Azobenzene synthesis from non-aromatic compounds enabled by alloy-controlled dehydrogenation catalysis

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Abstract

Azobenzenes have been ubiquitously utilised and synthesised in well-established methods represented as azo coupling since long; however, all the available azobenzene synthesis strategies use aromatic compounds as substrates, which inherently limit the regioselectivity of substituents because of *ortho/meta/para*-orientation and frequently require multi-step procedures. Dehydrogenative aromatisation from cyclohexanones, which can be regioselectively functionalised using classical methods without the aforementioned limitation, has recently attracted much attention, but the lack of multi-functional dehydrogenation catalysts for both aromatisation and azo bond formation and/or the difficult product selectivity control have hindered its application in azobenzene synthesis. Herein, we report an unprecedented strategy for the synthesis of diverse azobenzenes, including unsymmetrical ones, from non-aromatic compounds, i.e. cyclohexanones and hydrazine, using an Au–Pd alloy nanoparticle catalyst and nitrobenzene. Thorough mechanistic studies revealed that the present reaction is enabled by adsorption control and relay catalysis involving concerted dehydrogenation, which are unique features to alloy nanoparticles.

Graphical Abstract



Introduction

Azobenzenes are utilised in diverse fields as dyes, pigments, drugs, cosmetics, printing, textiles, indicators, photoresponsive devices and so on.^{1–7} Since azobenzene was synthesised by Noble in 1856⁸ after the first description by Mitscherlish in 1834⁹ and aniline yellow was commercially manufactured by Mene in 1861,^{1,3,4} structurally diverse azobenzenes have been synthesised and industrialised using diverse methods.^{5,10} The most classic yet widely used method is azo coupling, an electrophilic substitution reaction between diazonium salts and electronicrich aromatic compounds (Fig. 1a).^{5,10,11} Other methods include the Baeyer–Mills reaction between nitrosoarenes and anilines,^{5,10,12,13} reductive coupling of nitroarenes^{5,10,14} and oxidative coupling of anilines,^{5,10,15,16} and more recently, cross-coupling reactions using aryl hydrazine precursors,^{10,17–22} microwave-assisted coupling between nitroarenes and anilines²³ and dimerisation of aryl azides,^{24–26} among others^{27,28} (Fig. 1a). However, to our knowledge, azobenzene synthesis approaches from only non-aromatic compounds have not been achieved so far. Thus, previous azobenzene synthetic methods are intrinsically restricted to the *ortho/meta/para*-orientation of substituents in the substrate preparation and/or azobenzene synthesis itself, which usually require multi-step procedures with high environmental burdens and limit the available azobenzene structures.

Herein, we propose a novel azobenzene synthesis from only non-aromatic compounds, i.e. cyclohexanones and hydrazine (N_2H_4), through (i) condensation between N_2H_4 and cyclohexanones to azines via hydrazone formation, (ii) dehydrogenative aromatisation to 1,2-diarylhydrazines and (iii) NH-NH dehydrogenation (Fig. 1b). The stability of the azine/hydrazone structures enables the synthesis of unsymmetrical azobenzenes by sequentially condensing N₂H₄ with two different cyclohexanones. Dehydrogenative aromatisation from cyclohexanones has attracted much attention, enabling the synthesis of various aromatic compounds to date²⁹⁻⁴⁰ since Stahl et al. reported a Pd-catalysed phenol synthesis in 2011,³³ because substituents on cyclohexanones can be regioselectively installed using well-established reactions without the limitation derived from the *ortho/meta/para*-orientation of aromatic compounds.^{33,34} However, azobenzene synthesis from only cyclohexanones has not been reported so far, probably due to the lack of multi-functional dehydrogenation catalysts for both aromatisation and azo bond formation and the difficult product selectivity control, especially between azobenzenes and primary aniline derivatives (Fig. 1b). In fact, in our previous report on Pd nanoparticlecatalysed selective acceptorless dehydrogenative aromatisation from cyclohexanones and N2H4 to primary anilines, we found that hydrogenation of 1,2-diarylhydrazines was excessively fast.⁴⁰ Therefore, a catalytic system enabling simultaneously dehydrogenative aromatisation, hydrogenation inhibition and NH-NH dehydrogenation for azobenzene synthesis is essential.

