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Highly efficient dehydrogenation of indolines to indoles using hydroxyapatite-bound Pd catalyst

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Abstract—A hydroxyapatite-bound palladium catalyst was found to be effective for the dehydrogenation of various types of indolines to give the corresponding indoles. Moreover, the catalyst was readily recovered from the reaction mixture, and could be reused without any loss of its catalytic activity.

Indole and its myriad derivatives often possess physiological activities, and have served as important and versatile intermediates for the synthesis of pharmaceuticals, agrochemicals, and finechemicals.[1] A large number of methodologies for indole ring syntheses have been developed and this trend is still ongoing.[2] Among them, direct dehydrogenation of indolines to indoles is a promising protocol for accessing a wide variety of indole derivatives.[3] Although various oxidizing reagents, such as MnO_2,[4] Fremy's salt (potassium nitrosodisulfonate),[5] $CuCl_2$–pyridines,[6] azasulfonium salts,[7] *N*-*tert*-butylsulfinimidoyl chloride,[8] and trichlorocyanuric acid,[9] are generally available to accomplish this direct dehydrogenation, these reagents are often harmful and toxic, and require considerable amounts. Consequently, with respect to the environmental concerns, there is a strong demand for a clean and highly efficient catalytic methodology for the conversion of indolines to indoles.

Hydroxyapatites, the main component of bones and teeth, are of considerable interest in view of their potential use as biomaterials, adsorbents, and ion-exchangers.[10] To date, however, only a few applications as catalysts or as catalyst supports have emerged. Most recently, we have reported that a hydroxyapatite-bound Pd catalyst (PdHAP) can act as a highly efficient heterogeneous catalyst for the aerobic oxidation of alcohols,[11] and for the deprotection of *N*-benzyloxycarbonyl group from amino acids using molecular hydrogen.[12] During the course of our studies, the dehydrogenation of various indolines in the presence of PdHAP can also proceed efficiently. In addition to advantages such as simple work-up procedures and the ability to recycle the catalyst, the catalytic system described herein exhibits high catalytic activities as compared to other reported methods.

Calcium hydroxyapatite (HAP), $Ca_{10}(PO_4)_6(OH)_2$, was synthesized according to procedures described in the previous literature.[13] HAP (2.0 g) was stirred in a $PdCl_2(PhCN)_2$ (2.67×10^{-4} M) solution in acetone (150 mL) at room temperature for 3 h. The resulting slurry was filtered, washed with acetone and dried under vacuum, yielding the PdHAP (2.01 g, Pd content: 0.02 mmol g^{-1}) as a pale yellow powder. Characterization by elemental analysis, XPS, EDAX, and Pd–K edge XAFS revealed that a monomeric $PdCl_2$ species was grafted by chemisorption on the HAP surface.[11]

A typical reaction procedure is as follows: into a reaction vessel equipped with a reflux condenser were placed the PdHAP (0.05 g, Pd: 1 μmol), indoline (2.38 g, 20 mmol), and toluene (25 mL). After stirring the heterogeneous mixture at 120°C under an argon atmosphere for 6 h, the PdHAP was separated by filtration. GC analysis of the filtrate showed 99% yield of indole. Removal of the solvent under the reduced pressure, followed by recrystallization from *n*-hexane solution afforded pure indole (2.16 g, 92% isolated yield).

Keywords: dehydrogenation; indoline; indole; heterogeneous Pd catalyst; hydroxyapatite.

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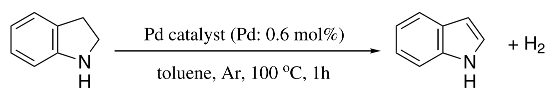
Initially, the dehydrogenation of indoline **1** to indole **2** was examined as a model reaction using various Pd catalysts. As shown in Table 1, the PdHAP exhibited the highest catalytic activity in toluene under an argon atmosphere to give **2** in almost quantitative yield after 1 h (entry 1). Other conventional heterogeneous Pd catalysts such as Pd/carbon (5 wt%) and Pd/activated carbon (10 wt%) were found to be less effective under similar reaction conditions (entries 3 and 4). The use of homogeneous Pd catalysts, e.g. $Pd(OAc)_2$, $PdCl_2(PhCN)_2$, and $Pd_2(dba)_3CH_3Cl$ also resulted in low yields, accompanied with the formation of palladium black (entries 5–8). Among the solvents examined, the use of DMF and 1,4-dioxane provided favorable results (94 and 80% yields, respectively), whereas chlorobenzene, nitromethane, and DMSO were not effective at all. It is notable that dehydrogenation under an oxygen atmosphere was significantly retarded (entry 2).[14]

