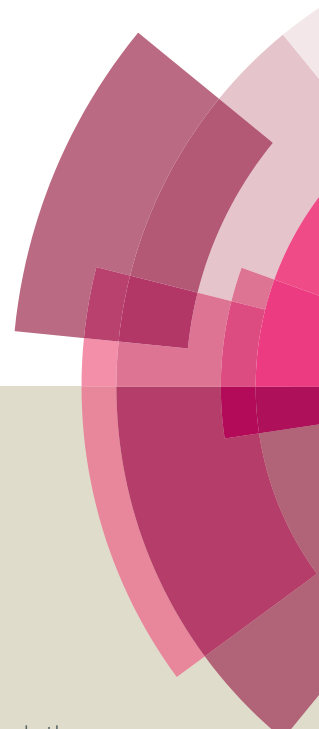


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Facile access to *N*-substituted anilines via dehydrogenative aromatization catalysis over supported gold–palladium bimetallic nanoparticles†

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Abstract

N-Substituted anilines are widely utilized important compounds, and the development of their diverse synthetic procedures is of great significance. Herein, we have successfully developed a widely applicable powerful catalytic route to *N*-substituted anilines. In the presence of a gold–palladium alloy nanoparticles catalyst (Au–Pd/Al₂O₃) and styrene, various kinds of structurally diverse *N*-substituted anilines (twenty three examples) could be synthesized starting from cyclohexanones and amines (including aliphatic primary and secondary amines and anilines). The catalytic performance was strongly influenced by the nature of catalyst. A supported gold catalyst (Au/Al₂O₃) was completely inactive for the present transformation. Although a supported palladium catalyst (Pd/Al₂O₃) gave the desired *N*-substituted anilines to some extent, the performance was inferior to that of Au–Pd/Al₂O₃. The catalytic activity of the palladium species in Au–Pd/Al₂O₃ was at least *ca.* three times higher than that in Pd/Al₂O₃. Moreover, the performance of Au–Pd/Al₂O₃ was superior to that of a physical mixture of Au/Al₂O₃ and Pd/Al₂O₃. Thus, palladium was intrinsically effective for the present transformation (dehydrogenative aromatization), and its performance was improved by alloying with gold. The present transformation proceeds through the sequence of the dehydrative condensation of cyclohexanones and amines to produce enamines (or ketimines), followed by the dehydrogenative aromatization to produce the corresponding *N*-substituted anilines. In the aromatization step, styrene could act as the effective hydrogen acceptor to selectively produce the desired *N*-substituted anilines without catalyzing the disproportionation of the enamine intermediates. The observed catalysis of Au–Pd/Al₂O₃ was truly heterogeneous in nature, and Au–Pd/Al₂O₃ could be reused.

Introduction

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Anilines and their *N*-substituted derivatives are an important class of chemicals that have widely been utilized as pharmaceuticals, agricultural chemicals, bioactive compounds, dyes, and color pigments, for example.¹ Aniline has industrially been produced by the reduction of nitrobenzene.¹ With regard to *N*-substituted anilines, a number of synthetic procedures have been developed up to the present.^{2–7} *N*-Alkylation of anilines remains one of the most frequently utilized synthetic procedures for *N*-alkyl anilines, and alkyl halides have traditionally been utilized as alkylating reagents.² However, the selectivity to the desired mono- or disubstituted anilines is low in some cases. Moreover, alkyl halides are toxic, and their use for the *N*-alkylation produces large amounts of wastes. Therefore, much attention has recently been paid to the use of environmentally-friendly alkylating reagents, *e.g.*, alcohols, for *N*-alkylation of anilines through a “borrowing hydrogen” strategy.³ Reductive amination of carbonyl compounds is also a powerful synthetic procedure for *N*-substituted anilines, and in some catalytic systems, nitrobenzenes can directly be utilized as the starting materials.⁴ The Buchwald–Hartwig coupling⁵ and the Chan–Lam coupling⁶ are two of the most versatile cross-coupling methodologies for synthesis of *N*-substituted anilines (including *N*-aryl anilines). Although these cross-coupling methodologies can precisely design *N*-substituted aniline scaffolds, they should utilize pre-activated substrates, which concurrently generate (super)stoichiometric amounts of wastes.

Recently, dehydrogenative (oxidative) aromatization has emerged as a reliable procedure for synthesis of various aromatic compounds.^{7–9} By the dehydrogenative aromatization protocol utilizing palladium-based catalysts (homogeneous catalysts in most cases), *N*-substituted anilines can be synthesized starting from cyclohexanones and amines.^{7a–c} In the immediate past, we reported a novel “dehydrogenative self-coupling aromatization route” to *N*-cyclohexylanilines or symmetrically substituted diarylamines starting from cyclohexylamines using O₂ (air) as the hydrogen acceptor (oxidant) (Scheme 1a and S1, ESI†).⁹ This transformation proceeds through the following sequential pathway (Scheme S1, ESI†).⁹ Initially, aerobic dehydrogenation of cyclohexylamine proceeds to give

cyclohexylimine (step 1 in Scheme S1, ESI†). Then, nucleophilic addition of another cyclohexylamine molecule to the cyclohexylimine intermediate takes place to afford *N*-cyclohexylidenecyclohexylamine (step 2 in Scheme S1, ESI†). Finally, disproportionation and/or aerobic dehydrogenation of the *N*-cyclohexylidenecyclohexylamine proceeds to give the corresponding *N*-cyclohexylaniline as the final product with the concurrent formation of cyclohexylamine and dicyclohexylamine (step 3 in Scheme S1, ESI†). These amines formed in the aromatization step can again aerobically be oxidized, and thus it can be considered that O₂ is formally the terminal oxidant (step 4 in Scheme S1, ESI†). For this transformation, the effect of catalysts is very crucial. Various cyclohexylamines can be converted into the corresponding *N*-cyclohexylanilines in high yields when using a supported gold–palladium bimetallic catalyst (Au–Pd/Al₂O₃), whereas Au/Al₂O₃, Pd/Al₂O₃, and a physical mixture of Au/Al₂O₃ and Pd/Al₂O₃ hardly afford the desired products (Scheme 1a).⁹ In this transformation, gold and palladium mainly catalyze the amine oxidation and the aromatization, respectively, and by alloying gold and palladium, the intrinsic abilities of gold and palladium for these transformations are possibly improved by electronic ligand effects.¹⁰

If the gold–palladium bimetallic catalyst is effective for aniline synthesis starting from various kinds of structurally diverse cyclohexanones and amines, the system will be a powerful procedure. And so, in order to synthesize *N,N*-disubstituted anilines, we performed several reactions using cyclohexanones and “secondary” amines in the presence of Au–Pd/Al₂O₃ using O₂ (air) as the hydrogen acceptor. Although the desired *N,N*-disubstituted anilines could be obtained to some extent, the concurrent formation of *N,N*-disubstituted cyclohexylamines was inevitable, resulting in low selectivities to the desired *N,N*-disubstituted anilines (Scheme 1b, discuss later in more detail). One possible explanation of the low selectivities is that O₂ is the poor hydrogen acceptor, and consequently the aromatization partly proceeds through the disproportionation of the enamine intermediates generated by the dehydrative condensation of cyclohexanones and secondary amines. Moreover, once *N,N*-disubstituted cyclohexylamines are formed, their dehydrogenation is quite

difficult (discuss later in more detail). With this situation in mind, we considered to explore the suitable hydrogen acceptors (instead of O₂) for the Au–Pd/Al₂O₃-catalyzed dehydrogenative aromatization starting from cyclohexanones and amines in order to avoid the formation of the undesired cyclohexylamine by-products.

Herein, we disclose for the first time that styrene can act as the effective hydrogen acceptor for the Au–Pd/Al₂O₃-catalyzed selective production of *N*-substituted anilines starting from cyclohexanones and amines (Scheme 1c). The present Au–Pd/Al₂O₃-catalyzed system with styrene as the hydrogen acceptor is applicable to a variety of substituted cyclohexanones and amines (including aliphatic primary and secondary amines and anilines), selectively affording the corresponding *N*-substituted anilines in moderate to high yields (twenty three examples). The observed catalysis is truly heterogeneous in nature, and the Au–Pd/Al₂O₃ catalyst can be reused.

