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Heterogeneously Palladium-catalyzed Acceptorless Dehydrogenative Aromatization of Cyclic Amines

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Heterogeneously Palladium-catalyzed Acceptorless Dehydrogenative Aromatization of Cyclic Amines

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In this manuscript, we report an efficient heterogeneously catalyzed acceptorless dehydrogenative aromatization of cyclic amines under relatively mild conditions. In the presence of a supported catalyst Pd/LDH (LDH = layered double hydroxide), various kinds of structurally diverse cyclic amines including piperidines, tetrahydro(iso)quinolines, and indolines could be converted into the corresponding heteroarenes. Pd/LDH could be reused several times though its catalytic activity gradually declined due to the increase in the palladium particle size.

Keywords: Dehydrogenative Aromatization, Cyclic amines, Palladium

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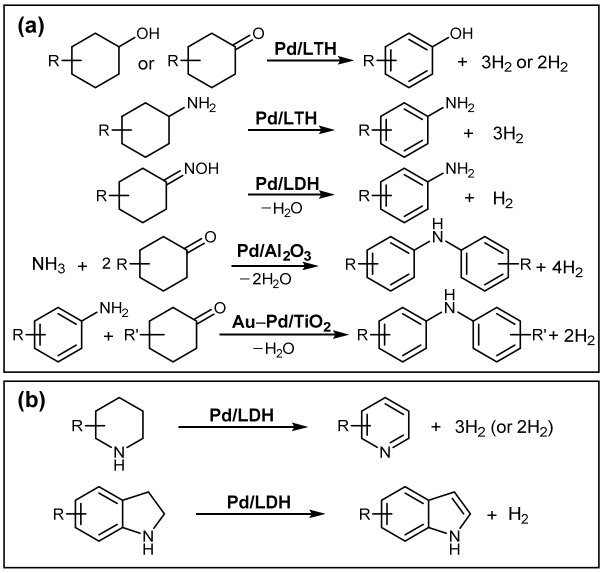
Catalytic dehydrogenation is one of the most fundamentally important reactions in both bulk and fine chemical productions.[1] In industrial alkene productions, dehydrogenation has frequently been performed using heterogeneous catalysts under harsh reaction conditions.[2] Several homogeneous complexes have been utilized for laboratory scale dehydrogenation-based fine chemical synthesis in the presence of appropriate hydrogen acceptors.[3] In recent years, development of functional group transformation methods with low environmental load and high atom efficiency under mild reaction conditions is highly demanded, especially attention is focused on development of reactions based on catalytic acceptorless dehydrogenation.[4] For example, considering alcohol oxidation, if the reaction can be realized as a highly efficient catalytic acceptorless dehydrogenation, H_2 gas can be taken out at the same time in addition to useful carbonyl compounds.[5] Therefore, development of catalytic dehydrogenation systems plays an important role not only from a synthetic point of view but also in H_2 production and transportation.[6]

From the above-mentioned viewpoint, we have focused on developing several acceptorless dehydrogenative aromatization systems using supported palladium-nanoparticles-based catalysts; namely, dehydrogenation of cyclohexanols/cyclohexanones to phenols,[7a] dehydrogenation of cyclohexylamines to anilines,[7a] transformation of cyclohexanone oximes to anilines,[7b] and synthesis of symmetrically[7c] and unsymmetrically[7d] substituted diarylamines (Scheme 1a). Based on these findings, we here aimed to develop a highly efficient catalytic system for acceptorless dehydrogenation of cyclic amines to produce heteroarenes. Heteroarenes are very important compounds which are frequently seen in many pharmaceuticals.[8] Dehydrogenative aromatization of cyclic amines is drawing attention as one of the methods for synthesizing heteroarenes, and many efficient catalytic systems using various kinds of oxidants (hydrogen acceptors) have been recently developed.[9] Also, many efficient catalytic systems for the acceptorless dehydrogenative aromatization of benzo-fused *N*-heterocycles, *e.g.*, tetrahydro(iso)quinolines and indolines, and piperazines have also been reported until now.[10] However, with respect to simple non-activated piperidines, there are almost no reports so far, including systems using hydrogen acceptors;[11] thus there is still room for development.[12]



Scheme 1. (a) Our recently developed acceptorless dehydrogenative aromatization reactions and (b) acceptorless dehydrogenative aromatization of cyclic amines (this work). LTH = Mg–Al–Ni layered triple hydroxide, LDH = Mg–Al layered double hydroxide.

