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Palladium-Catalyzed Tandem Allenyl and Aryl C–N Bond Formation: Efficient Access to *N*-Functionalized Multisubstituted Indoles

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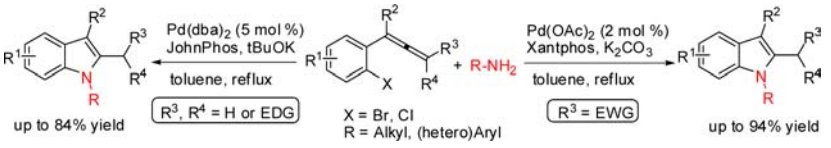
ABSTRACT



An efficient palladium-catalyzed synthesis of *N*-functionalized multisubstituted indoles from easily accessible *ortho*-haloarylallenes and primary amines has been developed. A wide range of electronically and structurally varied nitrogen fragments could be introduced through this tandem C–N bond-forming process by tuning the reaction conditions.

The indole skeleton is one of the most attractive frameworks with a wide range of biological and pharmacological activities, which has been generally recognized as a privileged structure in medicinal chemistry.[1] The prevalence of this physiologically important nucleus, found in therapeutic agents as well as in natural products,[2] has prompted the development of many useful methods for their preparation.[3,4] Recently, Jiao et al.[5] demonstrated a direct approach for constructing indoles from anilines and alkynes by C–H activation. However, much less attention has been paid for the assembly of *N*-functionalized multisubstituted indole frameworks.[6]

Allenes are uniquely versatile intermediates in organic synthesis because of their structural and reactive properties

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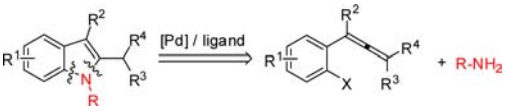
and have proven themselves to be powerful C3 building blocks toward a variety of desirable highly functionalized heterocycles.[7,8] For example, indole and its annelated derivatives could be synthesized through intra- or intermolecular cyclization of allenylanilines,[9a,b,g] allenyl azides,[9c,d,f] aminoallenes,[9e] or allenylbromide.[9h]

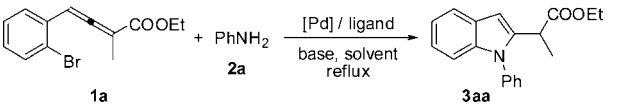
Among those reactions on indole synthesis with allenes, most of them involve only one intramolecular C−N bond formation to construct the pyrrole nucleus of indole.[9a−g] Herein, we describe a palladium-catalyzed tandem reaction, whereby a sequential double C−N bond was formed from easily accessible *ortho*-halo substituted arylallenes and primary amines to give multisubstituted indoles (Scheme 1). To our knowledge, the given approach represents the first report for the synthesis of *N*-functionalized multisubstituted indoles from easily available haloallenes and primary amines.

Scheme 1. New Synthetic Strategy on Indole Ring Synthesis



Preliminary investigation was started by examining the reaction of **1a**[10] with aniline (Table 1). An extensive screening of monodentate (Table 1, entries 1−5) and bidentate ligands (entries 6−8) revealed that the employment of Xantphos was proven to be the most favorable ligand and afforded product **3aa** in 77% yield in the presence of 5 mol % $Pd(dba)_2$ using Cs_2CO_3 as base (entry 8). Switching the solvent from toluene to DMF, DMSO or dioxane gave trace amount of product (entries 9−11). Improved yield could be achieved using 5 mol % of $Pd(OAc)_2$ with K_2CO_3 as base (entry 13). Decreasing the loading of $Pd(OAc)_2$ to 2 mol % gave satisfactory result (entry 14), and the yield was dropped to 75% with further decreased loading of palladium to 1 mol % (entry 15). The identity of **3aa** was determined by spectral analysis and further confirmed by X-ray crystallography from corresponding de-esterification product of **3aa**, 2-(1-phenyl-1*H*-indol-2-yl)-propanoic acid (**3aa′**).[11]

Table 1. Selected Conditions for Optimization of Indole Synthesis[a]