Results and discussion

To begin with, we carried out the dehydrogenative aromatization of cyclohexanone (**1a**) with morpholine (**2a**) to produce 4-phenylmorpholine (**3aa**) in the presence of various hydrogen acceptors and supported metal catalysts (Table 1). The reaction was typically carried out at 100 °C in toluene for 6 h. In the absence of hydrogen acceptors under Ar atmosphere (1 atm), the Au–Pd/Al₂O₃-catalyzed dehydrogenative aromatization of **1a** with **2a** gave a *ca.* 1:2 mixture of the desired aniline **3aa** (34% yield) and the undesired cyclohexylamine **4aa** (64% yield) (Table 1, entry 1). This result indicates that the aromatization proceeds through the “disproportionation” of the enamine intermediate **5aa** formed through the dehydrative condensation of **1a** and **2a**, that is, **5aa** itself acts as the hydrogen acceptor in this case. Under air atmosphere (1 atm), the Au–Pd/Al₂O₃-catalyzed dehydrogenative aromatization gave the desired aniline **3aa** in 41% yield with the concurrent formation of a significant amount of the cyclohexylamine by-product **4aa** (46% yield) (Table 1, entry 2), and thus the disproportionation of **5aa** inevitably occurred even when using O₂ as the hydrogen acceptor. In the separate experiment, we confirmed that the desired aniline **3aa**

was not formed at all when the reaction was carried out using the cyclohexylamine **4aa** as the starting material (Scheme 2a). Therefore, once **4aa** was formed through the disproportionation of the enamine intermediate **5aa**, the dehydrogenation of **4aa** hardly proceeded under the present reaction conditions even in the presence of hydrogen acceptors, resulting in the low selectivity to the desired aniline. When benzoquinone was utilized as the hydrogen acceptor, not only the substrates but also benzoquinone were mostly converted into unidentified by-products, and the desired **3aa** was obtained in only 5% yield (Table 1, entry 7). Thus, benzoquinone was not suitable for the present system. When utilizing styrene as the hydrogen acceptor under Ar atmosphere (1 atm), the desired aniline **3aa** was selectively obtained without the formation of the undesired cyclohexylamine **4aa** (Table 1, entry 3). When the reaction time was prolonged to 18 h for the Au–Pd/Al₂O₃-catalyzed dehydrogenative aromatization using styrene, the yield of **3aa** reached up to 76%, and **4aa** was not produced at all also in this case (Table 1, entry 4). Although other alkenes, such as 1-octene and cyclooctene, were utilized as the hydrogen acceptors, the disproportionation of **5aa** could not be avoided, resulting in the formation of **4aa** (Table 1, entries 5 and 6).

Next, the Au–Pd/Al₂O₃-catalyzed hydrogenation of alkene hydrogen acceptors, such as styrene, 1-octene, cyclooctene, and **5aa**, was carried out in order to explain the above-mentioned effect of hydrogen acceptors. In the presence of Au–Pd/Al₂O₃ and H₂ (1 atm) under the conditions described in Table S1, styrene was quantitatively converted into ethylbenzene (Table S1, entry 1, ESI†). While other alkenes, such as **5aa**, 1-octene, and cyclooctene, were also hydrogenated to the corresponding alkanes, their reaction rates were lower than that of styrene (Table S1, entries 1–4, ESI†). The results of the competitive hydrogenation reactions summarized in Scheme 3 are of extreme importance to understand the effect of hydrogen acceptors. When the Au–Pd/Al₂O₃-catalyzed competitive hydrogenation of an equimolar mixture of styrene and **5aa** was carried out, styrene was preferentially hydrogenated to afford ethylbenzene in 77% yield without occurring the hydrogenation of **5aa** (Scheme 3a). On the other hand, such preferential hydrogenation phenomena were not observed when using 1-octene and cyclooctene. When the competitive hydrogenation of an equimolar mixture

of 1-octene and **5aa** was carried out, a *ca.* 1:1 mixture of *n*-octane (63% yield) and **4aa** (67% yield) was obtained (Scheme 3b). In the case of the competitive hydrogenation of cyclooctene and **5aa**, the hydrogenation of **5aa** rather preferentially occurred to give **4aa** in 76% yield, and cyclooctane was obtained in only 6% (Scheme 3c). From these competitive hydrogenation reactions, we consider that the ability as the hydrogen acceptor for the present Au–Pd/Al₂O₃-catalyzed dehydrogenative aromatization increased in the order of cyclooctene < 1-octene \approx **5aa** \ll styrene, which is in good agreement with the results indicated in Table 1. It is known that the palladium nanoparticles-catalyzed hydrogenation of C=C double bonds of alkenes undergoes through the formation of di- σ -bonded intermediates on the palladium surface and that the interaction between alkene substrates and the palladium surface is very important.¹¹ One possible explanation of the above competitive hydrogenation reactions is as follows: The p orbitals and planar geometry of the aromatic ring of styrene can assist the formation of the di- σ -bond, which is preferable to hydrogenation, while the relatively sterically bulky alkyl groups in 1-octene, cyclooctene, and **5aa** do not positively contribute to but rather hinder the formation of the di- σ -bond in comparison with styrene.^{11a} For that reason, it is likely that styrene showed the excellent performance as the hydrogen acceptor for the present Au–Pd/Al₂O₃-catalyzed dehydrogenative aromatization system, and 1-octene and cyclooctene were not effective hydrogen acceptors (Table 1, entries 3–6).

The effect of catalysts was also very significant. As above-mentioned, the Au–Pd/Al₂O₃-catalyzed dehydrogenative aromatization of **1a** with **2a** using styrene selectively gave **3aa** in good yields (Table 1, entries 3 and 4).¹² On the other hand, the desired **3aa** was not produced at all in the presence of Au/Al₂O₃, thus showing that gold is completely inactive for the dehydrogenative aromatization (Table 1, entry 8). In the presence of Pd/Al₂O₃, **3aa** was produced to some extent (20% yield, Table 1, entry 9), thus indicating that palladium is essential for the dehydrogenative aromatization and that Au–Pd/Al₂O₃ has the superior catalytic activity to Pd/Al₂O₃. The physical mixture of Au/Al₂O₃ and Pd/Al₂O₃ gave **3aa** in 33% yield (Table 1, entry 10), and the yield was lower than that obtained with Au–Pd/Al₂O₃ (Table 1, entry 3). It was revealed by the

high-angle annular dark-field scanning transmission electron microscopy (HAADF-STEM) and energy dispersive X-ray spectroscopy (EDS) analyses of Au-Pd/Al₂O₃ that gold-palladium alloy nanoparticles were formed on Al₂O₃ (Fig. 1b-d). Thus, the catalytic performance of the palladium species in Au-Pd/Al₂O₃ was at least *ca.* three times higher than that in Pd/Al₂O₃, clearly indicating that the intrinsic catalytic performance of palladium for the dehydrogenative aromatization was improved by alloying with gold. This is likely due to the electronic ligand effect, and such effects are frequently observed for several oxidation reactions using gold-palladium alloy catalysts, *e.g.*, alcohol oxidation and H₂O₂ production.¹⁰ Thus, we hereafter utilized the most active Au-Pd/Al₂O₃ catalyst and the most effective styrene hydrogen acceptor for further investigation of the dehydrogenative aromatization.

