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Supported gold–palladium alloy nanoparticles catalyzed tandem oxidation routes to *N*-substituted anilines from non-aromatic compounds†

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In the presence of a supported gold–palladium alloy nanoparticles catalyst (Au–Pd/Al₂O₃), various kinds of *N*-substituted anilines can be synthesized from non-aromatic compounds. The observed catalysis is truly heterogeneous, and Au–Pd/Al₂O₃ can be reused without a significant loss of its catalytic performance.

In several biosynthetic transformations, a series of highly selective reactions are occurring in tandem, and desired products can selectively be produced with high efficiency. Such transformations have fascinated not only biochemists but also synthetic organic chemists, and one-pot tandem reactions have recently proven useful in organic synthesis.¹ They can avoid tedious isolation step(s) of the reaction intermediate(s), and consequently show higher synthetic efficiency in comparison with traditional step-by-step procedures. Nowadays, a tandem oxidation process, including one or more oxidation reaction(s) in the process, has become one of the powerful tools to synthesize a wide variety of valuable chemicals, such as alkenes, quinoxalines, imines, amides, and esters.^{2,3} In most of the previously developed tandem oxidation processes, alcohol oxidation is involved as the key step, and then the *in situ* formed aldehydes or ketones act as the electrophiles to react further with nucleophilic reagents, such as Wittig reagents, amines, and alcohols. Considering the potential utility of the tandem reactions, the development of novel tandem oxidation processes composed of a wide range of oxidation reaction steps is of great significance.

Anilines are very important compounds frequently utilized as synthons for pharmaceuticals, agricultural chemicals, dyes, and electronic devices, and the development of diverse synthetic procedures for *N*-substituted anilines has been a meaningful research subject.⁴ From the viewpoint of starting materials, the previously developed synthetic methods for *N*-substituted anilines are roughly divided into three classes; (A) *N*-alkylation of anilines, (B) arylation of amines (cross-coupling), and (C) oxidative

aromatization (Scheme S1, upper, ESI†). As for *N*-alkylation of anilines, alkyl halides have traditionally been utilized as alkylating reagents (Procedure A in Scheme S1, ESI†).⁵ Alternative environmentally-friendly approaches are *N*-alkylation with alcohols (borrowing hydrogen strategy)⁶ and reductive amination of carbonyl compounds.⁷ The Buchwald–Hartwig coupling⁸ and the Chan–Lam coupling⁹ are two of the most frequently utilized choices for arylation of amines (Procedure B in Scheme S1, ESI†). These cross-coupling methodologies show broad substrate scopes and thus have been frequently utilized as powerful procedures for late-stage aryl group installation into amino functional groups. Although these cross-coupling methodologies can precisely afford the desired aniline scaffolds, they should utilize pre-activated substrates, which concurrently generate (super)stoichiometric amounts of waste. Quite recently, oxidative aromatization has emerged as a novel attractive procedure for synthesis of aromatic compounds.^{10,11} By utilizing the oxidative aromatization strategy, anilines can be synthesized starting from cyclohexanones and various nitrogen nucleophiles such as amines, anilines, nitroarenes, thioureas, aminobenzenethiols, and aryl sulfonamides (Procedure C in Scheme S1, ESI†).¹¹

Because of the importance of aniline-based compounds, further development of the novel reliable synthetic procedures from diverse starting materials is still an important research subject. Herein, we report novel tandem oxidation routes to *N*-substituted anilines from non-aromatic compounds (Procedure D in Scheme S1, ESI†). In the presence of a supported gold–palladium alloy nanoparticles on Al₂O₃ (Au–Pd/Al₂O₃), various cyclohexylamine could be converted into the corresponding *N*-cyclohexylaniline. Diphenylamine could also be obtained as the major product through further dehydrogenation of *N*-cyclohexylaniline when simply changing the reaction conditions. Moreover, in the presence of Au–Pd/Al₂O₃, *N*-alkylanilines could be synthesized starting from cyclohexanones (or cyclohexanols) and amines. The present tandem oxidation processes have several noticeable features; for example (i) use of readily available starting materials, (ii) use of the greenest oxidant of air as the terminal oxidant, (iii) formation of water and ammonia as the co-products, and (iv) use of the reusable heterogeneous catalyst.