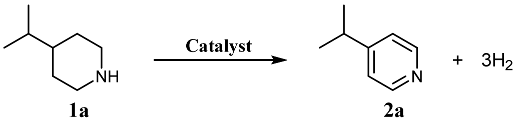
Herein, we report an efficient acceptorless dehydrogenative aromatization of cyclic amines by supported palladium nanoparticles on layered double hydroxide $Mg_6Al_2(OH)_{16}CO_3 \cdot 4H_2O$ (Pd/LDH) (Scheme 1b). In the presence of Pd/LDH, dehydrogenative aromatization of various kinds of structurally diverse cyclic amines including piperidines, tetrahydro(iso)quinolines, and indolines efficiently proceeded to afford the corresponding heteroarenes in moderate to high yields under relatively mild conditions (80–125 °C). The choice of solvents was very important to allow the reaction to proceed under mild conditions, and aliphatic hydrocarbon solvents such as octane gave good results. The observed catalysis was truly heterogeneous in nature, and the Pd/LDH catalyst could be reused at least four times for the reaction of a model substrate (4-isopropylpiperidine, **1a**) though its catalytic activity gradually declined due to the increase in the palladium particle size.

In our previous studies, we have found that only palladium-based catalysts exhibited high performance for dehydrogenative aromatization reactions.[7] Therefore, we prepared supported palladium catalysts using various supports by the following deposition-precipitation method (Pd/support, support = LDH, Al_2O_3, CeO_2, or TiO_2).[7] Support (1.0 g) was added to a 30 mL aqueous solution of $PdCl_2$ (8.3 mM) and KCl (two equivalents with respect to $PdCl_2$, 16.7 mM). The mixture was vigorously stirred at room temperature for 15 min. Then, the pH of the mixture was adjusted to 10 by using an aqueous solution of NaOH (1.0 M), and the resulting slurry was further stirred for 18 h at room temperature. The solid was then filtered off, washed with water (*ca.* 3 L), and dried in vacuo overnight to afford Pd/support as light brown powder.

The X-ray photoelectron spectroscopy (XPS) spectrum of the freshly prepared Pd/LDH catalyst showed that the binding energies of Pd $3d_{3/2}$ and Pd $3d_{5/2}$ were 341.1 eV and 335.9 eV, respectively (Figure S1a), indicating that the oxidation state of the palladium species was +2. The X-ray diffraction (XRD) pattern of Pd/LDH was almost the same as that of the parent LDH support, and no obvious signals due to palladium oxides and hydroxides were detected (Figure S2a, b). Thus, Pd(II) hydroxide species are likely highly dispersed on LDH. To begin with, we conducted the acceptorless dehydrogenative aromatization of **1a** to 4-isopropylpyridine (**2a**) in the presence of Pd/LDH. The Pd/LDH-catalyzed reaction in octane efficiently proceeded under relatively mild conditions (120 ºC) in comparison with previously reported dehydrogenation systems[10–12] including our systems,[7] giving the desired **2a** in 95% yield for 2 h without detectable by-products (Table 1, entry 1). It was confirmed by volumetric measurement and MS analysis of the evolved gas that three equivalents of H_2 gas with respect to **2a** was produced during the reaction. Under the present conditions, the reaction hardly proceeded in the absence of the catalysts or the presence of just LDH (Table 1, entry 16).

