



A novel route to 2,3-disubstituted indoles via palladium-catalyzed three-component coupling of aryl iodide, *o*-alkenylphenyl isocyanide and amine

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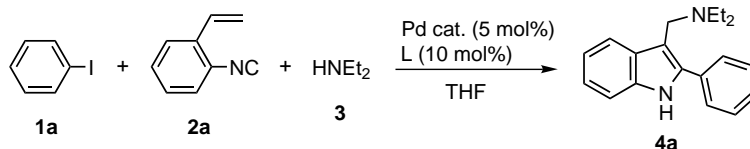
Abstract—Three-component coupling reactions of aryl iodide, *o*-alkenylphenyl isocyanide and amine in the presence of palladium catalysts produced 2,3-disubstituted indoles in moderate yields. © 2002 Elsevier Science Ltd. All rights reserved.

Since an indole nucleus is found in a wide variety of biologically active natural products, considerable attention has been directed toward the synthesis of indole derivatives.¹ Although many procedures have been developed for the synthesis of indoles,^{2,3} annulation mediated by palladium catalysts is one of the most powerful tools.⁴ On the other hand, *ortho*-functionalized aryl isocyanides are fascinating substrates for synthesis of the indole framework due to the high reactivity of isocyanides.^{5,6} Although an efficient route from *o*-alkenylphenyl isocyanides via radical cyclization has been developed,⁷ there are few reports on approaches to indole synthesis using transition metal mediators.^{5,8} We recently showed the formation of indole derivatives from *o*-alkenylphenyl isocyanide through the use of a stoichiometric amount of an organopalladium complex.⁹ We extended this finding to a catalytic process. We report here a novel catalytic synthesis of 2,3-disubstituted indoles by the three-component coupling of aryl iodide, *o*-alkenylphenyl isocyanide and amine (Scheme 1).

When a mixture of phenyl iodide (**1a**), *o*-vinylphenyl isocyanide (**2a**)¹⁰ and diethylamine (**3**) in a ratio of

1.2:1:18 in THF was stirred at 40°C for 10 h in the presence of 5 mol% of Pd(OAc)₂ and 10 mol% of dppp, 3-(diethylamino)methyl-2-phenylindole (**4a**) was obtained in 32% yield (Table 1, entry 1).¹¹ An increase in the ratio of **1a**:**2a** led to a slight increase in the yield of **4a** (entries 2 and 3). Although the reaction using 6 equiv. of **3** relative to **2a** gave **4a** in a yield similar to that using 18 equiv. of **3** (entry 4), a further decrease in the amount of **1** decreased the yield of **4a** (entry 5). At 60°C, no considerable difference in the yield of **4a** was observed (entry 6), while the reaction at 25°C hardly proceeded and **4a** was obtained in only 8% yield (entry 7).

Addition of PPh₃ to the reaction mixture instead of dppp remarkably decreased the yield of **4a** (entry 8). This phenomenon is likely due to the lower reactivity of the intramolecular successive insertion of **2a** toward organopalladium complexes with PPh₃ compared to those with dppp.⁸ The length of the alkyl chain of palladium catalysts also affected the reactivity of palladium catalysts. Thus, the use of dppe or dppb as a ligand decreased the yield of **4a** (entries 9 and 10). Although Pd₂(dba)₃ could be used as a catalyst precursor (entry



Scheme 1.

Keywords: indole; cyclization; isocyanide; palladium catalyst.

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Table 1. Three-component coupling reaction under several conditions

Entry	1a (equiv.) ^a	3a (equiv.) ^a	Pd cat. ^b	Ligand ^c	Temp. (°C)	Time (h)	Yield of 4a ^d (%) ^e
1	1.2	18	Pd(OAc) ₂	dppp	40	10	32
2	2.4	18	Pd(OAc) ₂	dppp	40	9	36
3	3.6	18	Pd(OAc) ₂	dppp	40	3.5	42
4	3.6	6	Pd(OAc) ₂	dppp	40	5.5	43
5	3.6	2.5	Pd(OAc) ₂	dppp	40	6	21
6	3.6	18	Pd(OAc) ₂	dppp	60	1	44
7	3.6	18	Pd(OAc) ₂	dppp	25	3.5	8
8	3.6	18	Pd(OAc) ₂	PPh ₃	40	33	6
9	3.6	18	Pd(OAc) ₂	dppe	40	33	18
10	3.6	18	Pd(OAc) ₂	dppb	40	7	9
11	3.6	18	Pd ₂ (dba) ₃	dppp	40	9	36
12	3.6	18	Pd ₂ (dba) ₃	bpy	40	26	3

^a Based on **2**.^b 5 mol%.^c 10 mol%.^d Compound **4a** isolated was characterized by spectral analyses.^e Determined by ¹H NMR.