To verify whether the observed catalysis was truly caused by “solid” Au-Pd/Al₂O₃ or “leached” gold and/or palladium species, the following control experiments were carried out. The reaction of **1a** with pyrrolidine (**2b**) to produce the corresponding aniline **3ab** was carried out under the conditions described in Fig. 2, and the Au-Pd/Al₂O₃ catalyst was removed from the reaction mixture by hot filtration at *ca.* 30% yield of **3ab**. Then, the filtrate was again heated at 80 °C. In this case, no further production of **3ab** was observed, as shown in Fig. 2. In addition, it was confirmed by inductively coupled plasma atomic emission spectroscopy (ICP-AES) analysis that no gold and palladium species were detected in the filtrate. These results clearly indicate that the observed catalysis for the present Au-Pd/Al₂O₃-catalyzed dehydrogenative aromatization is truly heterogeneous in nature.¹³ After the reaction was completed, Au-Pd/Al₂O₃ could easily be retrieved from the reaction mixture by simple filtration with >90% recovery. We performed the repeated reuse experiments using the retrieved catalyst. Unfortunately, the catalytic performance of Au-Pd/Al₂O₃ gradually decreased during the repeated reuse experiments; 76% yield of **3aa** for the reaction with the fresh catalyst, 67% yield for the first reuse, and 49% for the second reuse for the reaction of **1a** with **2a**; 87% yield of **3ab** for the reaction with the fresh catalyst and 67% yield for the first reuse for the reaction of **1a** with **2b** under the conditions described in Fig. 3. We confirmed by the TEM

analyses that the average particle size gradually increased during the repeated reuse experiments; the average particle size in the fresh Au–Pd/Al₂O₃ was 2.9 nm and increased up to 4.3 nm after the first reuse (Table S2, Fig. S1, ESI†). Therefore, the deactivation is likely caused by the increase in the particle size.

The scope of the present Au–Pd/Al₂O₃-catalyzed dehydrogenative aromatization was next examined. With the optimized reaction conditions in hand, various kinds of structurally diverse *N*-substituted anilines could be synthesized starting from substituted cyclohexanones and amines (including aliphatic primary and secondary amines and anilines) (Fig. 3 and S2, ESI†). The reaction of cyclohexanone (**1a**) with secondary amines, such as morpholine (**2a**) and pyrrolidine (**2b**), efficiently proceeded to afford the corresponding *N*-substituted aniline derivatives in high yields. By the reaction with cyclohexanones, aliphatic primary amines, such as cyclohexylamine (**2c**) and *n*-octylamine (**2d**), could also be converted into the corresponding *N*-substituted anilines. Besides aliphatic amines, aniline (**2e**) and its derivatives, such as 4-methoxyaniline (**2f**) and 4-methylaniline (**2g**), could be applied to the present system, affording the corresponding unsymmetrically substituted diaryl amines. Cyclohexanones possessing various substituents at each position, such as 4-methylcyclohexanone (**1b**), 3-methylcyclohexanone (**1c**), 4-ethylcyclohexanone (**1d**), and 4-phenylcyclohexanone (**1e**), could successfully be utilized as the coupling partners for secondary amines (**2a** and **2b**), primary amines (**2c** and **2d**), and anilines (**2e–2g**) in the present Au–Pd/Al₂O₃-catalyzed system. Interestingly, we found for the first time that Au–Pd/Al₂O₃ could catalyze the tandem 1,4-addition/1,2-addition/dehydrogenative aromatization reaction starting from cyclohex-2-en-1-one (**1f**) and pyrrolidine (**2b**), giving the corresponding 1,3-diaminobenzene (**3fb**) in a high yield (Scheme 4).

As above-mentioned, for the Au–Pd/Al₂O₃-catalyzed reaction of **1a** and **2a**, a significant amount of the enamine intermediate **5aa** was observed at 6 h, but not at 18 h (Table 1, entries 3 and 4). In the separate experiments, we confirmed that the desired aniline **3aa** was produced when the reaction was carried out using **5aa** as the starting material (Scheme 2b and c). Furthermore, as above-described,

the dehydrogenative aromatization of cyclohexylamine **4aa** hardly proceeded even in the presence of styrene as the hydrogen acceptor (Scheme 2a). Based on these experimental results, we here propose a possible reaction pathway for the present Au–Pd/Al₂O₃-catalyzed dehydrogenative aromatization reaction (Scheme 5). Initially, the condensation of cyclohexanone (**1**) with an amine (**2**) proceeds to give an enamine intermediate (**5**) with the concomitant formation of water (step 1 in Scheme 5). Then, the palladium-catalyzed dehydrogenation of **5** proceeds to give the corresponding diene intermediate **6** using styrene as the hydrogen acceptor with the concurrent formation of ethylbenzene (step 2 in Scheme 5). Finally, the dehydrogenation of **6** proceeds to give the desired *N*-substituted aniline **3** using styrene as the hydrogen acceptor with the concurrent formation of ethylbenzene (step 3 in Scheme 5). The desired *N*-substituted aniline **3** is selectively obtained in the present Au–Pd/Al₂O₃-catalyzed dehydrogenative aromatization system when utilizing styrene as the hydrogen acceptor. As above-mentioned, styrene could act as the suitable hydrogen acceptor, and the hydrogen accepting ability was superior to that of **5** (Scheme 3a). In contrast, the hydrogen accepting abilities of common alkenes, such as 1-octene and cyclooctene, were similar to or lower than that of **5** (Scheme 3b and c). Therefore, in the absence of styrene, the enamine intermediate **5** itself works as the hydrogen acceptor to concurrently afford the undesired cyclohexylamine **4** through disproportionation.

Conclusion

We have successfully developed the widely applicable synthetic procedure for *N*-substituted anilines. In the presence of a supported gold and palladium alloy nanoparticles catalyst (Au–Pd/Al₂O₃) and styrene as the hydrogen acceptor, various kinds of structurally diverse *N*-substituted anilines could be synthesized through dehydrogenative aromatization reaction of cyclohexanones with amines. The observed catalysis was truly heterogeneous, and the Au–Pd/Al₂O₃ catalyst could be reused.

Experimental section

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Instruments and reagents

GC analyses were performed on Shimadzu GC-2014 with a FID detector equipped using a InertCap5 or a Stabilwax capillary column. GC-MS spectra were recorded on Shimadzu GCMS-QP2010 equipped with a InertCap5 capillary column at an ionization voltage of 70 eV. Liquid-state ^1H and ^{13}C NMR spectra were recorded on JEOL JNM-ECA 500. ^1H and ^{13}C NMR were measured at 500 and 125 MHz, respectively, with TMS as an internal standard ($\delta = 0$ ppm). ICP-AES analyses were performed on Shimadzu ICPS-8100. TEM measurements were performed on JEOL JEM-2010HC. HAADF-STEM and EDS images were obtained using JEOL JEM-ARM 200F operating at 200 kV. TEM and STEM samples were prepared by placing a drop of the suspension on carbon-coated Cu grids and dried in air. XPS analyses were performed using JEOL JPS-9000 under Mg $K\alpha$ radiation ($h\nu = 1253.6$ eV, 8 kV, 10 mA). The peak positions were calibrated by the Al $2p_{3/2}$ peak (74.0 eV). Al_2O_3 ($160\text{ m}^2\text{ g}^{-1}$, Cat. No. KHS-24, Sumitomo Chemical) and TiO_2 ($316\text{ m}^2\text{ g}^{-1}$, Cat. No. ST-01, Ishihara Sangyo Kaisya) were commercially available. Solvents and substrates (cyclohexanones and amines) were obtained from Kanto Chemical, TCI, Wako, or Aldrich (reagent grade), and purified prior to the use, if necessary.¹⁴

Preparation of catalysts

$\text{Au-Pd/Al}_2\text{O}_3$ was prepared as follows.¹⁵ An aqueous solution of $\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$ and K_2PdCl_4 (4.2 mM each, 60 mL) containing Al_2O_3 (2.0 g) was vigorously stirred at room temperature for 15 min. Then, the pH of the solution was adjusted to 10.0 by using an aqueous solution of NaOH (1.0 M). Then, the resulting slurry was further stirred for 24 h at room temperature, giving 2.0 g of the hydroxide precursor. By the reduction of the hydroxide precursor using H_2 (1 atm) at $150\text{ }^\circ\text{C}$ for 30 min, the supported gold-palladium bimetallic nanoparticles catalyst, $\text{Au-Pd/Al}_2\text{O}_3$, was obtained. The contents of gold and palladium in $\text{Au-Pd/Al}_2\text{O}_3$ were 0.070 mmol g^{-1} and 0.109 mmol g^{-1} ,

respectively (determined by ICP-AES). HAADF-STEM and EDS mapping analyses indicated that alloyed gold–palladium bimetallic nanoparticles were formed on the Al₂O₃ support (Fig. 1). It was confirmed by the TEM analysis that the average particle size of gold–palladium alloy nanoparticles was 2.9 nm (standard deviation: 1.0 nm, Fig. 1). The size distribution was determined by using 200 particles in the TEM images. Other supported catalysts, such as Au/Al₂O₃ (Au: 0.158 mmol g⁻¹, average size: 3.2 nm, standard deviation: 1.1 nm, Fig. S3, ESI†), Pd/Al₂O₃ (Pd: 0.237 mmol g⁻¹, average size: 2.2 nm, standard deviation: 0.5 nm, Fig. S4, ESI†), and Au–Pd/TiO₂ (Au: 0.070 mmol g⁻¹, Pd: 0.118 mmol g⁻¹, average size: 1.8 nm, standard deviation: 0.4 nm, Fig. S5, ESI†) were prepared by the same manner as that for Au–Pd/Al₂O₃.