We previously reported the selective synthesis of primary anilines from cyclohexanones and ammonia using the preferential adsorption of styrene hydrogen acceptors and cyclohexaneimine intermediates on Pd nanoparticle catalysts over secondary imines, which proceeded via dehydrogenative aromatisation with hydrogenation inhibition (Fig. 1c).³⁸ Thus, we initially investigated various hydrogen acceptors using an Al₂O₃supported Pd nanoparticle catalyst (Pd/Al₂O₃) for the dehydrogenative aromatisation of azine **2a** derived from 4*tert*-butylcyclohexanone (**1a**) and hydrazine monohydrate (N₂H₄·H₂O); however, most of the hydrogen acceptors inhibited the dehydrogenation reaction (Supplementary Table 1) probably because they were preferentially adsorbed on the Pd nanoparticles compared with **2a** (Fig. 1c). In addition, 1,2-diarylhydrazine intermediates easily underwent disproportionation on the Pd nanoparticles to form anilines even in the presence of the hydrogen acceptors (Supplementary Table 2), which was likely caused by the excessively strong adsorption of 1,2diarylhydrazines on the Pd nanoparticles (Fig. 1c). Therefore, a new catalyst design for enabling the co-adsorption of azines and hydrogen acceptors and for proceeding with efficient hydrogen transfer from 1,2-diarylhydrazines to hydrogen acceptors is indispensable.

In this study, we successfully developed an unprecedented one-pot synthesis of azobenzenes, including unsymmetrical ones, from N₂H₄ and various cyclohexanones using an Al₂O₃-suported Au–Pd random alloy nanoparticle catalyst with an Au/Pd ratio of 71/29 (Au₇₁–Pd₂₉/Al₂O₃) in the presence of nitrobenzene (Fig. 1d). A combination of various experiments and density functional theory (DFT) calculations reveals that the reaction was achieved via a unique dehydrogenation catalysis controlled by Au-diluted Pd alloy nanoparticles. Specifically, i) an "ensemble effect" allowed for the co-adsorption of the nitrobenzene hydrogen acceptor and intermediates on Pd sites, and ii) "relay catalysis" enabled the desired aromatisation via successive dehydrogenation on Pd sites and fast NH–NH dehydrogenation via concerted two-electron/two-proton transfer on Au sites to afford azobenzenes while inhibiting undesired hydrogenation reactions (Fig. 1d).



Fig. 1: Background and overview of this study. a, Classical and recently reported synthetic methods of azobenzenes. **b,** Proposed azobenzene synthesis from only non-aromatic compounds, i.e. cyclohexanones and N_2H_4 , requiring a multi-functional catalyst and product selectivity control between azobenzenes and primary aniline derivatives. **c,** Our previous work on selective dehydrogenative aromatisation to primary anilines using a Pd nanoparticle catalyst with styrene as a hydrogen acceptor and the difficulty in applying hydrogen acceptors to the proposed azobenzene synthesis. **d,** This work: First example of azobenzene synthesis from only non-aromatic compounds enabled by an Au₇₁–Pd₂₉/Al₂O₃ catalyst in the presence of nitrobenzene as the hydrogen acceptor via alloy-controlled co-adsorption and relay catalysis involving concerted dehydrogenation.

Results

Catalyst characterisation

Au_x–Pd_y/Al₂O₃ catalysts with various Au/Pd ratios (x/y = 100/0, 77/23, 71/29, 59/41, 45/55 and 0/100, determined via inductively coupled plasma atomic emission spectroscopy (ICP-AES) analyses (Supplementary Table 3)) were prepared via deposition–precipitation of Au and Pd species on Al₂O₃ followed by reduction (see Methods and Supplementary Information for details). The X-ray diffraction (XRD) pattern of the optimised catalyst (Au₇₁– Pd₂₉/Al₂O₃) showed that the Al₂O₃ structure was preserved after loading Au and Pd species (Supplementary Fig. 1), which were dispersed on Al₂O₃ as nanoparticles with an average diameter (d) of 2.3 nm (standard deviation (σ): 0.6 nm), as revealed by a transmission electron microscopy (TEM) analysis (Fig. 2a). The X-ray photoelectron spectroscopy (XPS) results for the Au 4f and Pd 3d regions revealed that Au and Pd mainly existed as zero-valent species (Fig. 2b,c). Scanning transmission electron microscopy–energy-dispersive spectroscopy (STEM-EDS) mapping showed that the Au and Pd species were randomly located at the same nanoparticles on Al₂O₃ (Fig. 2d– g). These results confirmed that Au₇₁–Pd₂₉/Al₂O₃ comprised Al₂O₃-supported Au–Pd random alloy nanoparticles.



Fig. 2: Characterisation of Au₇₁–Pd₂₉/Al₂O₃. **a**, TEM image and nanoparticle size distribution. XPS spectra and fitting results of **b**, Au 4f region and **c**, Pd 3d region (black broken lines: data plots, solid lines: deconvoluted signals, red broken lines: sum of the deconvoluted signals). **d**, High-angle annular dark-field (HAADF)-STEM image. STEM-EDS mappings of nanoparticles showing the distributions of **e**, Au (cyan), **f**, Pd (magenta) and **g**, overlap of Au and Pd.

