ChemComm

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Cite this: *Chem. Commun.*, 2021, 57, 6530

Received 30th March 2021,
Accepted 1st June 2021

DOI: 10.1039/d1cc01686e

rsc.li/chemcomm

Selective primary aniline synthesis through supported Pd-catalyzed acceptorless dehydrogenative aromatization by utilizing hydrazine†

Wei-Chen Lin, Takafumi Yatabe * and Kazuya Yamaguchi *

By utilizing hydrazine (N_2H_4) as the nitrogen source in the presence of a hydroxyapatite-supported Pd nanoparticle catalyst (Pd/HAP), various primary anilines can be selectively synthesized from cyclohexanones *via* acceptorless dehydrogenative aromatization. The strong nucleophilicity of N_2H_4 and the stability of the hydrazone intermediates can effectively suppress the formation of the undesired secondary aniline byproducts.

Primary anilines are widely utilized for pharmaceuticals, agrochemicals, electronic materials, dyes, and polymers.[1] To date, several synthetic methods to obtain primary anilines have been developed, for example, nitration of arenes followed by reduction of nitrobenzenes,[2] and cross-coupling such as the Ullmann reaction or the Buchwald–Hartwig reaction of NH_3 with benzene derivatives (*e.g.*, aryl halides or aryl boronic acids).[3] Recently, phenols have also been utilized to produce primary anilines with NH_3 or N_2H_4 as the nitrogen source.[4] Although these synthetic methods are efficient, some disadvantages are still present—pre-functionalized aromatic compounds are required, and this functionalization step is sometimes restricted to specific *ortho*/*meta*/*para* positions according to the different substituents on the aromatic rings (Fig. 1a).

In this decade, dehydrogenative aromatization catalyzed by Pd species has been widely applied to synthesize various arenes from non-aromatic substrates.[5] By utilizing six-membered carbocyclic compounds, the regioselective installation of substituents at *ortho*/*meta*/*para* positions can be easily conducted through well-developed synthetic methods, such as nucleophilic addition of enolates, Michael addition, and the Diels–Alder reaction. Therefore, various aromatic compounds with the desired substituents can be synthesized more efficiently. Until now, this strategy has been successfully used in the synthesis of arylamines such as secondary or tertiary anilines *via in situ* condensation of amines with cyclohexanones followed by dehydrogenation to form aromatic rings.[6] However, the selective synthesis of primary anilines is still quite difficult because undesirable secondary anilines are easily formed *via* reductive amination, that is, condensation of the desired primary anilines with cyclohexanones or cyclohexylimine intermediates followed by Pd-catalyzed hydrogenation of the secondary imine intermediates. In our group's recent reports, primary anilines can be selectively synthesized from aqueous NH_3 and cyclohexanones in the presence of supported Pd nanoparticle catalysts (Fig. 1b);[7] however, the utilization of styrene as the hydrogen acceptor is necessary to inhibit the reductive amination. Otherwise, secondary anilines were produced as the major products due to the stronger nucleophilicities of the desired primary anilines than that of NH_3.[7] In terms of atom economy, acceptorless dehydrogenative aromatization is more ideal, theoretically producing H_2 and H_2O as the byproducts. Our group also reported the cyclohexanone oxime formation from

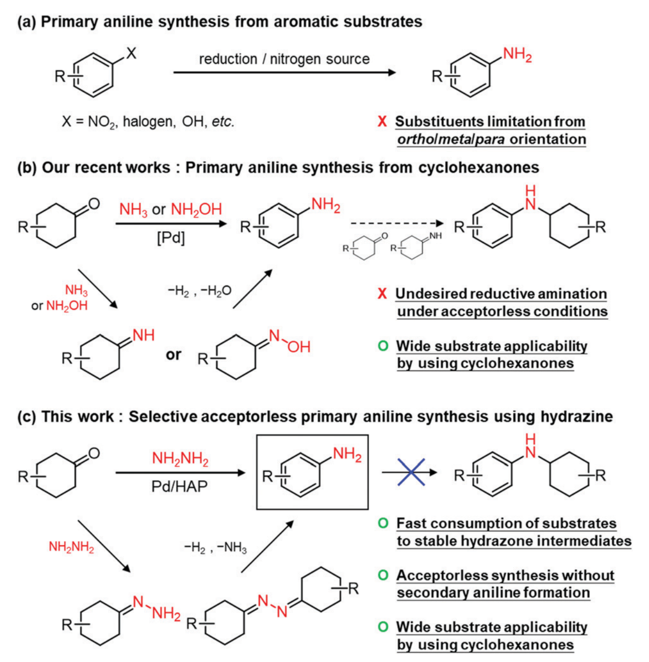

Fig. 1 Synthesis of primary anilines.

