroanilines was tolerated under the reaction conditions. Toward this end, we first examined the effect of methyl substitution on the reaction. 4-, 5-, and 6-Methyl groups were all well tolerated under the reaction conditions providing the indole derivatives in 46–67% yield (Table 1 entry 14, Table 3, entries 7 and 8). Allowing the reaction to proceed for 48 h provided higher yields of the desired indoles (Table 3, entry 6 vs entry 7 and entry 9 vs entry 10).

Next, we examined whether other functional groups would be tolerated under these reaction conditions. Electron-donating 3-methoxy and 5-methoxy groups were tolerated providing the 4-methoxy and 6-methoxy substituted indoles in moderate yields (Table 4, entries 1 and 2). In addition, the 5-carboxamide group is tolerated providing 50% conversion to the desired indole (Table 4,

Table 4
Effect of substitution on cascade reaction



Entry	Aniline	Time (h)	Conversion to **10**[a,b] (%)	Conversion to **13**[b] (%)
1		48	56[c]	
2		24	23	50
3		28	50	20
4		48	15	56
5		48	64[c]	
6		48	15	56
7		42	32[c]	28
8		22	61[c]	
9		48	17[c]	49[c]
10		22	16	16
11		48	20[c]	42

[a] Reactions were carried out at 1 mmol substrate in 5 mL DME with allylbromide (1 equiv), XPhos (10 mol %), $Pd(OAc)_2$ (5 mol %), K_2CO_3 (3 equiv) at 80 °C.
[b] Conversion was determined using ^1H NMR.
[c] Isolated yield.

entry 3). However, the 4-methyl carboxylate provided the desired indole in only 15% conversion with the corresponding *N*-allylaniline as the major observed product (Table 4, entry 4). 4- and 5-Trifluoromethyl substitution provided the corresponding 5- and 6-trifluoromethyl-3-methyl indoles in excellent yield (Table 3, entry 5 and Table 4, entry 5). In contrast, the 4-cyano group afforded low conversion while the 5-cyano functionality provided 3-methyl-5-cyano indole in 32% isolated yield (Table 4, entries 6 and 7). 4-Nitro and 5-nitro-anilines undergo conversion to 5- and 6-nitro-3-methylindole in moderate yield (Table 4, entries 8 and 9). By contrast, 6-nitro aniline provided the corresponding indole in low yield (16% conversion) with 16% conversion to the *N*-allylaniline observed (Table 4, entry 10). *N*-Alkyl substitution on 2-chloroaniline does not seem to be tolerated under the reaction conditions. For example, 2-chloro-*N*-methyl aniline provided 1,3-dimethylindole in 20% isolated yield with the corresponding *N*-allylaniline being the major product (Table 4, entry 11).

We have developed a one-pot N-alkylation/Heck cascade of 2-chloroanilines to access substituted indoles. The reaction is general and mild, tolerating several functional groups. The reaction employs simple and easily accessible and air stable starting materials and reagents. Several steric and electronic substituents are tolerated. Extending the reaction to substituted bromoanilines and other heterocycles is currently underway.[14] In addition, experiments to understand the solvent effect and reaction mechanism, including mechanistic rationale for the preference of aryl chlorides over aryl bromides, are planned.

Acknowledgment

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References and notes

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11. All reagents were purchased from commercial sources and were used without purification. Reagents were weighed out on the bench top and the reactions were carried out under normal atmosphere conditions. No special precautions to remove oxygen were taken.
12. *Typical procedure*: To substituted 2-chloro or 2-bromoaniline (1 mmol), potassium carbonate (3 mmol), XPhos (10 mol %), and allyl bromide (1 mmol) in a screw cap vial with stir bar was added 5 mL DME at room temperature followed by palladium acetate (5 mol %). The reaction vial was capped and heated to 80 °C with stirring for 24–48 h. The reaction was cooled to room temperature and concentrated under reduced pressure. The desired indole was separated and purified using flash chromatography (0–10% EtOAc in hexanes) giving an colorless oil. One example: Table 4, entry 8 ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm 8.56–8.60 (1H, m), 8.10–8.15 (1H, m), 7.35–7.40 (1H, m), 7.11–7.16 (1H, m), 2.39 (3H, d, J = 1.2 Hz).
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14. Nitrogen substitution on the aniline ring affording pyrrolopyridines was examined under the reaction conditions. Unfortunately, 3-chloropyrazin-2-amine did not produce the desired pyrrolopyrazine and limited conversion to the *N*-allyl derivative was observed (10% conversion determined from ^{1}H NMR). Both 3-chloro and 4-chloro pyridines analogs also failed to produce the corresponding pyrrolopyridines. On the other hand, 2-chloropyridin-3-amine afforded 13% conversion to the desired 3-methylpyrrolopyridine, but the corresponding *N*-allyl derivative was the major product. Prolonged heating for 48 h under the reaction conditions resulted in dechlorination of the substrate.