The XRD patterns of the Au_x -Pd_y/Al₂O₃ series were almost the same as that of the Al₂O₃ support (Supplementary Fig. 1), and the TEM analyses indicated that their nanoparticle size distributions were similar (d= 2.3–2.8 nm, σ = 0.6–0.7 nm) (Fig. 3a and Supplementary Fig. 2). The valences and electronic states of the Au and Pd species in the catalysts were confirmed via X-ray absorption near-edge structure (XANES) spectra and XPS spectra. The Au L_{III}-edge XANES spectra and Au 4f region XPS spectra of Au_x-Pd_y/Al₂O₃ (x/y = 77/23, 71/29, 59/41 and 45/55) indicated that all the Au species were zero-valent; however, lower Au/Pd ratios resulted in decreased white-line intensities of the Au L_{III}-edge XANES spectra around 11918 eV and negatively shifted binding energies in the Au 4f region XPS spectra (Fig. 3b,c), indicating the formation of electron-richer Au species with increasing amount of Pd species.^{41,42} Moreover, considering that the Pd K-edge XANES spectra and Pd 3d region XPS spectra showed that the Pd species were mainly zero-valent (Supplementary Figs. 3 and 4), the successful preparation of Au-Pd random alloy nanoparticles with various Au/Pd ratios was suggested. In fact, the fitting results of the Pd K-edge EXAFS spectra showed that the coordination numbers of Pd-Au increased, whereas those of Pd-Pd decreased, with increasing Au/Pd ratios, indicating the decrease of Pd ensembles in higher Au/Pd ratios (Fig. 3a,d, Supplementary Fig. 5 and Supplementary Table 4). The same trend was observed in the Au L_{III}-edge EXAFS fitting spectra (Supplementary Fig. 6 and Supplementary Table 5). Furthermore, the diffuse reflectance infrared Fourier transform spectroscopy (DRIFT) of CO species adsorbed on the metal nanoparticles of Au_x -Pd_y/Al₂O₃ (Fig. 3e) showed that the increase in the Au/Pd ratios decreased the bridge and three-fold adsorption of CO on Pd (C and F)⁴³⁻⁴⁶ and increased the adsorption of CO on the Au–Pd alloy (D and E),⁴³⁻⁴⁶ which also supported the EXAFS results. Therefore, various Al₂O₃-supported Au-Pd random alloy nanoparticle catalysts with different Au/Pd ratios and similar nanoparticle distributions were successfully prepared.



Fig. 3: Characterisation of Au_x–Pd_y/Al₂O₃ with various Au/Pd ratios. a, Summary of average nanoparticle size with standard deviations determined from the TEM results and coordination numbers (CN) in the primary coordination spheres derived from the Pd K-edge EXAFS fitting results. b, Au L_{III}-edge XANES spectra. c, Au 4f region XPS spectra. d, k^3 -weighted Fourier-transformed Pd K-edge EXAFS spectra. e, DRIFT spectra of CO adsorbed on Au and Pd species under 16 Torr of CO.

Catalyst effect and optimisation of reaction conditions

After azine intermediate **2a** was prepared via condensation of **1a** with N_2H_4 · H_2O with almost full conversion of **1a** (>95%), the one-pot azobenzene **3a** synthesis was performed using various catalysts in the presence or absence of a hydrogen acceptor (Table 1). Using Pd/Al₂O₃ without a hydrogen acceptor did not furnish **3a**; instead, aniline derivatives **4a** and **5a** were obtained (Table 1, entry 1). To inhibit the cleavage of N–N bonds via hydrogenation, various hydrogen acceptors were examined in the dehydrogenative aromatisation; however, none produced **3a** (Supplementary Table 1). For instance, cyclooctene could not inhibit the N–N hydrogenation (Table 1, entry 2), and styrene and nitrobenzene (**NB**) inhibited the dehydrogenative aromatisation of **2a** (Table 1, entries 3 and 4), implying that the co-adsorption of **2a**, the dehydrogenated intermediates and the hydrogen acceptors on the monometallic Pd nanoparticles was difficult to realise.