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† Electronic supplementary information (ESI) available: Experimental details, additional experimental results, characterization data, and spectral data of compounds (PDF). See DOI: 10.1039/d1cc01686e

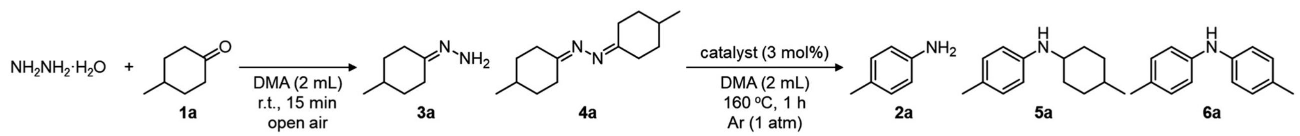
condensation of NH_2OH with cyclohexanones followed by acceptorless dehydrogenative aromatization using supported Pd nanoparticle catalysts to synthesize primary anilines (Fig. 1b).[8] In this case, however, the selectivity to the desired primary anilines is not yet perfect due to the formation of cyclohexylimines as the intermediates, which inevitably produced secondary anilines albeit in small amounts (of about 10%) *via* reductive amination. Recently, homogeneously catalyzed acceptorless dehydrogenative aromatization has also been developed to synthesize primary anilines using a photoredox Ir–Co system;[9] however, thermal reaction systems for acceptorless dehydrogenative aromatization to primary anilines with quite high selectivity are hitherto unknown.

Another potentially attractive nitrogen source is N_2H_4, which possesses strong nucleophilicity to react readily with ketones,[10] forming hydrazones as the stable products.[11] Therefore, we developed a new strategy for the selective synthesis of primary anilines by using N_2H_4 as the nitrogen source with supported Pd nanoparticles as the catalyst. Herein, a one-pot condensation reaction between N_2H_4 and cyclohexanones followed by acceptorless dehydrogenative aromatization to selectively produce primary anilines has been achieved in the presence of a hydroxyapatite-supported Pd nanoparticle catalyst (Pd/HAP) (Fig. 1c). Due to the strong nucleophilicity of N_2H_4 and the stability of the hydrazone intermediates, cyclohexanones were quickly consumed, and condensation of the desired primary anilines with cyclohexanones or other intermediates did not occur. Therefore, secondary aniline byproducts were hardly produced, and various primary anilines were successfully synthesized with quite high selectivity through the present Pd/HAP-catalyzed acceptorless dehydrogenative aromatization.

Initially, the Pd/HAP catalyst was prepared *via* the deposition–precipitation of Pd species on HAP, followed by $NaBH_4$ reduction. The transmission electron microscopy (TEM) analyses of the prepared Pd/HAP indicated that the Pd species were dispersedly supported on HAP as nanoparticles with an average diameter of 3.89 nm (standard deviation: 1.10 nm) (Fig. S1, ESI†). The X-Ray photoelectron spectroscopy (XPS) spectrum around the Pd 3d region revealed that the Pd nanoparticles mainly existed as Pd^0 (Fig. S2, ESI†). The X-Ray diffraction (XRD) patterns showed that the HAP structure was maintained after loading the Pd nanoparticles (Fig. S3, ESI†). Thus, the HAP-supported Pd nanoparticle catalyst was successfully prepared.