The color of Pd/LDH was changed from initial light brown to black within a few minutes after the start of the reaction. After completion of the reaction, the catalyst was recovered, and its XPS spectrum was measured. The peaks due to the binding energies of Pd $3d_{3/2}$ and Pd $3d_{5/2}$ were observed at 339.9 eV and 334.5 eV, respectively (Figure S1b). Therefore, the Pd(II) species in the freshly prepared catalyst was reduced to Pd(0) species during the reaction. The XRD pattern of the used Pd/LDH indicated that the structure of LDH was maintained and no large palladium particles were formed during the reaction (Figure S2c). The transmission electron microscopy (TEM) analysis of the used catalyst revealed that palladium nanoparticles were formed on the surface of LDH (average particle size (d_{av}) = 3.9 nm, standard deviation (σ) = 1.1 nm, Figure S3a). Based on the above experimental results, it was revealed that in situ generated Pd(0) nanoparticles were the active species for the present acceptorless dehydrogenative aromatization.

Table 1. Acceptorless dehydrogenative aromatization of **1a** to **2a** under various conditions[a]



Entry	Catalyst	Solvent	Time/ h	Yield/ %
1	Pd/LDH	Octane	2	95
2	Pd/LDH	Cyclooctane	2	19
3	Pd/LDH	*p*-Xylene	2	24
4	Pd/LDH	Mesitylene	2	20
5	Pd/LDH	DMA	2	17
6	Pd/LDH	Diglyme	2	3
7	Pd/LDH	DMF	2	1
8	Pd/Al_2O_3	Octane	2	88
9	Pd/CeO_2	Octane	2	73
10	Pd/TiO_2	Octane	2	58
11	Pd/C	Octane	2	82
12	LDH	Octane	3	<1

[a]Reaction conditions: **1a** (0.5 mmol), catalyst (metal: 3 mol%), solvent (2 mL), 120 °C, Ar atmosphere (1 atm). Yields were determined by GC analysis using decane as the internal standard.

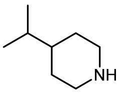
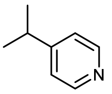
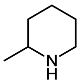
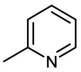
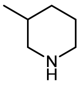
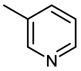
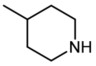
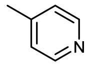
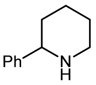
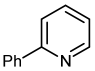
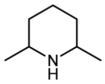
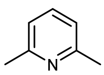
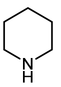
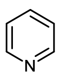
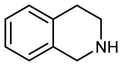
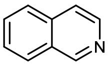
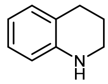
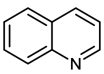
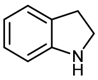
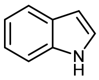
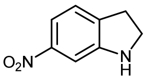
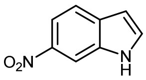
The effect of solvents on the reaction of **1a** appeared markedly. Among the solvents examined such as octane, cyclooctane, *p*-xylene, mesitylene, *N*,*N*-dimethylacetamide (DMA), diethyleneglycol dimethyl ether (diglyme), *N*,*N*-dimethylformamide (DMF), a linear aliphatic hydrocarbon solvent octane showed the best result (Table 1, entry 1). The reaction in a cyclic alkane solvent cyclooctane gave **2a** in only 19% yield (Table 1, entry 2). When the reaction of **1a** was carried out under the conditions described in Table 1 using aromatic solvents such as *p*-xylene and mesitylene, the yields of **2a** were 24% and 20%, respectively (Table 1, entries 3 and 4). For several reported functional group transformations by palladium nanoparticle catalysts, aromatic solvents have been utilized so far, and our research group has also often used aromatic solvents previously. However, we recognized that aromatic solvents are not suitable for reactions by palladium nanoparticle catalysts from the results of the above-mentioned solvent effect and the fact that the addition of an aromatic compound such as naphthalene completely inhibited the reaction of **1a**.[13] Also, polar solvents such as DMA, diglyme, and DMF were not effective for the reaction of **1a** (Table 1, entries 5–7).

For the reaction of **1a**, supported palladium catalysts prepared by the similar procedure as above, such as Pd/Al_2O_3, Pd/CeO_2, and Pd/TiO_2, and commercially available Pd/C also gave the desired **2a** in moderate to high yields (Table 1, entries 7–10). The average particle sizes of the catalysts used were almost the same (Table S1), thus indicating that the effect of supports was not so significant.