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To begin with, the tandem oxidation of cyclohexylamine (**1a**) into *N*-cyclohexylaniline (**2a**) was carried out in the presence of various kinds of supported metal catalysts (gold, palladium, and gold–palladium on Al₂O₃ or TiO₂; given in the format: metal/support; see ESI[†] for the preparation and characterization). The reactions were typically carried out at 130 °C in mesitylene under open air (1 atm). The gold and palladium bimetallic nanoparticles supported on Al₂O₃ (Au–Pd/Al₂O₃) showed the excellent catalytic performance for the transformation and gave **2a** in 95 % yield for 3 h (Fig. 1, Table S1, entry 1, ESI[†]). 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. S1, ESI[†]). The average size of the alloy nanoparticles was 1.7 nm (Fig. S2, ESI[†]). When using Au/Al₂O₃ or Pd/Al₂O₃, the desired **2a** was not produced at all under the present reaction conditions (Fig. 1, Table S1, entries 2 and 3, ESI[†]), and the starting material **1a** and/or the intermediates were undesirably converted into phenol, aniline, and unidentified by-products (possibly polymeric compounds) to some extent. When using Au/Al₂O₃, *N*-cyclohexylidencyclohexylamine (**4a**, possible intermediate for the present transformation) was observed (Table S1, entry 2, ESI[†]). The physical mixture of Au/Al₂O₃ and Pd/Al₂O₃ gave **2a** in only 3 % yield, and in this case also **1a** and/or the intermediates were converted into the undesirable by-products (Fig. 1, Table S1, entry 4, ESI[†]). In the absence of the catalysts or the presence of Al₂O₃ alone, no conversion of **1a** was observed (Table S1, entries 9 and 10, ESI[†]). The effect of the gold to palladium molar ratios on the transformation was significant, and the best Au/Pd ratio was 3.3 (Table S1, entries 1 and 6–8, ESI[†]). Thus, we hereafter utilized the best Au–Pd/Al₂O₃ catalyst (Au/Pd = 3.3) for the tandem oxidation reactions.

In order to verify whether the observed catalysis was truly caused by solid Au–Pd/Al₂O₃ or leached metal species (gold and/or palladium), the following experiments were carried out. The reaction of **1a** to **2a** was carried out under the conditions described in Fig. 1, and Au–Pd/Al₂O₃ was removed from the reaction mixture by filtration at ca. 50 % conversion of **1a**. Then, the filtrate was again heated at 130 °C under open air. In this case, no further production of **2a** was observed (Fig. S3, ESI[†]). Furthermore, we confirmed

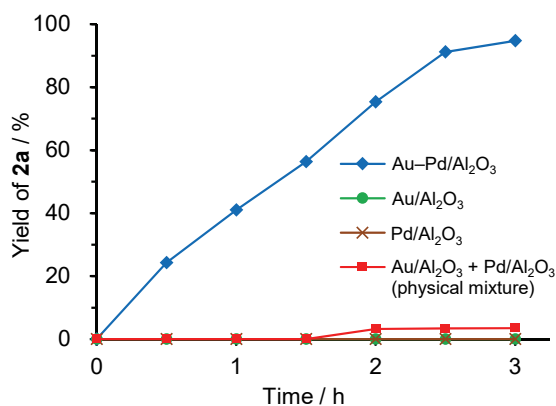


Fig. 1 Tandem oxidation of **1a** using various catalysts. Reaction conditions: **1a** (1.0 mmol), catalyst (Au: 1.15 mol%, Pd: 0.35 mol%), mesitylene (2 mL), 130 °C, open air (1 atm). Detailed data, e.g., conversions of **1a**, and yields of **2a** and other products **3a–5a**, are noted in Table S1, ESI[†].

by the inductively coupled plasma atomic emission spectroscopy (ICP-AES) analysis that no gold and palladium species were detected in the filtrate. These results strongly indicate that the observed catalysis for the present transformation is truly heterogeneous.¹² After the reaction of **1a** was completed, Au–Pd/Al₂O₃ could easily be retrieved from the reaction mixture by simple filtration (>90 % recovery). The retrieved Au–Pd/Al₂O₃ could be reused at least five times for the same reaction without a significant loss of its catalytic performance; even at the fifth reuse experiment, **2a** was still obtained in 75 % yield (Fig. S4, ESI[†]).¹³