Next, to evaluate other adsorption sites, various Al₂O₃-supported metal-Pd bimetallic nanoparticle catalysts (metal = Au, Pt, Ru, Cu and Ni) were investigated (Supplementary Table 6), finding that the Au-Pd nanoparticle catalysts were effective for the selective synthesis of 3a in the presence of NB (Table 1, entry 8 and Supplementary Table 6, entry 2). The choice of hydrogen acceptors was also important; only NB afforded 3a in the presence of the Au-Pd nanoparticle catalyst (Table 1, entries 5-8 and Supplementary Table 7). A screening of supports for the Au-Pd nanoparticles revealed that Al₂O₃ was the best support for the present reaction (Supplementary Table 8, see Supplementary Information for details). Then, the catalytic activities of Au_{x-} $Pd_{y}/Al_{2}O_{3}$ with different Au/Pd ratios (x/y = 77/23, 71/29, 59/41 and 45/55) were examined (Table 1, entries 9– 12), revealing that high Au/Pd ratios were necessary for the efficient production of 3a. When using the monometallic Pd or Au catalyst, 2a was hardly converted and no 3a was produced (Table 1, entries 13 and 14). Meanwhile, the physical mixture of Pd/Al_2O_3 and Au/Al_2O_3 produced **3a**, albeit in low yield (Table 1, entry 15), probably due to the in situ formation of Au-Pd alloy nanoparticles, as revealed by the STEM-EDS mapping of the physical mixture of Pd/Al₂O₃ and Au/Al₂O₃ after the reaction (Supplementary Fig. 7). Therefore, the specific structure of Au-Pd random alloy nanoparticle catalysts with high Au/Pd ratios is required for the selective synthesis of **3a**, possibly because the co-adsorption of **2a**, the dehydrogenated intermediates and **NB** occurs on the Pd sites surrounded by Au ensembles (details will be discussed later).

A screening of solvents, catalyst amounts, **NB** amounts and temperatures (Supplementary Tables 9– 12) allowed establishing the optimised reaction conditions, under which **3a** was obtained in 70% yield using Au_{71} – Pd₂₉/Al₂O₃ (Table 1, entry 8). The reaction was stopped by removing the Au_{71} –Pd₂₉/Al₂O₃ catalyst during the reaction through hot filtration (Supplementary Fig. 8) and Pd and Au species in the filtrate after the reaction were hardly observed by ICP-AES (Pd: 0.37%, Au: 0.02% of the metal species used for the reaction), indicating that the Au₇₁–Pd₂₉/Al₂O₃ catalytic system was truly heterogeneous. Although the catalyst could be reused, some catalytic activity loss was observed (Supplementary Fig. 9), possibly due to aggregation of Au–Pd nanoparticles and/or adsorption of organic compounds (Supplementary Figs. 10–13).

Substrate scope

Under the optimised reaction conditions using Au₇₁–Pd₂₉/Al₂O₃ with NB, the substrate scope was investigated. Various structurally different azobenzenes (Fig. 4) were selectively synthesised from cyclohexanones 1 and N₂H₄ (see Supplementary Tables 13 and 14 for the product distributions). Cyclohexanone and its derivatives with alkyl substituents at α -/ β -/ γ -positions (Fig. 4a, entries 1–7) as well as cyclohexanones bearing a phenyl substituent (Fig. 4a, entries 8 and 9) were successfully converted to the corresponding azobenzenes. Cyclohexanones possessing alkoxy, amino, amide, ester, nitrile, or trifluoromethyl groups were tolerated, affording the corresponding functionalised azobenzenes (Fig. 4a, entries 10–16). Notably, β -substituted cyclohexanones, which can be synthesised by functionalising 2-cyclohexen-1-one, were also applicable, yielding the corresponding *meta*-substituted azobenzenes (Fig. 4a, entries 4, 6, 7, 9 and 16). Furthermore, a multi-substituted cyclohexanone, which can be easily synthesised via a Diels–Alder reaction, was converted into the corresponding azobenzene, albeit in low yield (Fig. 4a, entry 17). Moreover, 3-methyl-2-cyclohexen-1-one could be applied to the present reaction system (Fig. 4a, entry 18).

The one-pot synthesis of unsymmetrical azobenzenes via unsymmetrical azine formation was also investigated (Fig. 4b). The stability of the azine intermediates allowed synthesising selectively various unsymmetrical azobenzenes. Unsymmetrical azobenzenes with different substituents on the two aromatic rings were synthesised regardless of the order of substrates (Fig. 4b, entries 1, 2, 5 and 6). Unsymmetrical *meta-/para-* and *meta-/meta-*substituted azobenzenes were also prepared (Fig. 4b, entries 3 and 4). Substrates with different functional groups were applicable, giving the corresponding unsymmetrical azobenzene (Fig. 4b, entry 7). In addition, 4-dimethylaminoazobenzene, an azo dye known as butter yellow,^{1–3} was successfully synthesised (Fig. 4b, entry 8).