We also prepared Ru/LDH, Rh/LDH, Ir/LDH, and Au/LDH according to the similar procedure as above and performed the reaction of **1a** using these catalysts; however, **2a** did not produce at all (Table S2). To date, Pt(0) nanoparticle catalysts have been often utilized for acceptorless dehydrogenative aromatization of organic hydrides such as methylcyclohexane under harsh conditions (typically >300 °C).[14] Thus, we examined the reaction of **1a** in the presence of a commercially available supported Pt(0) catalyst Pt/Al_2O_3; however, **2a** was not produced at all (Table S2). In addition, commercially available Ru/Al_2O_3 was not effective (Table S2). Therefore, it is due to the specific catalysis of Pd(0) nanoparticles that acceptorless dehydrogenative aromatization of cyclic amines could be realized under relatively mild conditions like this system.

To establish whether the observed catalysis for the acceptorless dehydrogenative aromatization of **1a** occurred heterogeneously on Pd/LDH or was a result of the presence of leached palladium species in the reaction solution, the catalyst was removed by hot filtration 1.5 h after the reaction was started (at *ca.* 60% conversion of **1a**) under the conditions described in Figure S4a, and the reaction was restarted with the filtrate under the same conditions. The production of **2a** immediately ceased upon the removal of Pd/LDH (Figure S4a). Additionally, after the reaction, the filtrate was analyzed using inductively coupled plasma atomic emission spectroscopy (ICP-AES), and it was observed that the palladium species was barely detectable (below 0.01%). Consequently, the observed catalysis for the reaction was determined to be truly heterogeneous.[15] After the reaction was completed, Pd/LDH could easily be retrieved from the reaction mixture by simple filtration with more than 90% recovery. We performed the repeated reuse experiments using the retrieved catalyst. Although Pd/LDH could be reused at least four times for the reaction of **1a**, its catalytic activity unfortunately gradually declined; 92% yield of **2a** with the fresh catalyst and 72% yield for the fourth reuse under the conditions described in Figure S4b. We confirmed by the TEM analyses that the average palladium particle size gradually increased during the repeated reuse experiments; the average particle size after the first run was 3.9 nm and increased up to 6.7 nm ($\sigma = 2.6$ nm) after the third reuse experiment (Figure S3b). Therefore, the deactivation is likely caused by the increase in the palladium particle size.

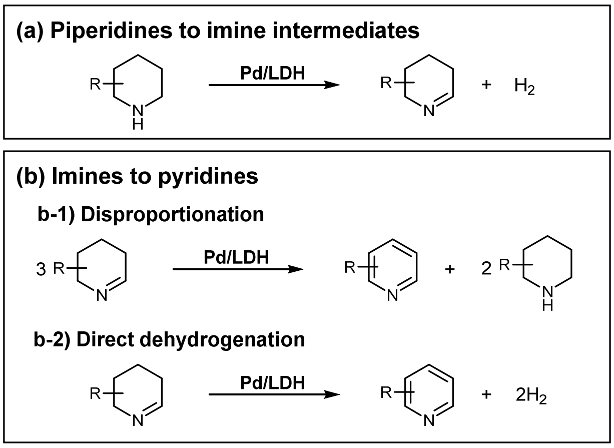
Table 2. Scope of the proposed Pd/LDH-catalyzed acceptorless dehydrogenative aromatization of cyclic amines[a]

Entry	Substrate	Product	T/ °C, t/ h	Yield/ %
1	 **1a**	 **2a**	120, 2	95
2[b]	 **1b**	 **2b**	100, 18	74
3[b]	 **1c**	 **2c**	100, 18	58
4[b]	 **1d**	 **2d**	100, 18	48
5	 **1e**	 **2e**	120, 2	84
6	 **1f**	 **2f**	120, 18	>99
7	 **1g**	 **2g**	125, 18	54
8[b]	 **1h**	 **2h**	100, 3	85
9	 **1i**	 **2i**	120, 18	58
10	 **1j**	 **2j**	80, 18	79
11[c]	 **1k**	 **2k**	80, 18	53[d]

[a] Reaction conditions: substrate (0.5 mmol), Pd/LDH (Pd: 3 mol%), octane (2 mL), Ar atmosphere (1 atm). Yields were determined by GC analysis using decane as the internal standard. [b] Heptane (2 mL) was used as the solvent. [c] DMA (2 mL) was used as the solvent, and the yield was determined using biphenyl added to the solution after the reaction as the internal standard. [d] Aminoindole was formed as the by-product (*ca.* 20%).