Next, the scope of the present Au–Pd/Al₂O₃-catalyzed tandem oxidation processes was examined. As shown in Fig. 2, various kinds of structurally diverse cyclohexylamines (**1**) could be converted into the corresponding *N*-cyclohexylanilines (**2**) in the presence of Au–Pd/Al₂O₃. All products could easily be isolated by simple column chromatography on silica gel (see ESI[†]), and the isolated yields are summarized in Fig. 2. The reaction of cyclohexylamine and its derivatives with methyl group at each position of the cyclohexane rings efficiently proceeded to afford the corresponding anilines (**2a–2d**). Cyclohexylamines with other alkyl groups such as ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, *tert*-butyl, and *n*-pentyl groups at the 4-positions could also be converted into the corresponding anilines (**2e–2k**). For the transformation of substituted cyclohexylamines **1b–1k**, the *cis/trans* ratios of the products **2b–2k** were slightly different from those of **1b–1k**. Notably, when simply changing the reaction conditions, i.e., increasing the amount of Au–Pd/Al₂O₃ and the reaction time, we could successfully synthesize diphenylamine (**3a**) directly from **1a** through the tandem oxidation of **1a** to **2a** followed by further oxidative dehydrogenation to **3a** (Scheme 1A, Fig. S5, ESI[†]). To the best of our knowledge, such a direct

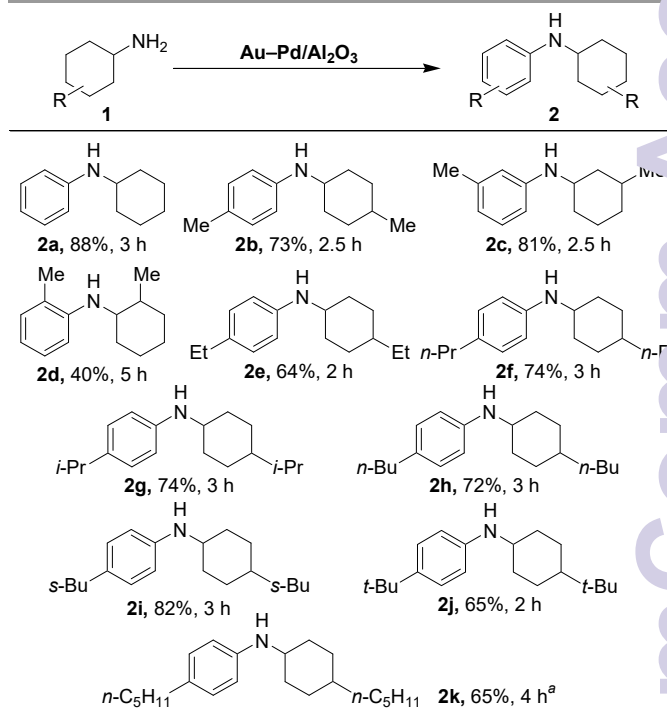


Fig. 2 Scope of substrates. Reaction conditions: **1** (1.0 mmol), Au–Pd/Al₂O₃ (Au: 1.15 mol%, Pd: 0.35 mol%), mesitylene (2 mL), 130 °C, open air (1 atm). Detailed data, e.g., conversions of **1**, yields of **2** and other products **3–5**, and *cis/trans* ratios of **1** and **2**, are noted in Table S2, ESI[†]. ^a Au–Pd/Al₂O₃ (Au: 2.3 mol%, Pd: 0.7 mol%).

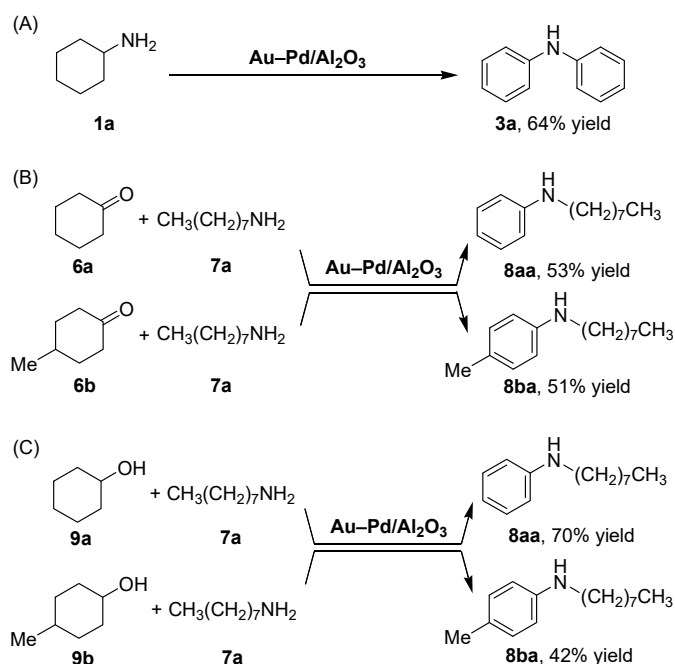
one-pot oxidative transformation of cyclohexylamine into diphenylamine has never been reported until now.