Fig. 4: Substrate scope. a, Symmetrical azobenzenes.^{*a*} ^{*a*}Conditions: First step, **1** (0.5 mmol), N₂H₄·H₂O (0.25 mmol), DMA (1 mL), 90°C, Ar (1 atm), 3 h. Second step, Au₇₁–Pd₂₉/Al₂O₃ (Pd: 0.5 mol% to **1**), **NB** (1.5 mmol), DMA (2 mL), 130°C, Ar (1 atm), 20 h. GC yields are shown. Isolated yields are shown in parentheses. ^{*b*}4-Nitrotoluene (1.5 mmol). ^{*c*}24 h for the first step. ^{*d*}Pd: 1.5 mol%. ^{*e*}NB (3.0 mmol). ^{*f*}NMR yield. ^{*g*}DMA (0.5 mL) for the first step. **b**, Unsymmetrical azobenzenes.^{*a*} ^{*a*}Conditions: First step, **1x** (0.25 mmol), N₂H₄·H₂O (0.25 mmol), DMA (0.5 mL), r.t., Ar (1 atm), 0.5 h. Second step, 4A-MS (50 mg), DMA (0.5 mL), r.t., Ar (1 atm), 0.5 h. Third step, after 4A-MS was filtered off and washed with DMA (0.5 mL), **1y** (0.25 mmol), DMA (1 mL), r.t., Ar (1 atm), 24 h. Fourth step, Au₇₁–Pd₂₉/Al₂O₃ (Pd: 3.0 mol% to **1x**), **NB** (1.5 mmol), DMA (2 mL), 130°C, Ar (1 atm), 20 h. GC yields are shown based on **1x**. Isolated yields are shown in parentheses. ^{*b*}48 h for the third step. ^{*c*}72 h for the third step. ^{*d*}NB (3.0 mmol).

Mechanistic studies

To study the effect of the Au–Pd alloy on the adsorption control, the time courses of the hydrogenation reactions of azine intermediate **2b** formed by the condensation between 4-methylcyclohexanone (**1b**) and N₂H₄·H₂O in the presence or absence of **NB** and the hydrogenation of **NB** without **2b** were determined under a H₂ atmosphere using Pd/Al₂O₃ or Au₇₁–Pd₂₉/Al₂O₃ (Fig. 5a,b and Supplementary Table 15). The hydrogenation of **NB** smoothly occurred using either of the catalysts to produce aniline selectively regardless of the presence or absence of **2b** (Fig. 5a,b). In the absence of **NB**, both catalysts promoted the hydrogenation of **2b**, indicating that **2b** was adsorbed on the catalysts (Fig. 5a,b and Supplementary Table 15, entries 1 and 3); however, in the presence of **NB**, the reaction rates of **2b** varied considerably (Fig. 5a,b and Supplementary Table 15, entries 2 and 4). In the case of Pd/Al₂O₃, the hydrogenation of **2b** did not proceed at all with **NB** but occurred after almost all **NB** was hydrogenated (Fig. 5a), suggesting that azines could not access the Pd nanoparticles owing to the preferential adsorption of **NB**. Conversely, when using Au₇₁–Pd₂₉/Al₂O₃, **NB** inhibited but did not cease the hydrogenation of **2b** (Fig. 5b), indicating that both **2b** and **NB** were simultaneously adsorbed on the Au₇₁–Pd₂₉/Al₂O₃ catalyst.

To elucidate the origin of the adsorption property change, DFT calculations were performed for the adsorption of **NB** and cyclohexanone (**1c**)-derived azine intermediate **2c** on Pd₂₀ and Au₁₈Pd₂ cluster models (Fig. 5c,d) using Gaussian 16 (M06 functional with SDD basis sets for Au and Pd and 6-31G(d,p) basis sets for C, H, N and O) according to previous reports⁴⁶⁻⁴⁸ (see Supplementary Information for details on the calculation methods, model selection and adsorption site selection; Supplementary Figs. 14–16). On the Pd₂₀ cluster model, the adsorption of **NB** ($\Delta G = -45.5$ kcal/mol) was substantially stronger than that of **2c** ($\Delta G = -21.1$ kcal/mol) due to multiple π -adsorption of the aromatic rings on the Pd atoms (Fig. 5c). Conversely, on the Au₁₈Pd₂ cluster model, where Pd atoms are isolated by Au atoms, the adsorption of **NB** ($\Delta G = -10.0$ kcal/mol) was weakened compared with that on the Pd₂₀ model (Fig. 5c,d) because multiple π -adsorption of the aromatic rings for **NB** ($\Delta G = -10.0$ kcal/mol) was weakened compared with that on the Pd₂₀ model (Fig. 5c,d) because multiple π -adsorption energies were obtained for **NB** and **2c** ($\Delta G = -10.1$ kcal/mol) (Fig. 5d), which is consistent with the experimental results indicating that the Au–Pd alloy with high Au/Pd ratios facilitated the co-adsorption of **NB** and azines.