Then, we carried out the acceptorless dehydrogenative aromatization from hydrazine monohydrate ($N_2H_4 \cdot H_2O$) and 4-methylcyclohexanone (**1a**) in the presence of various supported Pd catalysts to form *p*-toluidine (**2a**) with *N*,*N*-dimethylacetamide (DMA) as the solvent (Table 1). The DMA solution of **1a** and $N_2H_4 \cdot H_2O$ was first stirred at room temperature to perform the condensation between **1a** and $N_2H_4 \cdot H_2O$. Due to the strong nucleophilicity of N_2H_4, it was confirmed that after stirring for only 15 min, **1a** was fully consumed with the formation of the hydrazone intermediates (**3a** and **4a**). Then, the catalyst was added to the solution and the dehydrogenative aromatization reaction was started at 160 °C under an Ar atmosphere. Among these supported Pd catalysts indicated in Table 1, Pd/HAP showed the highest activity; 87% yield of **2a** was obtained without the formation of secondary anilines (**5a** and **6a**) (Table 1, entry 1). HAP support alone did not promote the dehydrogenation reaction, confirming that Pd nanoparticles were active species for this reaction (Table 1, entry 8). After the Pd/HAP-catalyzed reaction, H_2 and NH_3 were detected in the gas phase by GC-MS analysis, indicating that **2a** was synthesized *via* acceptorless dehydrogenative aromatization of **3a** and **4a**. In the cases of basic supports, such as CeO_2 and layered double hydroxide (LDH), the yields of the detected products became lower (Table 1, entries 3 and 4). The physical mixture of Pd/HAP and LDH also led to the decrease of product yields (Table S1, entry 2, ESI†). The Fourier transform infrared spectroscopy (FT-IR) results of Pd/LDH showed a band around 1500 cm^{-1} after the reaction (Fig. S4, ESI†), indicating that there were possibly intermediates or products adsorbed on the surface of basic supports, which led to lower product yields. Acidic supports, such as Al_2O_3, ZrO_2, and TiO_2, led to the formation of small amounts of **5a** and **6a** (Table 1, entries 2, 6, and 7), and these supports also promoted the further condensation of the

Table 1 Effect of catalysts[a]

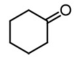
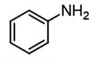
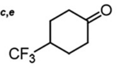
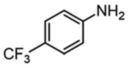
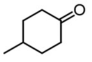
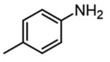
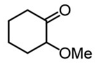
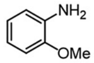
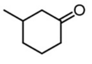
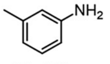
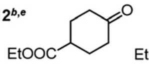
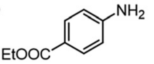
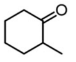
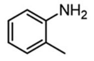
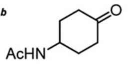
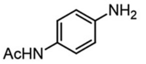
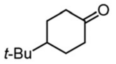
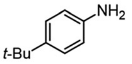
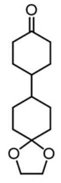
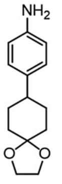
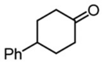
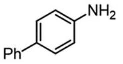
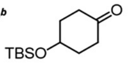
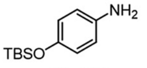
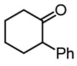
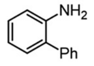
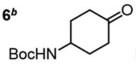
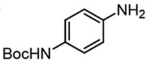
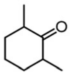
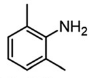
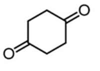
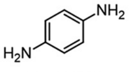
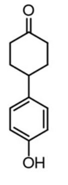
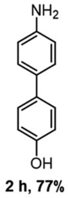
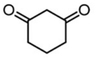
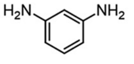


Entry	Catalyst	Conv. [%]	Yield [%]				
		1a	**2a**	**3a**	**4a**	**5a**	**6a**
1	Pd/HAP	>99	**87**	<1	<1	<1	<1
2	Pd/Al_2O_3	>99	**77**	<1	<1	1	<1
3	Pd/CeO_2	>99	**63**	<1	<1	<1	<1
4	Pd/LDH	>99	**58**	<1	<1	<1	<1
5	Pd/C	>99	**58**	<1	<1	16	23
6	Pd/ZrO_2	>99	**39**	<1	<1	2	1
7	Pd/TiO_2	>99	**3**	<1	29	4	<1
8[b]	HAP	>99	**<1**	4	91	<1	<1

[a] Reaction conditions: (first step) **1a** (0.5 mmol), $N_2H_4 \cdot H_2O$ (1.0 mmol), DMA (2 mL), r.t., open air, 15 min. (second step) catalyst (Pd: 3 mol% to **1a**), 160 °C, Ar (1 atm), 1 h. [b] HAP (60 mg). Conversions and yields were determined by GC analysis using *n*-hexadecane as the internal standard.

produced **2a** with DMA solvent, which also resulted in lower yields of **2a** (Table S2, ESI†). Adding acetic acid into the present Pd/HAP-catalyzed system also led to low **2a** yield and selectivity (Table S1, entry 3, ESI†). The use of Pd/C led to the significant formation of undesirable **5a** and **6a** (Table 1, entry 5). The study by Li and co-workers has indicated that Pd/C promotes the reduction of the hydrazone intermediates in the presence of H_2O, to form cyclohexylamines.[4b] The produced cyclohexylamines then reacted with **2a**, leading to the formation of **5a** and **6a**. It is possible that H_2O acted as the weak acid to promote the reduction of the hydrazone intermediates. In fact, adding 4A-MS into the present Pd/C-catalyzed system successfully suppressed the formation of **5a** and **6a** (Table S1, entry 4, ESI†). The above results revealed that HAP, a support with weak basicity,[12] was the most suitable for the present acceptorless dehydrogenative aromatization to selectively produce **2a** without any additives.