Encouraged by the above successful transformation of cyclohexylamines, we next turned our attention to the utilization of Au–Pd/Al₂O₃ for tandem oxidation of cyclohexanones with amines into the corresponding *N*-alkylanilines.¹¹ For example, Au–Pd/Al₂O₃ could catalyze the tandem oxidation of cyclohexanones (**6a** and **6b**) with *n*-octylamine (**7a**), giving the corresponding *N*-alkylanilines (**8aa** and **8ba**) (Scheme 1B).¹⁴ Interestingly, cyclohexanols could be utilized as the starting materials, and the tandem oxidation of cyclohexanols (**9a** and **9b**) with **7a** efficiently proceeded to afford the corresponding *N*-alkyl anilines (**8aa** and **8ba**) (Scheme 1C).¹⁴

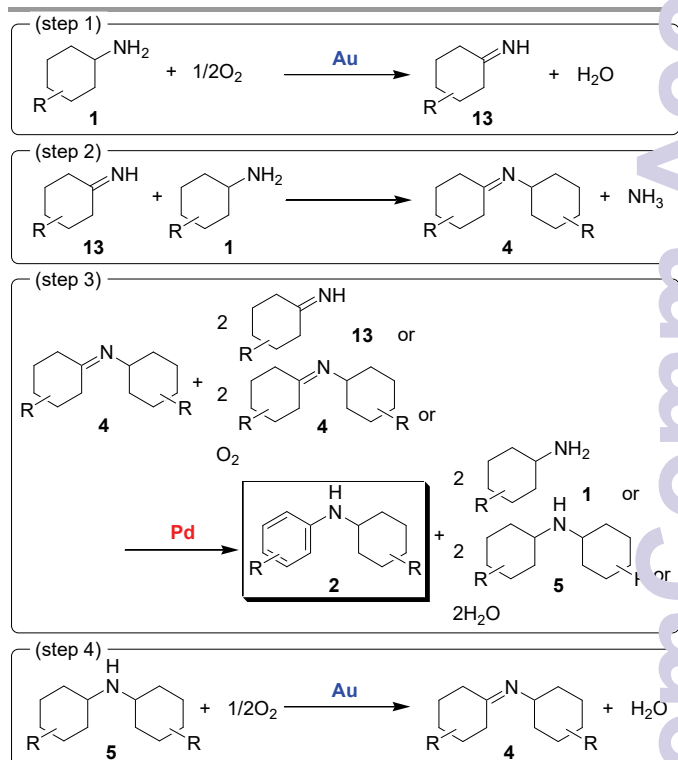
As above-mentioned, the desired aniline **2a** was obtained in a high yield for the transformation of **1a** when using Au–Pd/Al₂O₃ and hardly produced using Au/Al₂O₃, Pd/Al₂O₃, and the physical mixture of Au/Al₂O₃ and Pd/Al₂O₃ (Fig. 1). To elucidate the roles of metals and the possible reaction pathway, the following several experiments were carried out. Firstly, the reaction of dicyclohexylamine (**5a**) was carried out with Au–Pd/Al₂O₃, Au/Al₂O₃, Pd/Al₂O₃, and the physical mixture of Au/Al₂O₃ and Pd/Al₂O₃. In the presence of Au–Pd/Al₂O₃, **5a** was efficiently converted into **2a** in 79 % yield for 2 h (Fig. S6). In the case of Au/Al₂O₃, **5a** was oxidized to the imine **4a** followed by decomposition to unidentified by-products without the formation of **2a** (Fig. S7), showing that gold possesses the ability to oxidize amines to imines but does not show the activity for aromatization of the imine intermediates. As shown in Fig. S8, Pd/Al₂O₃ was completely inactive for the oxidation of **5a**. In the separate experiments, we confirmed that the oxidative