To determine the reaction pathway of the present azobenzene synthesis, the time course of the reaction from **2b** to **3b** under the optimised conditions using Au_{71} –Pd₂₉/Al₂O₃ was investigated (Fig. 5e). During the reaction of **2b**, mono-, di- and tri-dehydrogenated products **7b**, **8b** and **9b** (Fig. 5f) were observed as intermediates before the formation of substantial amounts of **3b** and **4b**. Although the corresponding 1,2-diarylhydrazine **6b** was not detected during the reaction, treatment of 1,2-diphenylhydrazine (**6c**) under the optimised conditions afforded azobenzene (**3c**) selectively within 10 min (Fig. 5g). Thus, 1,2-diarylhydrazines are probably the intermediates, which cannot be detected because of the excessively fast NH–NH dehydrogenation. We previously reported that some dehydrogenative aromatisation reactions efficiently proceeded via fast disproportionation of dehydrogenated intermediates on nanoparticles;^{36,37,39,49} however, in the present system, all mono-, di- and tri-dehydrogenated intermediates were observed, and the reaction starting from azine **8d'** possessing α , β -unsaturated structures derived from 3-methyl-2-cyclohexen-1-one (**1r**) afforded the corresponding dehydrogenated intermediate **9d** and azobenzene **3d** but no hydrogenated azines (Fig. 5h and Supplementary Fig. 17), suggesting that this dehydrogenative aromatisation proceeds via successive dehydrogenation instead of disproportionation. Moreover, the amount of intermediates **7b**, **8b** and **9b** decreased as the reaction proceeded, whereas that of **4b** did not decrease (Fig. 5e) and azobenzenes derived from **NB** were not detected at all, indicating that oxidative/reductive couplings of **NB** or anilines did not occur and azobenzenes and anilines were formed via irreversible dehydrogenation/hydrogenation of 1,2-diarylhydrazine intermediates derived from dehydrogenative aromatisation of azines (Fig. 5f).

Finally, the fast NH-NH dehydrogenation of 1,2-diarylhydrazine intermediates was investigated in detail using various catalysts and hydrogen acceptors for the reaction from 1,2-diphenylhydrazine (6c) (Table 2). Although the disproportionation of 6c to azobenzene (3c) and aniline (4c) proceeded using Pd/Al₂O₃ regardless of the presence or absence of 4-nitrotoluene (Table 2, entries 1 and 2), using 4-nitrotoluene with Au₇₁–Pd₂₉/Al₂O₃ inhibited the disproportionation, affording 3c selectively (Table 2, entries 3 and 4). Indeed, DFT calculations for the adsorption of **6c** on the Pd₂₀ cluster model indicated that **6c** is more strongly adsorbed than **NB** ($\Delta G = -50.2$ vs -45.5 kcal/mol) (Fig. 5c,i), which is consistent with the results using Pd/Al₂O₃. However, the adsorption of 6c at the Pd sites on the Au₁₈Pd₂ cluster model ($\Delta G = -20.6$ kcal/mol) is also stronger than that of NB ($\Delta G = -10.0$ kcal/mol) (Fig. 5d,j), which is inconsistent with the results using Au₇₁–Pd₂₉/Al₂O₃ if Pd sites were assumed to be the active species for the dehydrogenation/hydrogenation of 6c. In fact, as in the case of Au₇₁-Pd₂₉/Al₂O₃, Au/Al₂O₃ with 4-nitrotoluene selectively afforded 3c from 6c within 10 min (Fig. 5g, Table 2, entries 4 and 6), whereas Au/Al₂O₃ without 4-nitrotoluene and Al₂O₃ with/without 4-nitrotoluene did not catalyse the selective dehydrogenation of 6c to 3c (Table 2, entries 5, 7 and 8), indicating that Au species, rather than Pd species, catalysed the fast NH-NH dehydrogenation of 1,2-diarylhydrazines using nitroarene hydrogen acceptors. In contrast, in the case of the hydrogenation of nitrobenzene using H₂, Au₇₁–Pd₂₉/Al₂O₃ showed almost the same catalytic activity as Pd/Al₂O₃ based on the Pd amount despite the presence of additional Au sites (Fig. 5a,b), suggesting that nitrobenzene on Au nanoparticles cannot accept hydrogen species via formation of Au-H species