Catalytic reaction

The catalytic reaction was typically carried out according to the following procedure. Into a Schlenk flask reactor (volume: *ca.* 20 mL) were successively placed Au–Pd/Al₂O₃ (Au: 1.4 mol%, Pd: 2.2 mol% with respect to an cyclohexanone), cyclohexanone (**1**, 0.5 mmol), amine (**2**, 1.0 mmol), styrene (1.0 mmol), *n*-decane (0.1 mmol, internal standard), toluene (2 mL), and a Teflon-coated magnetic stir bar, and then the mixture was stirred at 100 °C under Ar (1 atm). The conversions and product yields were determined by GC analysis using *n*-decane as an internal standard. As for isolation of products, an internal standard was not used. After the reaction, the catalyst was removed by simple filtration (>90% catalyst recovery), and then the filtrate was concentrated by evaporation of the toluene solvent. The crude product was subjected to column chromatography on silica gel (typically using *n*-hexane/diethyl ether as an eluent), giving the pure *N*-substituted aniline product. The products were confirmed by the comparison of their GC retention times, GC-MS spectra, and/or NMR (¹H and ¹³C) spectra with those of the authentic data. As for the reuse experiment, Au–Pd/Al₂O₃ was retrieved by filtration, washed with a mixed solvent of methanol and dichloromethane. The retrieved Au–Pd/Al₂O₃ was dried at 100 °C in air, and activated at 150 °C in 1 atm of H₂ prior to being used for the reuse experiment.

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Notes and references

- (a) S. A. Lawrence, *Amines: Synthesis Properties and Applications*, Cambridge University Press, Cambridge, 2004; (b) Z. Rappoport, *The Chemistry of Anilines*, John Wiley & Sons, New York, 2007; (c) A. Ricci, *Amino Group Chemistry: From Synthesis to the Life Sciences*, John Wiley & Sons, New York, 2008; (d) J. Magano and J. R. Dunetz, *Chem. Rev.*, 2011, **111**, 2177.
- (a) R. N. Salvatore, C. H. Yoon and K. W. Jung, *Tetrahedron*, 2001, **57**, 7785; (b) S. Hayat, A.-u. Rahman, M. I. Choudhary, K. M. Khan, W. Schumann and E. Bayer, *Tetrahedron*, 2001, **57**, 9951.
- (a) G. Guillena, D. J. Ramón and M. Yus, *Chem. Rev.*, 2010, **110**, 1611; (b) L. He, X.-B. Lou, J. Ni, Y.-M. Liu, Y. Cao, H.-Y. He and K.-N. Fan, *Chem. Eur. J.*, 2010, **16**, 13965; (c) R. Kawahara, K. Fujita and R. Yamaguchi, *Adv. Synth. Catal.*, 2011, **353**, 1161; (d) S. Bähn, S. Imm, L. Neubert, M. Zhang, H. Neumann and M. Beller, *ChemCatChem*, 2011, **3**, 1853; (e) Y. Du, S. Oishi and S. Saito, *Chem. Eur. J.*, 2011, **17**, 12262; (f) D. Weichmann, W. Frey and B. Plietker, *Chem. Eur. J.*, 2013, **19**, 2741; (g) X. Cui, X. Dai, Y. Deng and F. Shi, *Chem. Eur. J.*, 2013, **19**, 3665; (h) F. Santoro, R. Psaro, N. Ravasio and F. Zaccheria, *RSC Adv.*, 2014, **4**, 2596.
- (a) R. Apodaca and W. Xiao, *Org. Lett.*, 2001, **3**, 1745; (b) O.-Y. Lee, K.-L. Law and D. Yang, *Org. Lett.*, 2009, **11**, 3302; (c) P. D. Pham, P. Bertus and S. Legoupy, *Chem. Commun.*, 2009, 6207; (d) V. N. Wakchaure, J. Zhou, S. Hoffmann and B. List, *Angew. Chem. Int. Ed.*, 2010, **49**,

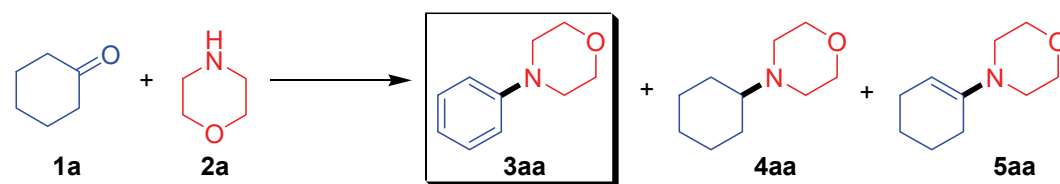
- 4612; (e) C. Wang, A. Pettman, J. Bacsá and J. Xiao, *Angew. Chem. Int. Ed.*, 2010, **49**, 7548; (f) M. Zhang, H. Yang, Y. Zhang, C. Zhu, W. Li, Y. Cheng and H. Hu, *Chem. Commun.*, 2011, **47**, 6605; (g) J. Deng, L.-P. Mo, F.-Y. Zhao, L.-L. Hou, L. Yang and Z.-H. Zhang, *Green Chem.*, 2011, **13**, 2576; (h) S. Werkmeister, K. Junge and M. Beller, *Green Chem.*, 2012, **14**, 2371; (i) V. Kumar, S. Sharma, U. Sharma, B. Singh and N. Kumar, *Green Chem.*, 2012, **14**, 3410; (j) V. Kumar, U. Sharma, P. K. Verma, N. Kumar and B. Singh, *Adv. Synth. Catal.*, 2012, **354**, 870; (k) Q. Lei, Y. Wei, D. Talwar, C. Wang, D. Xue and J. Xiao, *Chem. Eur. J.*, 2013, **19**, 4021.
- 5 (a) F. Paul, J. Patt and J. F. Hartwig, *J. Am. Chem. Soc.*, 1994, **116**, 5969; (b) A. S. Guram and S. L. Buchwald, *J. Am. Chem. Soc.*, 1994, **116**, 7901; (c) A. S. Guram, R. A. Rennels and S. L. Buchwald, *Angew. Chem. Int. Ed. Engl.*, 1995, **34**, 1348.
- 6 (a) D. M. T. Chan, K. L. Manaco, R. P. Wang and M. P. Winters, *Tetrahedron Lett.*, 1998, **39**, 2933; (b) P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan and A. Combs, *Tetrahedron Lett.*, 1998, **39**, 2941; (c) J. X. Qiao and P. Y. S. Lam, *Synthesis*, 2011, 829.
- 7 For dehydrogenative (oxidative) aromatization of cyclohexanones with amines to anilines: (a) S. A. Girard, X. Hu, T. Knauber, F. Zhou, M.-O. Simon, G.-J. Deng and C.-J. Li, *Org. Lett.*, 2012, **14**, 5606; (b) A. Hajra, Y. Wei and N. Yoshikai, *Org. Lett.*, 2012, **14**, 5488; (c) M. Sutter, M.-C. Duclos, B. Guicheret, Y. Raoul, E. Métaý and M. Lemaire, *ACS Sustainable Chem. Eng.*, 2013, **1**, 1463; (d) M. T. Barros, S. S. Dey, C. D. Maycock and P. Rodrigues, *Chem. Commun.*, 2012, **48**, 10901; (e) J. Zhao, H. Huang, W. Wu, H. Chen and H. Jiang, *Org. Lett.*, 2013, **15**, 2604; (f) Y. Xie, S. Liu, Y. Liu, Y. Wen and G.-J. Deng, *Org. Lett.*, 2012, **14**, 1692; (g) Y. Liao, P. Jiang, S. Chen, F. Xiao and G.-J. Deng, *RSC Adv.*, 2013, **3**, 18605; (h) X. Cao, Y. Bai, Y. Xie and G.-J. Deng, *J. Mol. Catal. A: Chem.*, 2014, **383**, 94.
- 8 For other dehydrogenative (oxidative) aromatization: (a) Y. Izawa, D. Pun and S. S. Stahl, *Science*, 2011, **333**, 209; (b) T. Imahori, T. Tokuda, T. Taguchi and H. Takahata, *Org. Lett.*, 2012, **14**, 1172; (c) Y. Izawa, C. Zheng and S. S. Stahl, *Angew. Chem. Int. Ed.*, 2013, **52**, 3672; (d) Y. Liao, P. Jiang, S. Chen, H. Qi and G.-J. Deng, *Green Chem.*, 2013, **15**, 3302; (e) K. Kikushima

