

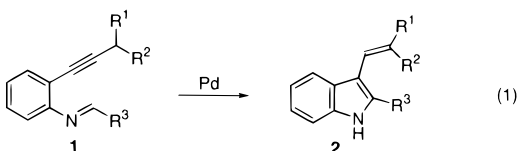
Indole Synthesis via Palladium-Catalyzed Intramolecular Cyclization of Alkynes and Imines

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Indole is one of the most basic units among a wide variety of naturally occurring alkaloids, and much attention has been paid to developing a new methodology for the construction of this structural framework.¹ Among the approaches employing transition metal catalysts,² the palladium-catalyzed ring construction of indole has been investigated widely.³ The previous methods are categorized under the following three types: the intramolecular cyclization of 2-alkynylanilines (**a** in Scheme 1),^{3a–d} Heck-type cyclization of 2-halo-*N*-allyl-^{3e} or vinyylanilines (**b**),^{3f,g} and intermolecular cycloaddition of 2-haloanilines and internal alkynes (**c**).^{3h–j} Therefore, the indole ring is formed between N and C-2 (**a**), between C-3 and C-aryl (**b**), and between N and C-2 and between C-3 and C-aryl (**c**). We report an entirely new palladium-catalyzed indole synthesis in which 2-(1-alkynyl)-*N*-alkylideneanilines **1** give 2-substituted-3-(1-alkenyl)indoles **2** in good yields (eq 1). Here the bond formation takes place between C-2

and C-3 (**d**).⁴

The results are summarized in Table 1. When *N*-benzylidene-2-(1-pentynyl)aniline (**1a**) was heated at 100 °C for 25 h in the presence of 5 mol % palladium acetate and 20 mol % tri-*n*-butylphosphine in 1,4-dioxane, 3-((*E*)-1-butenyl)-2-phenylindole (**2a**) was formed in 88% NMR yield (entry 1). It is known that 2- or 3-alkenylindoles are unstable,⁵ and actually at the beginning we had difficulty isolating **2a** in a pure form. However, we found that pure **2a** could be isolated with Al₂O₃ column chromatography (hexane–AcOEt 50–20/1) in 58% yield (entry 1). The hydro-

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(5) (a) Bergamasco, R.; Porter, Q. N.; Yap, C. *Aust. J. Chem.* **1977**, *30*, 1531. (b) Lambert, J. D.; Porter, Q. N. *Aust. J. Chem.* **1981**, *34*, 1483. (c) *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, U.K., 1984; Vol. 4, p 282.

Scheme 1. Palladium-Catalyzed Indole Syntheses

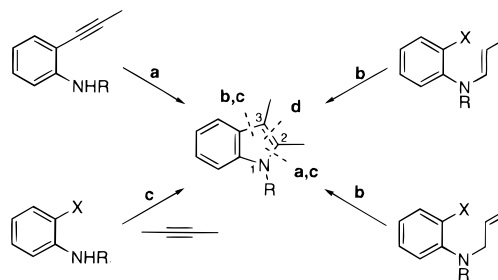
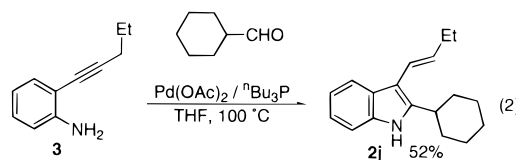


Table 1. Palladium-Catalyzed Cyclization of Alkynylimines **1**^a

entry	1	R ¹	R ²	R ³	2	yield (%) ^b
1	1a	Et	H		2a	58 (88)
2	1b	Et	H		2b	70 (65)
3	1c	Et	H		2c	64 (99)
4	1d	Et	H		2d	70 (78)
5	1e	Et	H		2e	63 (82)
6 ^c	1f	–(CH ₂) ₅ –	H		2f	71
7	1g	OTHP ^d	H		2g^e	56 (61)
8	1h	CH ₂ OMOM ^f	H		2h	55 (60)
9	1i	(CH ₂) ₂ CO ₂ Et	H		2i	59 (73)

^a Pd(OAc)₂ (5 mol%), *n*Bu₃P (20 mol%), 1,4-dioxane (0.5 M), 100 °C in the sealed vial. ^b Isolated yield. Yield in parentheses was determined by ¹H NMR. ^c Reaction was carried out at 80 °C. ^d THP, tetrahydropyranyl. ^e Trans:cis = 4:1 as determined by ¹H NMR. ^f MOM, methoxymethyl.