from Pd–H species derived from H₂ cleavage on the Pd sites. Thus, the fast NH–NH dehydrogenation of 1,2diarylhydrazines with nitroarenes most likely proceeds via their co-adsorption on Au ensembles, which is supported by the DFT calculation results (Fig. 5k), and a following concerted two-electron/two-proton transfer from 1,2-diarylhydrazines to nitroarenes as previously proposed for some dehydrogenation reactions on metal nanoparticle catalysts.^{49,50} Furthermore, among the examined hydrogen acceptors, only nitroarenes were effective for the selective NH–NH dehydrogenation to **3c** (Table 2, entries 4, 6 and 9–14, Supplementary Tables 16 and 17), which supported the concerted mechanism. Regarding the dehydrogenative aromatisation from azines, as mentioned above, successive dehydrogenation occurred on the Pd sites to form Pd–H species, which could not react with nitroarenes on the Au sites. Therefore, the co-adsorption of azines and nitroarenes on the Pd sites is indispensable for the desired dehydrogenation to occur along with hydrogenation inhibition.

In summary, the following reaction mechanism can be proposed for the present azobenzene synthesis (Fig. 6). Azine and nitrobenzene molecules are adsorbed together on the Pd sites, where the azine is deprotonated/metalated probably with the assistance of the basic sites of Al₂O₃. Then, β-hydride elimination occurs to produce the dehydrogenated azine intermediate and Pd–H species. The nitrobenzene co-adsorbed on the Pd sites accepts the hydrogen species to form nitrosobenzene, which is probably quickly hydrogenated to aniline because no nitrosobenzene-derived compounds other than aniline, including azoxybenzene and azobenzene,⁵¹ were observed. Likewise, successive dehydrogenation occurs on the Pd sites via Pd–H species formation to produce a 1,2-diarylhydrazine intermediate. Finally, the concerted two-electron/two-proton transfer from the 1,2-diarylhydrazine on the Pd or Au sites towards nitrobenzene on the Au sites proceeded very fast, affording the desired azobenzene selectively. The unique catalysis control of Au–Pd alloy nanoparticles with high Au/Pd ratio enabled this unprecedented azobenzene synthesis; specifically, i) the ensemble effect enabled the co-adsorption of the nitrobenzene hydrogen acceptor and intermediates on the Pd sites, thereby inhibiting the undesired hydrogenation, and ii) the relay catalysis of Pd sites for the successive dehydrogenation leading to aromatisation and Au sites for the fast concerted NH–NH dehydrogenation afforded the azobenzenes.



Fig. 5: Studies on the Au–Pd alloy effects, reaction pathways and dehydrogenation mechanism. Time courses of independent or competitive hydrogenation of **2b** and/or **NB** using **a**, Pd/Al₂O₃ and **b**, Au₇₁–Pd₂₉/Al₂O₃ under the following conditions: **2b** (0.23 mmol) and/or **NB** (1.5 mmol), catalyst (Pd: 1 mol% to **2b**), H₂ (1 atm), DMA (2 mL), 100°C. DFT calculation results on the optimised structures of **NB** or **2c** adsorbed on **c**, Pd₂₀ and **d**, Au₁₈Pd₂. **e**, Time course of the synthesis of **3b** from **2b** under the conditions of Table 1, entry 8. **f**, Proposed reaction pathway from azines to azobenzenes. **g**, Synthesis of **3c** from **6c** under the conditions indicated in the figure. **h**, Synthesis of **3d** from **8d'** under the conditions indicated in the figure. DFT calculation results on the optimised structures of **NB** adsorbed on Au₂₀.



Fig. 6: Proposed mechanism of the present azobenzene synthesis from azines using Au₇₁-Pd₂₉/Al₂O₃ and nitrobenzene.

Conclusion

A selective synthesis of azobenzenes from cyclohexanones and hydrazine was developed for the first time using a heterogeneous Au₇₇–Pd₂₃/Al₂O₃ alloy catalyst and nitrobenzene. Structurally diverse azobenzenes, including unsymmetrical ones, were successfully synthesised from different non-aromatic cyclohexanone substrates, which will overcome the drawbacks of the well-established azobenzene synthesis from aromatic compounds. Catalyst effect investigation using Au–Pd random alloy nanoparticle catalysts with similar nanoparticle distributions and different Au/Pd ratios, which were confirmed to be successfully prepared by thorough spectroscopic characterisation, indicated the importance of Au-diluted Pd ensembles for the present azobenzene synthesis. Various control experiments combined with DFT calculations revealed that the Au-diluted Pd alloy nanoparticle structure enables i) the co-adsorption of the nitrobenzene hydrogen acceptor and intermediates on Pd sites for the dehydrogenative aromatisation while inhibiting the undesired hydrogenation and ii) the fast NH–NH dehydrogenation via a concerted two-electron/two-proton transfer on Au sites to afford azobenzenes. Our findings will promote the development of novel selective organic transformations based on unique heterogeneous catalytic systems relying on catalysis control/integration by alloying.