- and Y. Nishina, *RSC Adv.*, 2013, **3**, 20150; (f) D. Ding, X. Lv, J. Li, G. Xu, B. Ma and J. Sun, *Chem. Asian J.*, 2014, **9**, 1539; (g) S. R. Kandukuri and M. Oestreich, *J. Org. Chem.*, 2012, **77**, 8750; (h) W. P. Hong, A. V. Iosub and S. S. Stahl, *J. Am. Chem. Soc.*, 2013, **135**, 13664; (i) F. Zhou, M.-O. Simon and C.-J. Li, *Chem. Eur. J.*, 2013, **19**, 7151; (j) S. Chen, Y. Liao, F. Zhao, H. Qi, S. Liu and G.-J. Deng, *Org. Lett.*, 2014, **16**, 1618; (k) J. Kim, Y. Moon, S. Lee and S. Hong, *Chem. Commun.*, 2014, **50**, 3227; (l) M.-O. Simon, S. A. Girard and C.-J. Li, *Angew. Chem. Int. Ed.*, 2012, **51**, 7537; (m) M. Sutter, N. Sotto, Y. Raoul, E. Métaay and M. Lemaire, *Green Chem.*, 2013, **15**, 347; (n) J. Zhang, Q. Jiang, D. Yang, X. Zhao, Y. Dong and R. Liu, *Chem. Sci.*, 2015, **6**, 4674; (o) S. A. Girard, H. Huang, F. Zhou, G.-J. Deng and C.-J. Li, *Org. Chem. Front.*, 2015, **2**, 279.
- 9 K. Taniguchi, X. Jin, K. Yamaguchi and N. Mizuno, *Chem. Commun.*, 2015, **51**, 14969.
- 10 (a) S. Nishimura, Y. Yakita, M. Katayama, K. Higashimine and K. Ebitani, *Catal. Sci. Technol.*, 2013, **3**, 351; (b) J. Pritchard, M. Piccinini, R. Tiruvalam, Q. He, N. Dimitratos, J. A. Lopez-Sanchez, D. J. Morgan, A. F. Carley, J. K. Edwards, C. J. Kiely and G. J. Hutchings, *Catal. Sci. Technol.*, 2013, **3**, 308.
- 11 (a) J. S. Zhu and Y.-S. Shon, *Nanoscale*, 2015, **7**, 17786; (b) A. M. Doyle, S. K. Shaikhutdinov and H.-J. Freund, *Angew. Chem. Int. Ed.*, 2005, **44**, 629; (c) A. M. Doyle, S. K. Shaikhutdinov and H.-J. Freund, *J. Catal.*, 2004, **223**, 444; (d) A. M. Doyle, S. K. Shaikhutdinov, S. D. Jackson and H.-J. Freund, *Angew. Chem. Int. Ed.*, 2003, **42**, 5240.
- 12 One referee asked us to examine the effect of supports. Thus, according to the comment, we prepared the Au–Pd/TiO₂ catalyst by the same manner as that for Au–Pd/Al₂O₃ (Au: 0.070 mmol g⁻¹, Pd: 0.118 mmol g⁻¹), and the catalytic performance was examined. It was revealed by the HAADF-STEM and EDS analyses of Au–Pd/TiO₂ that Au–Pd alloy nanoparticles were formed on TiO₂ (Fig. S5b–d, ESI†). The TEM analysis revealed that the average size of the alloy nanoparticles was 1.8 nm (Fig. S5a, ESI†) and smaller than that in Au–Pd/Al₂O₃. When the dehydrogenative aromatization of **1a** with **2a** was carried out using the Au–Pd/TiO₂ catalyst

under the conditions described in Table 1, the desired aniline **3aa** was produced in 84% yield (cf. 59% yield using Au–Pd/Al₂O₃; Table 1, entry 3). The average particle sizes of Au–Pd/Al₂O₃ and Au–Pd/TiO₂ were 2.9 nm and 1.8 nm, respectively. From these average particle sizes and the palladium contents, we estimated the numbers of the surface exposed palladium atoms in Au–Pd/Al₂O₃ and Au–Pd/TiO₂.¹⁵ Assuming that the nanoparticles are homogeneous and that the sizes are unchanged during the reaction, the turnover numbers (TONs) based on the surface exposed palladium atoms were calculated to be 98 for Au–Pd/Al₂O₃ and 86 for Au–Pd/TiO₂ and almost the same to each other. Therefore, we consider that the high performance of Au–Pd/TiO₂ is possibly due to the small average particle size rather than the electronic effect from the support.

- 13 R. A. Sheldon, M. Wallau, I. W. C. E. Arends and U. Schuchardt, *Acc. Chem. Res.*, 1998, **31**, 485.
- 14 W. L. F. Armarego and C. L. L. Chai, *Purification of Laboratory Chemicals*, Butterworth-Heinemann, Oxford, 5th edn, 2003.
- 15 The numbers of the surface exposed metal atoms were estimated by using the model cluster with fcc structure according to the following literatures: (a) N. Toshima, M. Harada, Y. Yamazaki and K. Asakura, *J. Phys. Chem.*, 1992, **96**, 9927; (b) M. Harada, K. Asakura and N. Toshima, *J. Phys. Chem.*, 1993, **97**, 5103; (c) Y. Shiraishi, D. Ikenaga and N. Toshima, *Aust. J. Chem.*, 2003, **56**, 1025; (d) H. Zhang, T. Watanabe, M. Okumura, M. Haruta and N. Toshima, *Nat. Mater.*, 2012, **11**, 49.

Table 1 Dehydrogenative aromatization of **1a** with **2a** using various hydrogen acceptors and catalysts^a



Entry	Catalyst	Hydrogen acceptor	Yield (%)		
			3aa	4aa	5aa
1	Au–Pd/Al ₂ O ₃	none	34	64	<1
2 ^b	Au–Pd/Al ₂ O ₃	O ₂ (air)	41	46	13
3	Au–Pd/Al ₂ O ₃	styrene	59	<1	12
4 ^c	Au–Pd/Al ₂ O ₃	styrene	76	<1	<1
5	Au–Pd/Al ₂ O ₃	1-octene	51	47	<1
6	Au–Pd/Al ₂ O ₃	cyclooctene	41	56	<1
7 ^d	Au–Pd/Al ₂ O ₃	benzoquinone	5	<1	<1
8 ^e	Au/Al ₂ O ₃	styrene	<1	<1	40
9 ^f	Pd/Al ₂ O ₃	styrene	20	<1	12
10 ^g	Au/Al ₂ O ₃ + Pd/Al ₂ O ₃	styrene	33	<1	48

^a Reaction conditions: catalyst (Au: 1.4 mol%, Pd: 2.2 mol% with respect to **1a**), **1a** (0.5 mmol), **2a** (1.0 mmol), hydrogen acceptor (1.0 mmol), toluene (2 mL), 100 °C, Ar (1 atm), 6 h. Yields (based on **1a**) were determined by GC analysis using *n*-decane as an internal standard. ^b Open air (1 atm). ^c 18 h. ^d Substrates and benzoquinone were mostly converted into unidentified by-products. ^e Au: 1.4 mol% with respect to **1a**. ^f Pd: 2.2 mol% with respect to **1a**. ^g A physical mixture of Au/Al₂O₃ and Pd/Al₂O₃ (Au: 1.4 mol%, Pd: 2.2 mol% with respect to **1a**).