The results of PdHAP-catalyzed dehydrogenation of various indolines are summarized in Table 2. All methyl substituted indolines were dehydrogenated to give the corresponding indoles in high yields (entries 3–7) without the influence of substituted positions except for 2,3-dimethylindoline (entry 8).[15] Remarkably, even sterically hindered indolines such as carbazoline,[16] *N*-benzylindoline, and 2-phenylindoline were converted to the corresponding indoles in 94, 92, and 92% yields, respectively (entries 9–11). Among the indoline derivatives, 6-nitroindoline and 5-bromoindoline were scarcely oxidized under the above conditions.

To highlight the applicability of the present protocol, a 20 mmol scale reaction of **1** was undertaken using 5×10^{-3} mol% of the Pd catalyst. Dehydrogenation was completed within 6 h to afford **2** in 99% yield, in which the TON based on Pd approached up to 20 000 with an excellent TOF of approximately 2800 h^{-1}. *These TON and TOF values are significantly higher than those reported for other catalytic systems*, such as tetrapropylammonium perruthenate (TPAP)/NMO (TON = 15, TOF = 4 h^{-1}),[17] Co(salen)/O_2 (TON = 9, TOF = 2 h^{-1}),[18] and the conventional Pd/carbon (TON = 100, TOF = 50 h^{-1}).[1a] From the viewpoint of recent environmental consciousness, it is desirable to use water instead of organic solvents as the reaction medium.[19] It is noteworthy that the PdHAP was proved to be an efficient catalyst even under aqueous conditions. For example, dehydrogenation of **1**, 2-methylindoline, and carbazoline proceeded smoothly to give **2**, 2-methylindole, and 1,2,3,4-tetrahydrocarbazole in excellent yields for 3 h, respectively (Scheme 1).[20]

Table 1. Dehydrogenation of indoline using various Pd catalysts[a]



1 **2**

Entry	Catalyst	Convn (%)[b]	Yield (%)[b]
1	PdHAP	>99	>99
2[c]	PdHAP	15	15
3	Pd/carbon (5 wt%)[d]	28	28
4	Pd/activated carbon (10 wt%)[d]	49	49
5	$Pd(OAc)_2$	48	48
6	$PdCl_2(PhCN)_2$	45	43
7	$Pd_2(dba)_3CHCl_3$	48	47
8	$Pd(acac)_2$	45	43

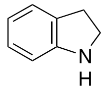
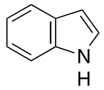
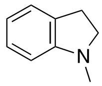
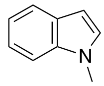
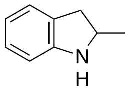
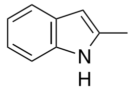
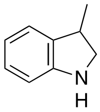
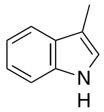
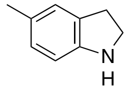
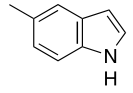
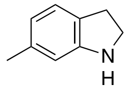
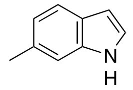
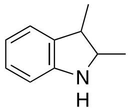
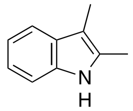
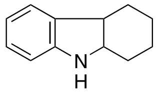
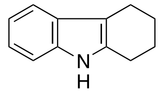
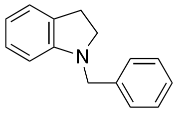
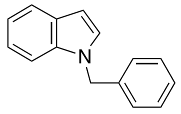
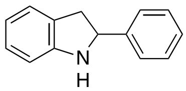
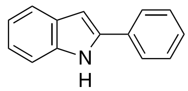
[a] *Reaction conditions*: Pd catalyst (Pd: 0.6 mol%), indoline (1 mmol), toluene (5 mL), 100°C, Ar, 1 h.

[b] Determined by GC using an internal standard technique.

[c] Under O_2 atmosphere.