With the optimized reaction conditions, the substrate scope for the proposed Pd/LDH-catalyzed acceptorless dehydrogenative aromatization was investigated. As shown in Table 2, various cyclic amines including piperidine, tetrahydro(iso)quinoline, and indoline derivatives could be converted into the corresponding heteroarenes under relatively mild conditions (80–125 °C). When piperidines substituted with an alkyl group at the 2-, 3-, or 4-position (**1a**–**1d**) were used as the substrates, the reaction proceeded efficiently to give the corresponding monoalkylated pyridines in moderate to high yields (Table 2, entries 1–4). 2-Phenylpiperidine (**1e**) also gave the corresponding pyridine in a good yield (Table 2, entry 5). The reaction of 2,6-dimethylpiperidine (**1f**) also proceeded efficiently to afford a quantitative yield of 2,6-dimethylpyridine (Table 2, entry 6), indicating that the influence of the steric crowding around the nitrogen atom is not considered significant. It is noteworthy that this reaction system was also applicable to the reaction of non-substituted piperidine (**1g**) (Table 2, entry 7). The reaction of benzo-fused piperidines such as tetrahydroisoquinoline (**1h**) and tetrahydroquinoline (**1i**) gave isoquinoline and quinoline, respectively (Table 1, entries 8 and 9). The reaction of indolines (**1j** and **1k**) smoothly proceeded even at 80 °C (Table 1, entries 10 and 11). In the case of 6-nitroindoline (**1k**), 6-nitroindole was obtained as the major product with concomitant formation of 6-aminoindole as the by-product (Table 2, entry 11).

Finally, the reaction pathway for the Pd/LDH-catalyzed acceptorless dehydrogenative aromatization of piperidines was investigated. The reaction profile for the Pd/LDH-catalyzed reaction of **1e** exhibited that an imine 2,3,4,5-tetrahydro-6-phenylpyridine (**3e**) was detected during the reaction albeit in only small amounts (Figure S5), suggesting that the reaction proceeds through the imine intermediate. In our previous reports of palladium-nanoparticles-catalyzed dehydrogenative aromatization of cyclohexanones or cyclohexylamines, the reactions were composed of the rate-limiting substrate dehydrogenation followed by the fast disproportionation.[7] We considered that the proposed Pd/LDH-catalyzed aromatization of cyclic amines also proceeds through such a dehydrogenation-disproportionation sequence. Thus, we prepared **3e** according to the reported procedure, and the reaction of **3e** was carried out under the standard conditions. As shown in Figure S6, it was confirmed that the corresponding pyridine **2e** was formed by the imine disproportionation. However, the production rate of **2e** starting from **3e** was significantly smaller than that starting from **1e** (Figure S6 *vs* Figure S5). In a separate experiment, we confirmed that the presence of an excess of an imine relative to the catalyst strongly inhibited the amine dehydrogenation; the addition of **3e** (1.3 equivalents to **1a**) in the reaction of **1a** totally inhibited the dehydrogenation while the disproportionation of **3e** preferentially occurred (Table S3). We interpret these experimental results as follows. Firstly, acceptorless dehydrogenation of an amine proceeds to afford an imine intermediate (Scheme 2a). Then, the corresponding pyridine is immediately formed through disproportionation before the imine accumulates (Scheme 2b-1). However, since the possibility of a direct dehydrogenation pathway (Scheme 2b-2) cannot be completely denied, we consider that further detailed investigations are necessary.



Scheme 2. Plausible reaction path for the Pd/LDH-catalyzed acceptorless dehydrogenative aromatization of piperidines.

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Supporting Information is available on http://dx.doi.org/10.1246/cl.#####.

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