Table 2 Substrate scope[a]

Entry	Substrate	Product	Entry	Substrate	Product
1		 1 h, 95%	10[b,c,e]		 2 h, 51%
2		 1 h, 87(59)%	11[b]		 2 h, 75(34)%
3		 1 h, 91%	12[b,e]		 4 h, 76(45)%
4		 1 h, 84%	13[b]		 2 h, 63%
5[b]		 1 h, 83(56)%	14[b]		 1 h, 85(61)%
6[b]		 1 h, 88(66)%	15[b]		 3 h, 50%
7[b]		 1 h, 65%	16[b]		 2 h, 37(17)%
8[b,c,d]		 3 h, 47%	17[f]		 1 h, 68(75)%
9[b]		 2 h, 77%	18[f]		 1 h, 50%

[a] Reaction conditions: (first step) substrate (0.5 mmol), $N_2H_4 \cdot H_2O$ (1.0 mmol), DMA (2 mL), r.t., open air, 15 min. (second step) Pd/HAP (Pd: 3 mol% to substrate), 160 °C, Ar (1 atm). [b] 30 min for the first step. [c] Pd/HAP (Pd: 9 mol% to substrate). [d] $N_2H_4 \cdot H_2O$ (3.0 mmol). [e] 4A-MS (100 mg) was added. [f] $N_2H_4 \cdot H_2O$ (2.0 mmol). Yields were determined by GC analysis. The isolated yields are shown in parentheses.

Metals other than Pd, such as Pt and Ru, were examined, and they showed no catalytic activity for the dehydrogenation reaction (Table S3, ESI†). Decreasing the temperature to 150 °C or 140 °C significantly lowered the rate of the dehydrogenative aromatization (Table S4, ESI†). Various solvents, such as DMA, *N*-methyl-2-pyrrolidone (NMP), diethylene glycol dimethyl ether (diglyme), and mesitylene, were also examined, and DMA was the most suitable solvent for the present reaction (Table S5, ESI†). This Pd/HAP-catalyzed system was confirmed to be truly heterogeneous by hot filtration experiment (Fig. S5, ESI†) and inductively coupled plasma atomic emission spectroscopy (ICP-AES) analysis, and the catalyst can be reused despite the loss of its catalytic activity possibly due to Pd nanoparticle aggregation (Fig. S6, ESI†).[13]

Under the optimized reaction conditions in hand, we next investigated the substrate scope of the present Pd/HAP-catalyzed system. The dehydrogenative aromatization reactions were started after the complete conversion of cyclohexanones to hydrazone intermediates at room temperature except in the case of 2,6-dimethylcyclohexanone. As a result, a variety of primary anilines shown in Table 2 were selectively synthesized with no detection of secondary anilines except for entry 11 (Table S6, ESI†). Cyclohexanone and its derivatives with alkyl and phenyl substituents were efficiently converted to the corresponding primary anilines (Table 2, entries 1–7). The more sterically hindered substrate, 2,6-dimethylcyclohexanone, was also converted to the corresponding primary aniline (Table 2, entry 8). The steric hindrance made it difficult for both the condensation step and the dehydrogenation step to proceed (Table S7, ESI†). A hydroxyphenyl-substituted cyclohexanone was also applicable (Table 2, entry 9). Cyclohexanones possessing a trifluoromethyl, an alkoxy, an ester, or an amide group were tolerated in the present reaction system without hydrogenolysis of these functional groups (Table 2, entries 10–13).[14] Substrates possessing an acetal, a *tert*-butyldimethylsilyl (TBS), or a *tert*-butoxycarbonyl (Boc) protecting group were also converted into the corresponding primary anilines (Table 2, entries 14–16). When using cyclohexanediones in our previous Pd-catalyzed system using NH_3, aminophenols were formed as the major products.[7] In contrast, applying cyclohexanediones to this reaction led to the formation of benzenediamines because N_2H_4 can easily attack both ketone sites in these substrates (Table 2, entries 17 and 18).