1a 3aa

entry	Pd source	ligand	base	solvent	time (h)	yield (%)[b]
1	$Pd(dba)_2$	PPh_3	Cs_2CO_3	toluene	4	47
2	$Pd(dba)_2$	tBu_3P	Cs_2CO_3	toluene	9	40
3	$Pd(dba)_2$	PCy_3	Cs_2CO_3	toluene	3	40
4	$Pd(dba)_2$	JohnPhos	Cs_2CO_3	toluene	9	49
5	$Pd(dba)_2$	TFP	Cs_2CO_3	toluene	3	19
6	$Pd(dba)_2$	BINAP	Cs_2CO_3	toluene	6	40
7	$Pd(dba)_2$	DPPP	Cs_2CO_3	toluene	4.5	62
8	$Pd(dba)_2$	Xantphos	Cs_2CO_3	toluene	2	77
9	$Pd(dba)_2$	Xantphos	Cs_2CO_3	DMF	24	<5[c]
10	$Pd(dba)_2$	Xantphos	Cs_2CO_3	DMSO	24	<5[c]
11	$Pd(dba)_2$	Xantphos	Cs_2CO_3	dioxane	24	<5
12	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	toluene	2	80
13	$Pd(OAc)_2$	Xantphos	K_2CO_3	toluene	5	84
14	**$Pd(OAc)_2$**	**Xantphos**	**K_2CO_3**	**toluene**	**5**	**82[d] (90)**
15	$Pd(OAc)_2$	Xantphos	K_2CO_3	toluene	23	75[e]

[a] Reaction conditions: **1a** (0.355 mmol), aniline (1.5 equiv), [Pd] (5 mol %), ligand (10 mol %), base (2.0 equiv), solvent (1.5 mL), under nitrogen. BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. DPPP = 1,3-Bis(diphenylphosphino)propane. JohnPhos = 2-(Di-*t*-butylphosphino)biphenyl. PCy_3 = tricyclohexylphosphine. TFP = Trifuran-2-ylphosphine. Xantphos = 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene. [b] Isolated yield. NMR yield was given in brackets. [c] At 120 °C. [d] $Pd(OAc)_2$ (2 mol %), Xantphos (4 mol %) were used. [e] $Pd(OAc)_2$ (1 mol %), Xantphos (2 mol %) were used.

Having developed conditions for the catalytic formation of indoles, we then extended the reaction to a range of commercially available primary amines. A wide variety of substitution patterns and functionalities were tolerated, as shown in Scheme 2. Substrates containing both electron-donating (**3ab**, **3ac** and **3ag**) and electron-withdrawing groups (**3ad**−**3af**, and **3ah**), or bearing *para*- (**3ab**−**3af**) and *meta*- groups (**3ag**−**3ah**) proceeded efficiently with good to excellent yields. However, anilines with a methyl or chloro substitution at *ortho*- position afforded **3ai** and **3aj** with atropisomeric structures,[12] which indicated that the indole derivatives possessing a steric bulky group on the nitrogen atom have a high rotational energy barrier around the N−Ar bond and significantly affect the reactivity. When pyridin-2-amine (**2k**) was used as the substrate, the corresponding amidated product **3ak** was obtained in 43% yield, and pyrimidin-5-amine (**2l**) could transform into **3al** in 70% yield. Intriguingly, *n*-butylamine and benzylamine can also be transformed into products in 91 and 73% yield, respectively (**3am** and **3an**).

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(11) Crystallographic data for **3aa′**: $C_{17}H_{15}NO_2$, M = 265.30, monoclinic, $C2/c$ (No. 15), a = 12.391(5) Å, b = 11.044 (5) Å, c = 20.158 (5) Å, β = 100.261 (5)°, V = 2714.4 (18) Å^3, Z = 8, Crystal size: 0.30 × 0.25 × 0.20 mm, T = 295 K, ρ_{calcd} = 1.298 g·cm^{-3}, R_1 = 0.0645 ($I > 4\sigma(I)$), wR_2 = 0.1911 (all data), GOF = 1.048, reflections collected/unique: 6427/2379 (*R*int = 0.0499), Data: 2379, restraints: 0, parameters: 182.

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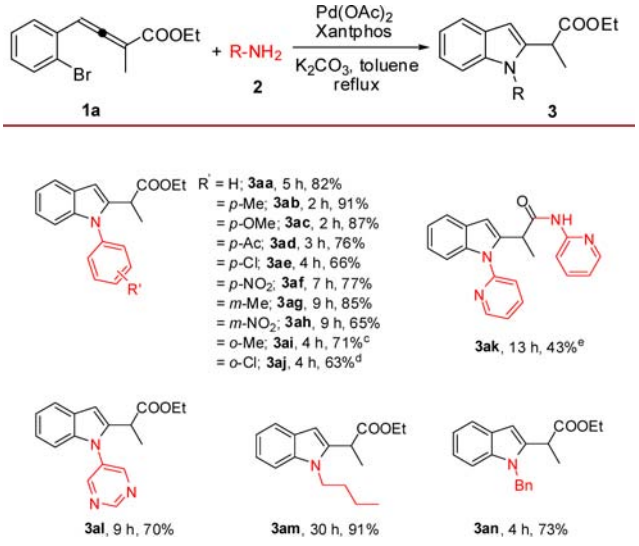
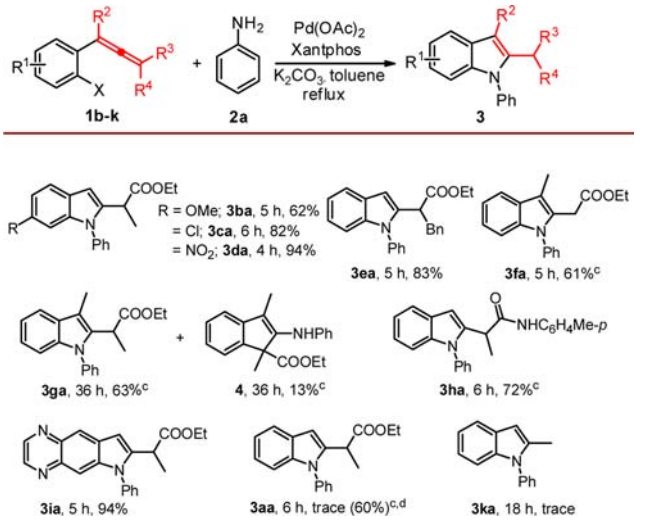
Scheme 2. Palladium-Catalyzed Reaction of **1a** with Primary Amines[a,b]