11), 2,2'-bipyridine was not suitable as a ligand (entry 12).

This reaction could be applied to a substituted aryl iodide, as summarized in Table 2. *p*-Methoxyphenyl iodide **1b** and *p*-nitrophenyl iodide **1c** also produced 2,3-substituted indole derivatives **4b** and **4c**, respectively (entries 2 and 3). However, the reaction using phenyl triflate **1d** gave **4a** in 10% yield (entry 4). When *o*-(methoxycarbonylphenyl)phenyl isocyanide (**2b**)⁸ was used instead of **2a**, the corresponding indole derivative was not formed.

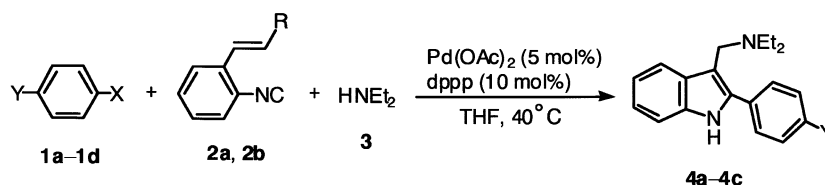
Based on our previous results on the stoichiometric reaction of palladium complexes with *o*-alkenylphenyl isocyanide,⁸ the catalytic cycle that may be responsible for the formation of **4** is illustrated in Scheme 2. Phenylpalladium complex **6** generated by the oxidative addition of aryl iodide to Pd(0) species **5** reacts with **2** to induce the successive insertion of the alkenyl and isocyno groups followed by the 1,3-migration of

hydrogen to give (η^3 -indolylmethyl)palladium complex (**7**). Nucleophilic attack by diethylamine produces 2,3-disubstituted indoles along with palladium hydride complex **8**, which is converted into Pd(0) species **5** by the reaction with amine.

In summary, we have demonstrated a new route to 2,3-disubstituted indoles through the three-component coupling of aryl iodide, *o*-alkenylphenyl isocyanide and amine using palladium catalysts. Further studies on the scope and limitations of this catalytic reaction are now in progress.

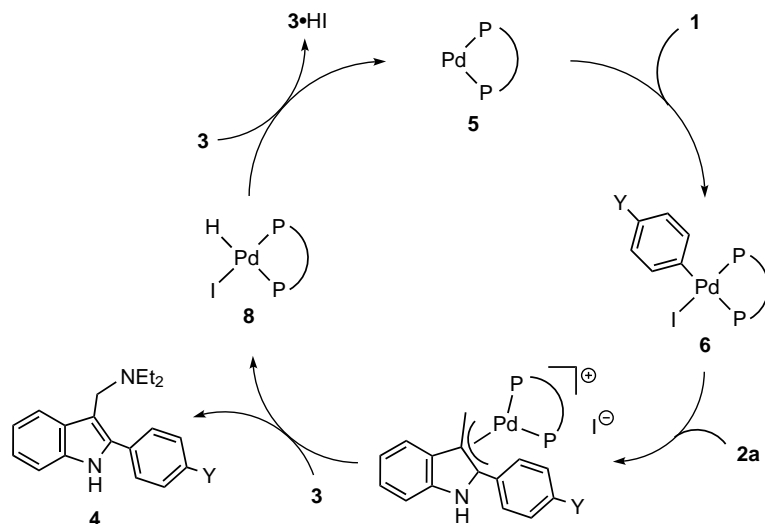
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Table 2. Three-component coupling reaction^a

Entry	Aryl halide	<i>o</i> -Alkenylphenyl isocyanide	Time (h)	Yield (%) ^b
1	1a (Y=H, X=I)	2a (R=H)	3.5	42 (4a)
2	1b (Y=OMe, X=I)	2a (R=H)	21	39 ^c (4b)
3	1c (Y=NO ₂ , X=I)	2a (R=H)	2	24 ^c (4c)
4	1d (Y=H, X=OTf)	2a (R=H)	27	10 (4a)
5	1a (Y=H, X=I)	2b (R=CO ₂ Me)	30	–

^a **1/2/3**=3.6/1/18.^b Determined by ¹H NMR.^c Isolated yield.



Scheme 2.

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