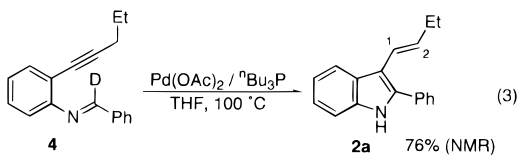
genation of **2a** with H₂/Pd–C gave 3-butyl-2-phenylindole in 60% yield, confirming the structure of **2a** unambiguously. The *p*-nitrophenyl-substituted substrate **1b** reacted smoothly within 7 h to give **2b** in 70% yield. 4-Pyridyl **1c**, 2-thienyl **1d**, and 2-(5-methylfuryl) derivatives **1e** afforded the corresponding indoles **2c–e**, respectively, in good yields (entries 3–5). Cyclohexyl derivative **1f** afforded the β,β-disubstituted vinylindole **2f** in a good yield. Not only ethyl-substituted derivatives but also the functional group-substituted **1g–i** gave the corresponding indoles **2g–i** in moderate isolated yields. An attempt to prepare alkyl-substituted imines failed because of lack of stability of the resulting imines.⁶ Accordingly, we attempted the in situ formation of the imine from the 2-alkynylaniline **3** and cyclohexanecarboxaldehyde followed by subsequent cyclization. This trial proceeded well and **2j** was obtained in 52% yield (eq 2). The in



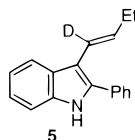
2k: R¹ = Et, R² = H, R³ = (Ph)₂CH
2l: R¹ = Et, R² = H, R³ = Ph(Me)CH
2m: R¹ = Et, R² = H, R³ = (CH₃)₂CH

situ reaction of **3** with the other secondary aliphatic aldehydes, such as 2,2-diphenylethanal, 2-phenylpropanal, and 2-methylpropanal, proceeded without problem to give the corresponding indoles **2k**, **2l**, and **2m**, respectively, in good to acceptable yields. The in situ reaction of **3** with benzaldehyde gave **2a** in 74% NMR yield.

To clarify the mechanism of this unprecedented palladium-catalyzed cyclization, the reaction of the deuterated substrate **4** was examined (eq 3). Nondeuterated **2a** was produced in 76%



NMR yield. If the oxidative addition of the C–D bond of imine **4** to palladium followed by the carbopalladation or hydroypalladation to alkyne takes place, the product deuterated at the C-1 position of the alkenyl substituent should be obtained.⁷ On the other hand, when the reaction of nondeuterated **1a** was carried out in the presence of deuterium oxide (1.0 equiv), the deuterated product **5** was obtained in 80% NMR yield in which D content



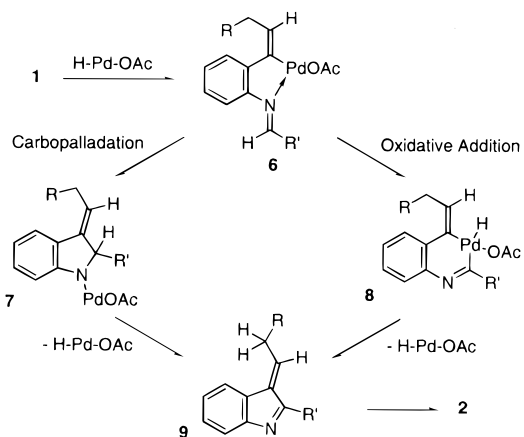
at the C-1 position of the alkenyl substituent was 29%.⁸ Accordingly, the reaction proceeds most probably through the regioselective insertion of a palladium–hydride species to the alkyne of **1** (Scheme 2). The resulting vinylpalladium **6** would give **9** either through the carbopalladation (leading to **7**)– β -hydride elimination pathway or through the oxidative addition (leading to **8**)–reductive elimination route.⁹ The bond rearrangement of the indolenine **9** would give **2**. It is known that the reaction of Pd(OAc)₂ with Bu₃P gives Pd(0), Bu₃P=O, and Ac₂O

(6) The reaction of **3** with the corresponding aromatic aldehydes with Na₂SO₄, MgSO₄, and Dean–Stark dehydrator was very sluggish and not completed even after a prolonged reaction time. However, the use of molecular sieves gave **1a–i** in high yields with shorter reaction times. In the case of aliphatic aldehydes, there was no need to use molecular sieves: (a) Sandler, S. R.; Karo, W. *Organic Functional Group Preparations*; Academic Press: Orlando, FL, 1986; Chapter 12. (b) Layer, R. B. *Chem. Rev.* **1963**, 63, 489.

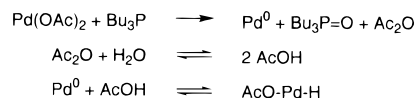
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(8) No deuterium was found in the other carbons of the indole product.

Scheme 2. Plausible Mechanism



Scheme 3



(Scheme 3).¹⁰ As previously reported,¹¹ a palladium–hydride species would be formed by the reaction of Pd(0) with AcOH, which is generated in situ by the hydrolysis of Ac₂O with H₂O.¹² Actually the reaction of **1a** in the presence of 2.5 mol % Pd₂-dba₃·CHCl₃, 10 mol % *n*-Bu₃P, and 1.1 equiv of AcOD gave **5** in 42% NMR yield in which D content at C-1 position of alkenyl substituent was 21%. Furthermore, the above reaction did not occur in the absence of AcOD.

The palladium-catalyzed intramolecular cyclization of the alkyne and imine functional groups of **1** gives functionalized 3-alkenyloindoles **2**, which are not easily available via the traditional synthetic methods, in good yields. Especially, the *three-component coupling reaction* (amine, aldehyde, alkyne) for the indole synthesis (as shown in eq 2) is attractive. Further studies are in progress in our laboratories.

Supporting Information Available: Experimental procedures and spectroscopic and analytical data for relevant compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(12) It is thought that trace amounts of H₂O exist in the reaction media, although a dry solvent was used.