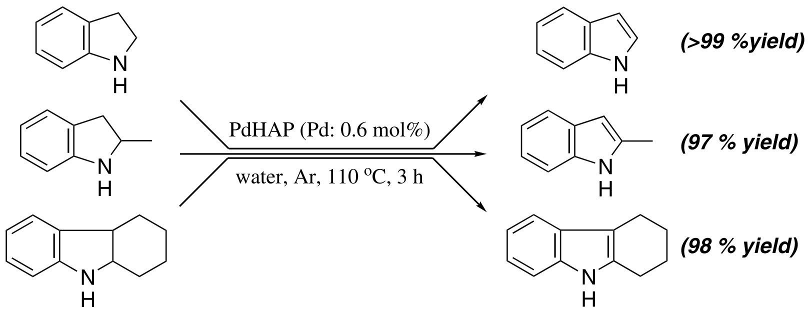
[d] Purchased from Wako Pure Chemical Industries, Ltd.

Table 2. Dehydrogenation of indoline derivatives catalyzed by PdHAP[a]

entry	substrate	time (h)	product	yield (%)[b]
1 2[c]		1		>99 (88) 97
3		1		>99
4		1		>99 (94)
5		3		98
6		3		97
7		3		98
8[d]		24		25
9[e]		2		94
10		2		92 (86)
11[f]		1		92

[a] *Reaction conditions*: substrate (1 mmol), PdHAP (0.3 g, Pd: 0.6 mol%), toluene (5 mL), 100 °C, atmospheric Ar. [b] Determined by GLC using an internal standard technique. Values in parenthese are isolated yield. [c] Recycling experiment.

[d] Substrate (*cis*:*trans* = 1:3). [e] The *cis* isomer was synthesized according to the literature procedure. See ref. 16. Substrate (0.5 mmol).



Scheme 1. Dehydrogenation of indolines catalyzed by PdHAP in water.

Upon completion of the reaction, the catalyst was easily separated from the reaction mixture. ICP analysis of the filtrate confirmed that no leaching of the Pd species occurred during the above dehydrogenation. Subsequently, it was shown that the recovered PdHAP could be reused without any loss of its catalytic activity (Table 2, entry 2). In the reaction of **1**, the PdHAP was removed after 40% conversion. The filtrate was further reacted at 100°C for 1 h and no dehydrogenation was occurred. TEM images for the isolated PdHAP revealed the presence of Pd nanoparticles with diameters of ca. 9 nm, showing that the monomeric Pd(II) species on HAP are reduced to Pd(0) under the reaction conditions, and the dehydrogenation occurs on the Pd particles located on the HAP surface.

We here propose a possible mechanism for this indoline dehydrogenation. Initially, a nitrogen atom of indoline coordinated to the Pd(0) species, followed by oxidative addition at the C–H bond adjacent to the nitrogen atom to give a σ-alkyl Pd species.[21] Subsequently, this intermediate species undergoes β-hydride elimination to afford the corresponding indole and Pd(0), along with the evolution of molecular hydrogen.[22] Vide supre, the stereoselective dehydrogenation of 2,3-dimethylindoline shows that the β-elimination occurs in a *syn* manner.

In conclusion, the PdHAP was demonstrated to be an efficient heterogeneous palladium catalyst for the dehydrogenation of indolines to indoles. The present catalytic system can offer significant benefits in achieving the simple and clean synthesis of indoles.

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14. Generally, indoles are sensitive to oxygen, and consequently, the decrease in the catalytic activity may be attributed to the deactivation of PdHAP by the over-oxidized products.
15. In the case of 2,3-dimethylindoline (*cis*:*trans* = 1:3), only the *cis* isomer was exclusively dehydrogenated to 2,3-dimethylindole, whereas the *trans* isomer remained intact.
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20. Typical work-up procedures for the dehydrogenation under aqueous conditions are as follows: the reaction mixture was extracted with ethyl acetate, and then the organic layer was dried over $MgSO_4$. Removal of ethyl acetate under the reduced pressure, followed by recrystallization from *n*-hexane solution afforded pure **2** (0.112 g, 93% isolated yield).
21. For the α-C–H-bond activation mechanism in the alkyl exchange reaction of amines, see Murahashi, S.-I.; Yoshida, N.; Tsumiyama, T.; Kojima, T. *J. Am. Chem. Soc.* **1983**, *105*, 5002.
22. The evolution of hydrogen gas was measured by the following experiment: PdHAP (Pd: 0.6 mol%) was placed in a sidearmed flask attached to a gas buret. The system was evacuated and filled with Ar, followed by the addition of toluene (5 mL) and **1** (1 mmol), and then reacted for 1 h at 100°C. The molar ratio of evolved H_2 gas to **2** was ca. 1:1.