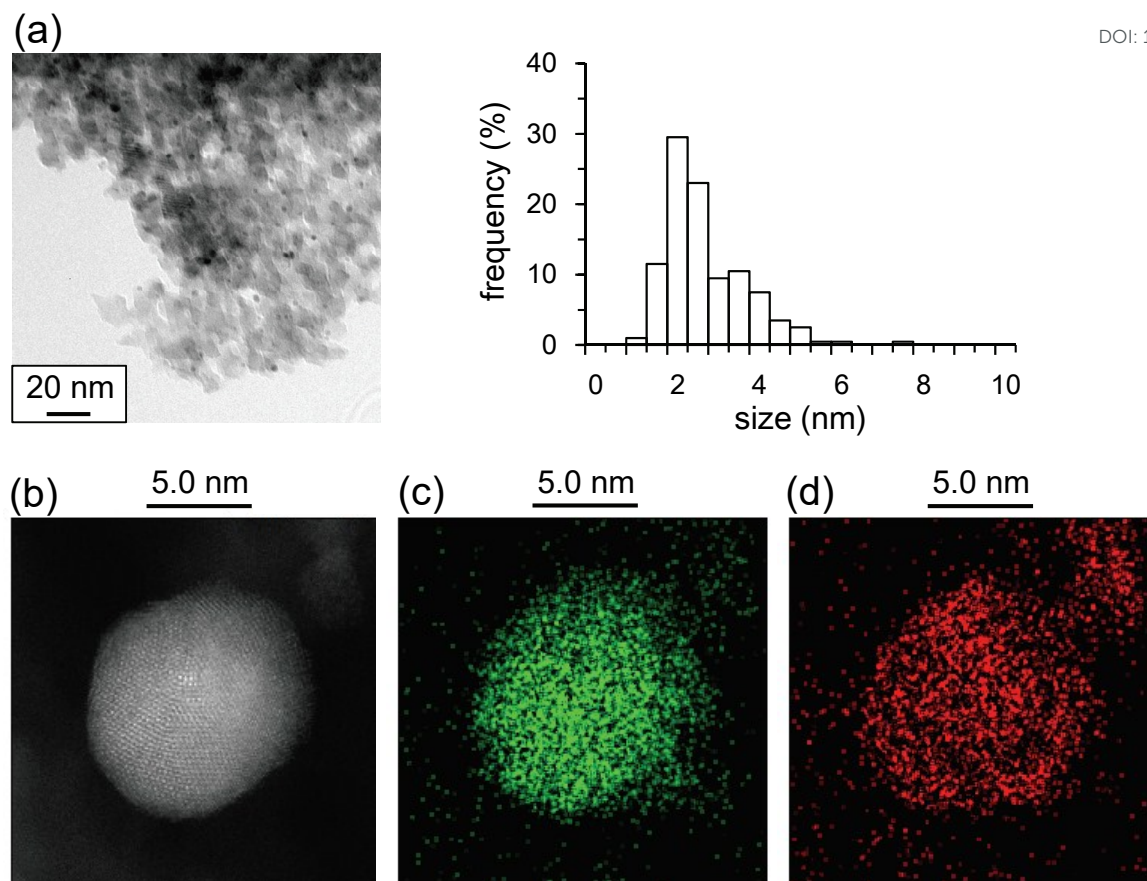


Fig. 1 (a) TEM image of Au-Pd/Al₂O₃ and the size distribution of bimetallic nanoparticles (average: 2.9 nm, σ : 1.0 nm). The size distribution was determined using 200 particles. (b) HAADF-STEM image of Au-Pd/Al₂O₃. (c) EDS images (Au element) of Au-Pd/Al₂O₃. (d) EDS images (Pd element) of Au-Pd/Al₂O₃.

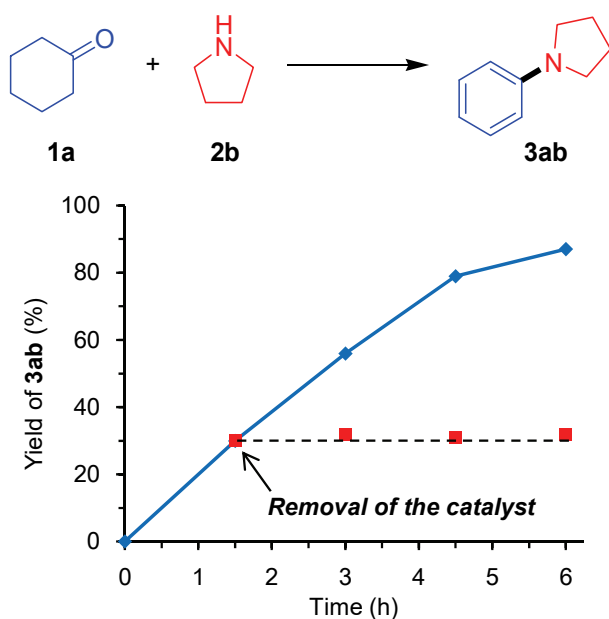


Fig. 2 The effect of removal of the Au–Pd/Al₂O₃ catalyst (verification of heterogeneous catalysis). Reaction conditions: Au–Pd/Al₂O₃ (Au: 1.4 mol%, Pd: 2.2 mol% with respect to **1a**), **1a** (0.5 mmol), **2b** (1.0 mmol), styrene (1.0 mmol), toluene (2 mL), 80 °C, Ar (1 atm). Yields (based on **1a**) were determined by GC analysis using *n*-decane as an internal standard.