aromatization of *N*-cyclohexylideneisopropylamine (**10**) proceeded in the presence of Au–Pd/Al₂O₃ and Pd/Al₂O₃, affording *N*-isopropylaniline (**11**) with the concomitant formation of *N*-isopropylcyclohexylamine (**12**) and that Au/Al₂O₃ hardly catalyzed the formation of **11** and **12** (Scheme S2).¹⁵ Therefore, we conclude that the role of palladium is to promote aromatization (disproportionation and aerobic oxidative dehydrogenation) of the imine intermediates.¹⁵ When utilizing the physical mixture for the transformation of **5a**, **2a** was obtained in 22 % yield for 2 h but the intermediate **4a** still remained (11 % yield) (Fig. S9). According to the results with Au–Pd/Al₂O₃ and the physical mixture of Au/Al₂O₃ and Pd/Al₂O₃, one can recognize that the catalytic activities of Au–Pd/Al₂O₃ for both amine oxidation and oxidative aromatization are significantly higher than those of the physical mixture (Fig. S6 and Fig. S9). By alloying gold and palladium, the intrinsic abilities of gold for amine oxidation and/or palladium for aromatization are likely improved by electronic ligand effects.¹⁶ This is one possible explanation of the excellent catalytic performance of Au–Pd/Al₂O₃ for the present transformation, and such effects are frequently observed for several oxidation reactions using gold–palladium alloy catalysts, e.g., alcohol oxidation and H₂O₂ production.¹⁶

Considering the above experimental evidences, we hereby propose a possible reaction pathway for the present Au–Pd/Al₂O₃-catalyzed tandem oxidation processes (Scheme 2). Initially, aerobic oxidation of cyclohexylamine (**1**) proceeds to give cyclohexylimine (**13**), which is mainly catalyzed by gold (step 1 in Scheme 2). Then, nucleophilic addition of another cyclohexylamine molecule to the ketimine intermediate **13** takes place to afford *N*-cyclohexylidene-cyclohexylamine (**4**) (step 2 in Scheme 2). Finally, the palladium-catalyzed aromatization (disproportionation and



Scheme 1 Various tandem oxidations. Reaction conditions (A): **1a** (1.0 mmol), Au–Pd/Al₂O₃ (Au: 7.8 mol%, Pd: 2.2 mol%), mesitylene (2 mL), 130 °C, open air (1 atm), 6 h. Reaction conditions (B): **6** (0.5 mmol), **7a** (1.0 mmol), Au–Pd/Al₂O₃ (Au: 7.8 mol%, Pd: 2.2 mol%), mesitylene (2 mL), 130 °C, open air (1 atm), 2 h. Reaction conditions (C): **9** (0.5 mmol), **7a** (1.0 mmol), Au–Pd/Al₂O₃ (Au: 7.8 mol%, Pd: 2.2 mol%), mesitylene (2 mL), 130 °C, open air (1 atm), 3 h. Yields (based on limited substrates) were determined by GC analysis using an internal standard.



Scheme 2 Possible reaction pathway for the present Au–Pd/Al₂O₃-catalyzed tandem oxidation of cyclohexylamines to *N*-substituted anilines.

aerobic oxidative dehydrogenation) of **4** proceeds to give the corresponding *N*-cyclohexylaniline (**2**) as the final product with the concurrent formation of **1** and dicyclohexylamine (**5**) (step 3 in Scheme 2). In the aromatization step, **13**, **4**, and/or molecular oxygen can act as the hydrogen acceptors.¹⁵ Amines **1** and **5** formed in the aromatization step are again aerobically oxidized by gold (steps 1 and 4 in Scheme 2). Consequently, it can be considered that molecular oxygen is formally the terminal oxidant in the present tandem oxidation processes. As above-mentioned, the *cis/trans* ratios of the products were slightly different from those of the substrates for the transformation of substituted cyclohexylamines. This is likely due to the disproportionation of **4** (step 3 in Scheme 2) and the oxidation of **5** (step 4 in Scheme 2).

The successive oxidative aromatization of *N*-cyclohexylaniline to diphenylamine is possibly proceeds through the similar way.

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- The average size of gold–palladium alloy nanoparticles in the fresh Au–Pd/Al₂O₃ was 1.7 nm and increased to 4.6 nm after the fifth reuse experiment (Fig. S2, ESI[†]). The yields of **2a** were gradually decreased by repeating reuse experiment (Fig. S4, ESI[†]), and the decrease was likely caused by the increase in the particle size.
- Although Pd/Al₂O₃ could catalyze the transformations in Schemes 1B and 1C, the performances for these transformations (based on palladium) were inferior to those of Au–Pd/Al₂O₃ (Scheme S3, ESI[†]).
- Under Ar atmosphere, the Au–Pd/Al₂O₃-catalyzed transformation of **10** gave a 1:2 mixture of **11** and **12** (Scheme S2, ESI[†]). Considering the results of Au–Pd/Al₂O₃-catalyzed transformation of **10** under aerobic and anaerobic conditions, the disproportionation and the aerobic oxidative dehydrogenation of the imine intermediate are possibly included in the step 3 in Scheme 2.
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