[a] Reaction conditions: **1a** (0.355 mmol), amine (1.5 equiv), $Pd(OAc)_2$ (2 mol %), Xantphos (4 mol %), K_2CO_3 (2 equiv), toluene (1.5 mL), reflux, under nitrogen. [b] Isolated yield. [c] The ratio of atropisomeric product is 1:1. [d] The ratio of atropisomeric product is 1.8:1. [e] Pyridin-2-amine (4 equiv) was used.

Scheme 3. Allene Scope in the Palladium Catalyzed Indole Synthesis[a,b]



[a] Reaction conditions: allene (1.0 equiv), aniline (1.5 equiv), $Pd(OAc)_2$ (2 mol %), Xantphos (4 mol %), K_2CO_3 (2 equiv), toluene (1.5 mL), reflux, under nitrogen. X = Br. [b] Isolated yield. [c] $Pd(OAc)_2$ (5 mol %), Xantphos (10 mol %), Cs_2CO_3 (2 equiv), xylene (1.5 mL), reflux, under nitrogen. [d] 4-(2-Chloro-phenyl)-2-methyl-buta-2,3-dienoic acid ethyl ester (**1j**) was used, X = Cl.

To study the effects of the electronic properties of substituents on this tandem process, cyclization of a series of substituted allenes **1b**–**k** were investigated, which could be readily obtained through the Wittig–Horner reaction.[10] As shown in Scheme 3, allenes bearing both electron-donating and electron-withdrawing group on the aryl ring could afford indole products **3ba**–**3da** efficiently, and electron-withdrawing substituent had more effect on the yield (**3da**). Changing the methyl substitution to benzyl group in **1a**, the indole **3ea** could be obtained in good yield. For multisubstituted allenes (**3fa**, **3ga**) or allenamide (**3ha**), better results could be achieved using Cs_2CO_3 as base under refluxed xylene. It should be noted that phenylamine substituted 1*H*-indene **4** could be isolated in 13% yield together with 63% yield of corresponding indole **3ga**. To further expand the scope of the reaction, substrate **1i** with quinoxaline moiety was investigated under standard conditions. Gratifyingly, the corresponding indole product **3ia** could also be well achieved in 94% yields. Furthermore, the less reactive chloro-substituted substrate **1j** gave trace amount of product **3aa**, while 60% yield of indole could be achieved using Cs_2CO_3 as base. However, when 1-bromo-2-(propa-1,2-dienyl)benzene (**1k**) was used under optimized reactions, no desired product (**3ka**) could be generated.

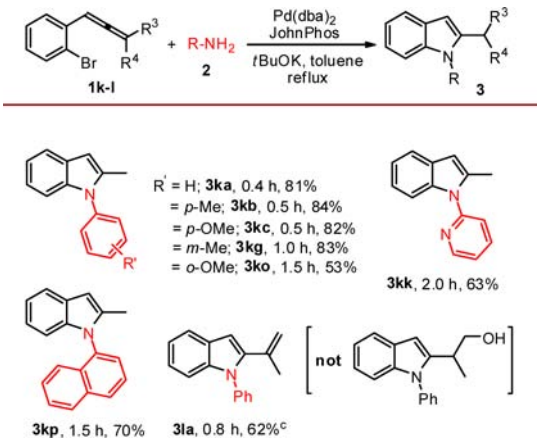
To settle this question, an extensive screening of palladium catalysts and ligands together with solvents and bases was next carried out, and we found that indole product **3ka** could be achieved significantly in the presence of $Pd(dba)_2$ and JohnPhos using 3.0 equiv of *t*BuOK as base in toluene.[13,14] The strong base *t*BuOK is essential to process this reaction; other bases such as K_2CO_3, Cs_2CO_3 and *t*BuONa gave only trace amount of indole product. Under the optimized conditions, the reaction proceeded very fast, and a series of aryl or heteroaryl amines could be tolerated in this tandem reaction as shown in Scheme 4. All of those substrates can react smoothly to provide the corresponding indoles in moderate to good yield. Aryl amines having substituents at *ortho*-, *meta*- or *para*- position gave 2-methyl substituted indoles in high yields (**3ka**–**3ko**). Amine substrates containing the substructure of pyridine (**3kk**) and naphthalene (**3kp**) also gave the corresponding indoles in good yield. In particular, when hydroxymethyl substituted allene **1l** was applied in this reaction, the dehydration reaction took place and gave **3la** in 62% yield. Furthermore, when we used **1a** as substrate under this condition, no product was detected, which implied that this condition is specifically adaptive to unsubstituted allene substrates.