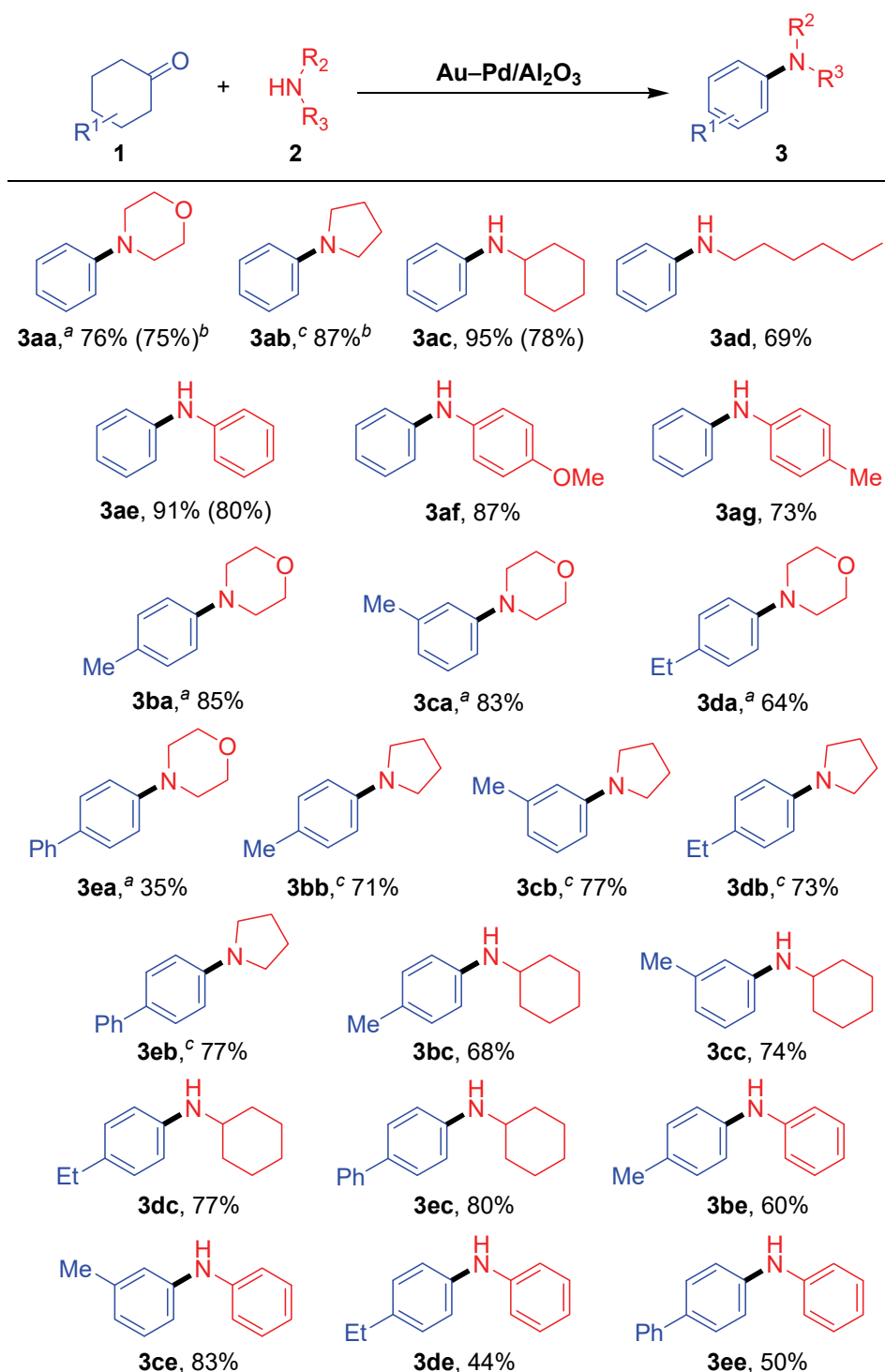
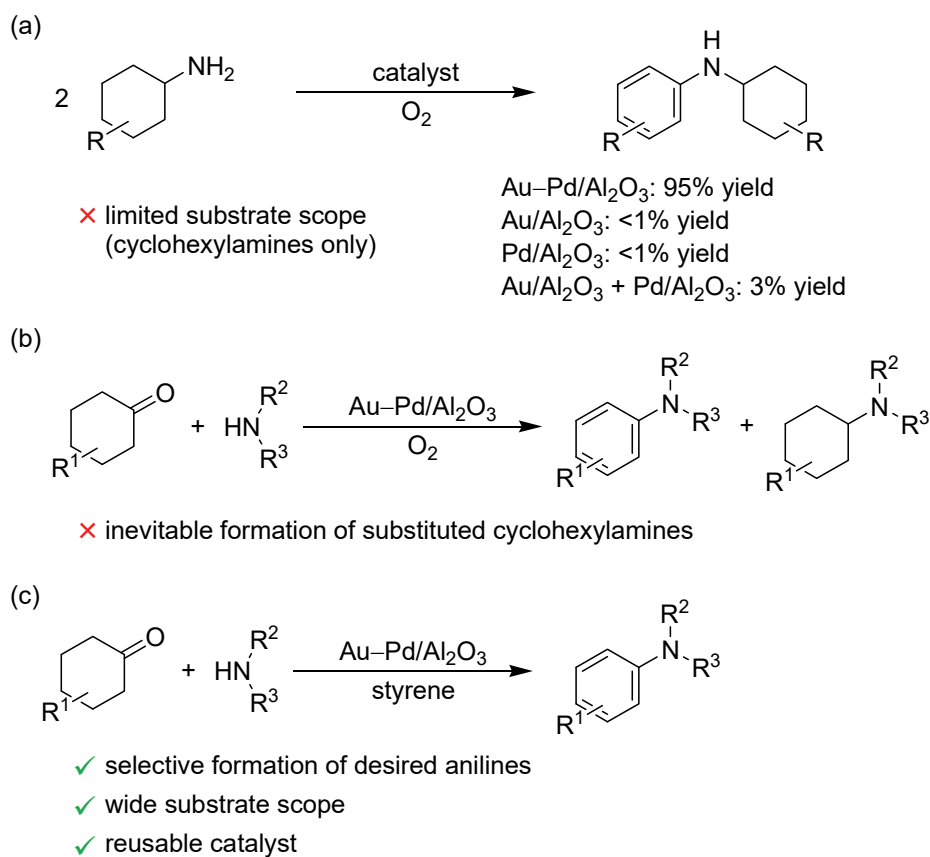
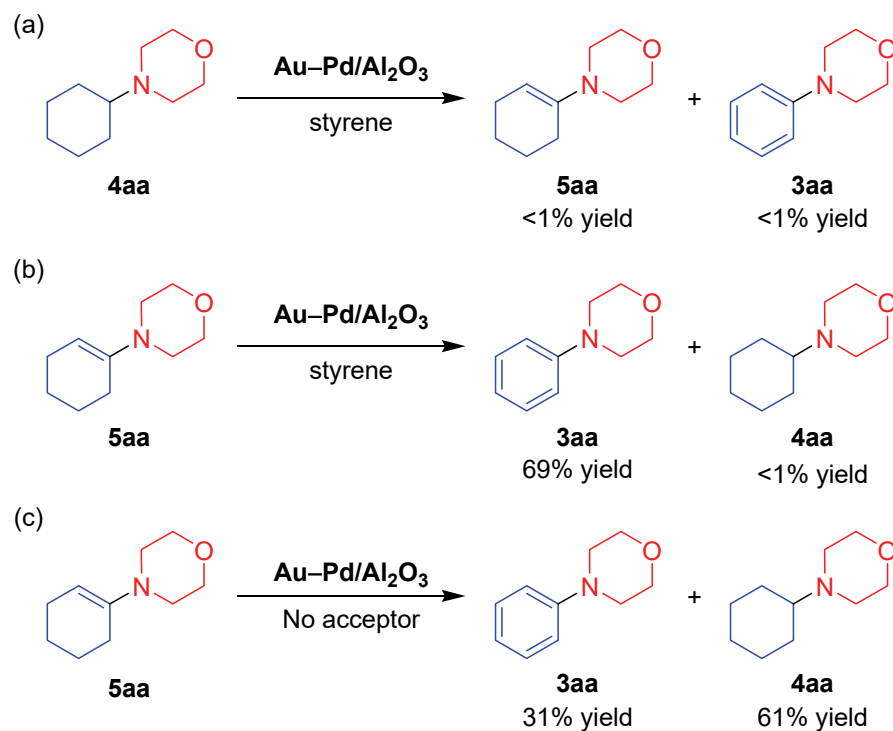


Fig. 3 Scope of the present Au-Pd/Al₂O₃-catalyzed dehydrogenative aromatization of cyclohexanones with amines. Reaction conditions: Au-Pd/Al₂O₃ (Au: 1.4 mol%, Pd: 2.2 mol% with respect to **1**), **1** (0.5 mmol), **2** (1.0 mmol), styrene (1.0 mmol), mesitylene (2 mL), 130 °C, Ar (1 atm), 24 h. Yields (based on **1**) were determined by GC analysis using *n*-decane or naphthalene as an internal standard. ^a Toluene (2 mL), 100 °C, 18 h. ^b The values in the parentheses indicate the isolated yields. ^c Toluene (2 mL), 80 °C, 6 h.