To verify the reaction pathway, several control experiments were conducted. First, the time profile of the reaction between **1a** and $N_2H_4 \cdot H_2O$ was examined (Fig. S7, ESI†). Before the reaction was started at 160 °C, it was found that **1a** had been fully consumed, and hydrazones **3a** and **4a** were formed through condensation of **1a** with $N_2H_4 \cdot H_2O$. When the solution was heated to 160 °C in the presence of Pd/HAP, **3a** and **4a** were gradually converted to **2a** with a trace amount of cyclohexanone phenylhydrazone (**7a**) formed as the intermediate.

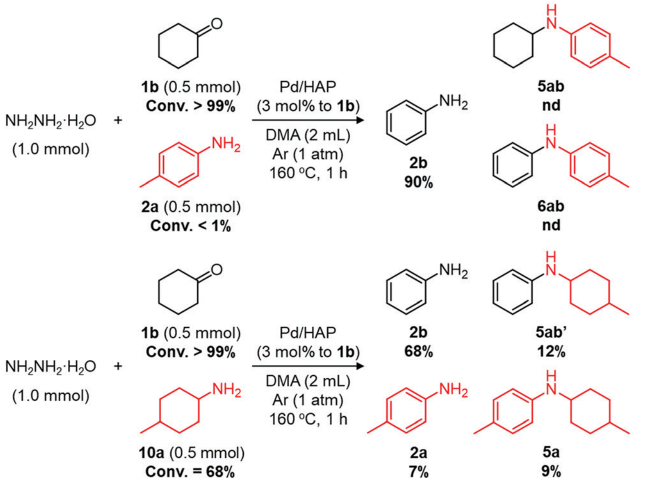


Fig. 2 Control experiments of reactions in the presence of **2a** or **10a** under the following conditions: (first step) **1b** (0.5 mmol), $N_2H_4{\cdot}H_2O$ (1.0 mmol), DMA (2 mL), r.t., open air, 15 min; (second step) **2a** or **10a** (0.5 mmol), Pd/HAP (Pd: 3 mol% to **1b**), 160 °C, Ar (1 atm), 1 h.

Then, although phenylhydrazines were not detected in the time profile, control experiments with phenylhydrazine (**8b**) and 1,2-diphenylhydrazine (**9b**) as the starting materials in the present reaction system were carried out (Fig. S8, ESI†). Both **8b** and **9b** were fully converted to the corresponding primary aniline (**2b**) with >99% selectivity *via* reductive N–N bond cleavage, indicating that **8b** and **9b** were the possible intermediates produced from the dehydrogenation of the corresponding hydrazones. In addition, the reaction of cyclohexanone (**1b**) with $N_2H_4{\cdot}H_2O$ in the presence of **2a** was carried out (Fig. 2). In this case, **2b** was selectively obtained without the formation of secondary anilines **5ab** and **6ab.** On the other hand, for the reaction of **1b** with $N_2H_4{\cdot}H_2O$ in the presence of 4-methylcyclohexylamine (**10a**), secondary anilines **5ab′** and **5a** were produced in significant amounts (Fig. 2). These results indicated that in the cases of catalysts giving **5a** and **6a** shown in Table 1, **5a** and **6a** were derived from the coupling of **2a** with **10a**, which was proposed to be produced from the hydrogenolysis of hydrazones **3a** and **4a.**[4b] Therefore, the hydrazone intermediates were proved to be stable enough in the present Pd/HAP-catalyzed reaction system, where cyclohexylamines were not produced during the reaction, leading to the high selectivity to the desired primary anilines. Besides, the results also indicated that primary anilines were not produced through the dehydrogenation of cyclohexylamines. From these results, we summarized the pathway of this reaction in Fig. S9, ESI.†

This work was financially supported by JSPS KAKENHI Grant No. 19H02509 and 20K22547.

Conflicts of interest

There are no conflicts to declare.

Notes and references

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13 For the details of the leaching test and reuse test, see the ESI†.
14 In the case of cyclohexanones with electron-withdrawing groups, hydrogenation of the hydrazone intermediates occurs comparatively easily to cause low selectivity to the desired primary anilines, which can be inhibited by the addition of 4A-MS (Table S8, ESI†).