To probe the mechanism, reactions were carried out to define the possible pathways, including (i) under optimized reaction conditions (Table 1, entry 14), only trace amount of **3aa** was found from chloro-substituted substrates **1j**; (ii) no enamine intermediate, which generated from addition product of **1a** and aniline, could be detected during the reaction or under refluxed toluene without palladium catalyst; (iii) when the reaction was conducted under

(13) For the conditions optimization for unsubstituted allene **1k**, see Table S1 in the Supporting Information.

(14) For the coordination chemistry of phosphine ligands, see: (a) Snelders, D. J. M.; van Koten, G.; Klein Gebbink, R. J. M. *Chem.—Eur. J.* **2011**, *17*, 42–57. (b) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741–2769.

Scheme 4. Amine Scope in the Palladium Catalyzed Indole Synthesis[a,b]



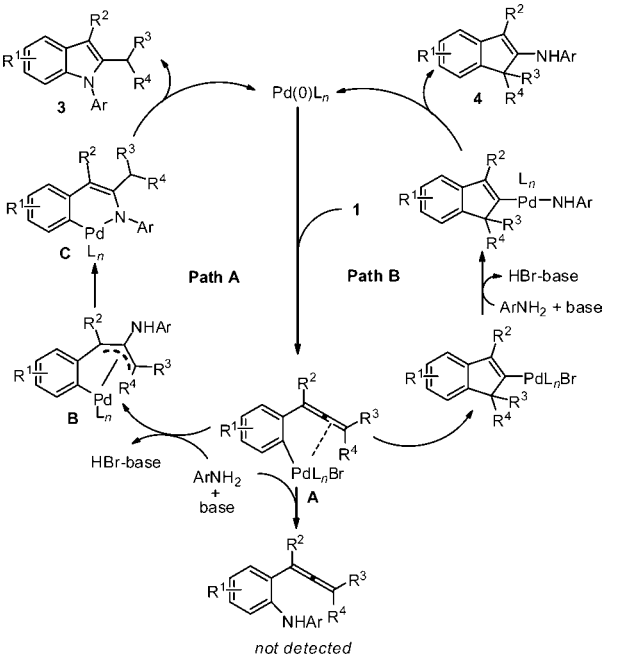
[a] Reaction conditions: allene (1.0 equiv), amine (1.5 equiv), $Pd(dba)_2$ (5 mol %), JohnPhos (10 mol %), *t*BuOK (3 equiv) in toluene, reflux, under nitrogen. $R^3 = R^4 = H$, unless otherwise indicated. [b] Isolated yield. [c] 4-(2-Bromophenyl)-2-methylbuta-2,3-dien-1-ol (**1l**) was used, $R^3 = CH_2OH$, $R^4 = CH_3$.

optimized reaction conditions, no direct Buchwald−Hartwig amination product was isolated or could be detected by LC−MS.

On the basis of these results, we proposed the plausible mechanism for the formation of indole **3** and 1*H*-indene **4** (Scheme 5). This tandem reaction may involve the oxidative addition of Pd(0) to the C−Br bond in **1**. The propadiene moiety in the formed intermediate **A** could be activated through coordination to the palladium and attacked by aniline to form intermediate **B**. The steric and electronic effects of ligand[14] may affect this activation of double bond, which will depend on the nature of allenes. The formation of **3** will go through intermediate **C** followed by reductive elimination of Pd(0).

In summary, an efficient palladium-catalyzed synthesis of *N*-functionalized multisubstituted indoles was developed in good to excellent yields from easily accessible *ortho*-haloarylallenes and primary amines. A wide range of electronically and structurally varied nitrogen fragments could be introduced through this tandem C−N bond-forming process by tuning the reaction conditions.

Scheme 5. Plausible Mechanism for Synthesis of **3** from **1**



The characteristics of excellent functional group tolerance and synthesis modularity will make the described reaction a broad utility in organic synthesis. Further insight into the scope and mechanism are now under investigation in our laboratory and will be reported in due course.

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Supporting Information Available. Experimental procedures and characterization data for all compounds, X-ray structure of **3aa′** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.