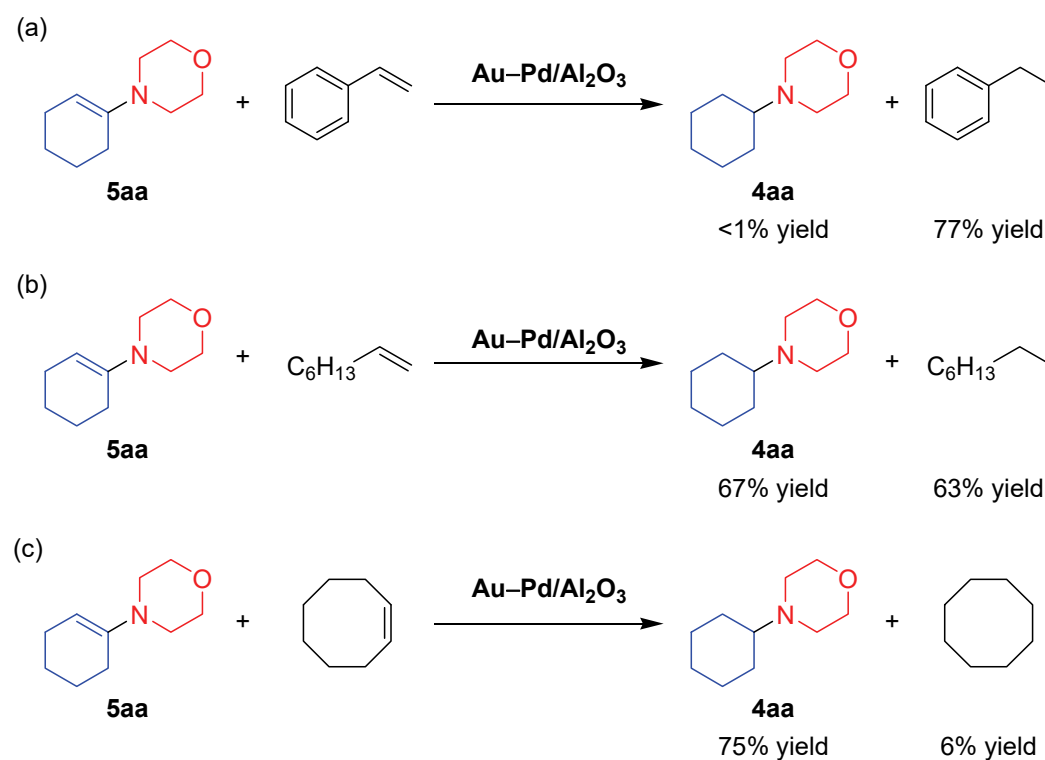


Scheme 1 Heterogeneously catalyzed dehydrogenative aromatization routes to *N*-substituted anilines. (a) Our recently reported Au-Pd/Al₂O₃-catalyzed system from cyclohexylamines (see ref. 9), (b) Au-Pd/Al₂O₃-catalyzed aerobic routes from cyclohexanones and amines (see Table 1, entry 2), and (c) the reactions utilizing styrene as the hydrogen acceptor.



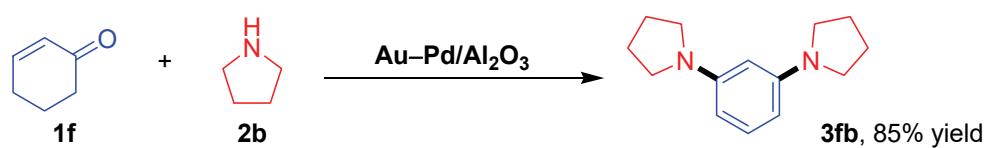
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Scheme 2 (a) Dehydrogenative aromatization starting from **4aa**. Reaction conditions: Au–Pd/Al₂O₃ (Au: 1.4 mol%, Pd: 2.2 mol% with respect to **4aa**), **4aa** (0.5 mmol), styrene (1.0 mmol), toluene (2 mL), 100 °C, Ar (1 atm), 6 h. (b and c) Dehydrogenative aromatization starting from **5aa**. Reaction conditions: Au–Pd/Al₂O₃ (Au: 1.4 mol%, Pd: 2.2 mol% with respect to **5aa**), **5aa** (0.5 mmol), hydrogen acceptor (0 or 1.0 mmol), toluene (2 mL), 100 °C, Ar (1 atm), 6 h. Yields (based on **4aa** or **5aa**) were determined by GC analysis using *n*-decane as an internal standard.

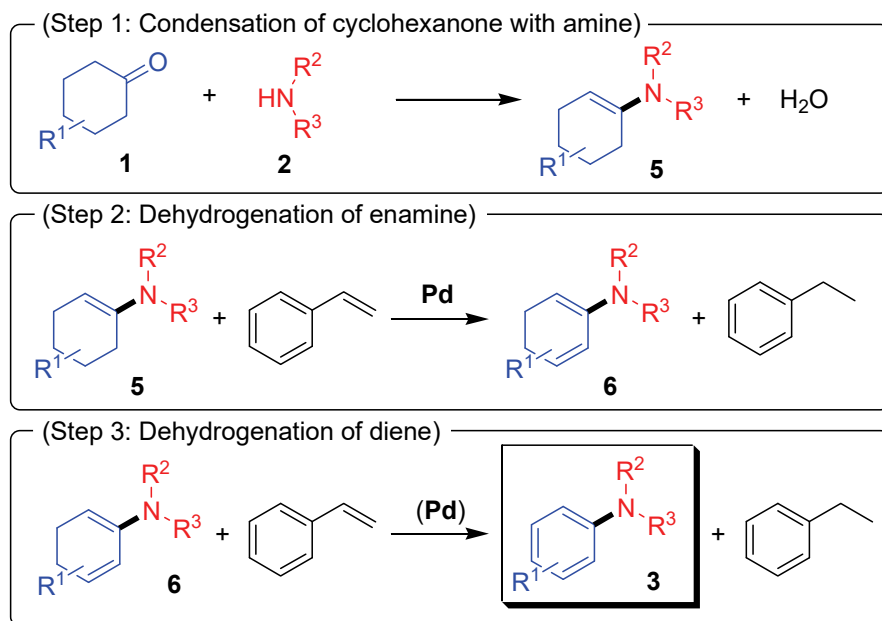


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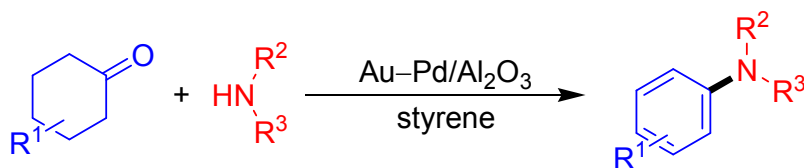
Scheme 3 Au–Pd/Al₂O₃-catalyzed hydrogenation of an equimolar mixture of hydrogen acceptor (styrene, 1-octene, and cyclooctene) and **5aa**. Reaction conditions: Au–Pd/Al₂O₃ (Au: 0.4 mol%, Pd: 0.6 mol% with respect to alkenes), hydrogen acceptor (1.0 mmol), **4aa** (1.0 mmol), ethanol (2 mL), room temperature, H₂ (1 atm), 1 h. Yields (based on **5aa** and hydrogen acceptor, respectively) were determined by GC analysis using *n*-decane as an internal standard.



Scheme 4 Au-Pd/Al₂O₃-catalyzed tandem 1,4-addition/1,2-addition/dehydrogenative aromatization reaction of **1f** with **2b** to **3fb**. Reaction conditions: Au-Pd/Al₂O₃ (Au: 1.4 mol%, Pd: 2.2 mol% with respect to **1f**), **1f** (0.5 mmol), **2b** (2.0 mmol), styrene (1.0 mmol), toluene (2 mL), 50 °C, Ar (1 atm), 6 h. Yields (based on **1f**) were determined by GC analysis using *n*-decane as an internal standard.



Scheme 5 Possible reaction pathway for the present Au–Pd/Al₂O₃-catalyzed dehydrogenative aromatization starting from cyclohexanones and amines to produce *N*-substituted anilines. When using primary amines ($R^2 = \text{H}$), the corresponding ketimines are formed as the intermediates.

Graphical abstract

- ✓ selective formation of desired anilines
- ✓ wide substrate scope
- ✓ reusable catalyst

In the presence of a gold–palladium alloy nanoparticles catalyst (Au–Pd/Al₂O₃) and styrene, various kinds of structurally diverse *N*-substituted anilines (twenty three examples) could be synthesized starting from cyclohexanones and amines.