Methods

Preparation of supported metal catalysts

An Al₂O₃-supported Au–Pd nanoparticle catalyst (Au₇₁–Pd₂₉/Al₂O₃) with an Au/Pd molar ratio of 71/29 was prepared via deposition precipitation as follows. First, Al₂O₃ (2.0 g) was added to a 60 mL aqueous solution of HAuCl₄·4H₂O (154.4 mg, 6.25 mM) and K₂PdCl₄ (2.08 mM, which was generated in situ from a mixture of PdCl₂ (22.2 mg, 0.125 mmol) and KCl (18.6 mg, 0.250 mmol)). After stirring vigorously for 15 min at room temperature, 1 M NaOH aq. was added dropwise to adjust the pH of the solution to 10.0. The resulting slurry was further stirred at room temperature for 24 h. The solid was then filtered off, washed with water (2 L) and dried in vacuo to afford an Au-Pd hydroxide precursor. The hydroxide precursor was then dispersed in 50 mL water and treated by NaBH₄ (70 mg). The resulting slurry was further stirred vigorously at room temperature for 2 h. The solid was again filtered off, washed with water (2 L) and dried in vacuo overnight to afford the Au₇₁-Pd₂₉/Al₂O₃ catalyst (brown powder, Au content: 2.62 wt%, Pd content: 0.58 wt%). Other Al₂O₃-supported Au-Pd nanoparticle catalysts (Au_x-Pd_y/Al₂O₃) with a Au/Pd molar ratio of x/y (x/y = 77/23, 59/41, 45/55 or 0) were prepared by the method similar to Au₇₁-Pd₂₉/Al₂O₃ while adjusting the concentration of HAuCl₄·4H₂O to 6.67 mM, 5.56 mM, 4.17 mM or 0 mM; K₂PdCl₄ to 1.67 mM, 2.78 mM, 4.17 mM or 8.33 mM, respectively, to afford the Au₇₇-Pd₂₃/Al₂O₃ (brown powder, Au content: 2.75 wt%, Pd content: 0.44 wt%), Au₅₉-Pd₄₁/Al₂O₃ (brown powder, Au content: 2.07 wt%, Pd content: 0.79 wt%), Au₄₅-Pd₅₅/Al₂O₃ (brown powder, Au content: 1.80 wt%, Pd content: 1.18 wt%) and Pd/Al₂O₃ (gray powder, Pd content: 2.37 wt%) catalysts. The supported Au and Pd contents were determined by ICP-AES analysis.

Catalytic reaction

The catalytic reactions for the synthesis of symmetrical azobenzenes were typically carried out as follows. In a glovebox filled with an Ar gas, *n*-hexadecane (internal standard, 0.1 mmol), cyclohexanones (1, 0.5 mmol), *N*,*N*-dimethylacetamide (DMA, 1 mL), hydrazine monohydrate (N_2H_4 · H_2O , 0.25 mmol), and a Teflon-coated magnetic stir bar were successively added into a 20 mL Pyrex glass reactor. Then, the solution was vigorously stirred at 90 °C for 3 h. Next, after the solution was cooled down, in a glovebox filled with an Ar gas, nitrobenzene (1.5 mmol), Au_{71} – Pd_{29}/Al_2O_3 (Pd: 0.5 mol% with respect to 1), and additional DMA (1 mL, with a total of 2 mL) were added into the reactor. Then, the reaction mixture was vigorously stirred at 130 °C. After the reaction was completed, the reaction mixture was diluted by chloroform, and the catalyst was removed by simple filtration. The yields of products were determined by GC analysis using *n*-hexadecane as the internal standard.

When the products were difficult to be detected by GC due to their high boiling points, NMR analyses were conducted using 1,3,5-trimethoxybenzene as the internal standard (in the case of 3q after the following column chromatography). As for the isolation of the desired azobenzene products, the solution was evaporated to remove solvents. The crude products were subjected to column chromatography on silica gel (typically using *n*-hexane/chloroform as an eluent), giving the pure products. The products were identified by GC-MS and NMR (¹H, ¹³C, and ¹⁹F) analyses.

The catalytic reactions for the synthesis of unsymmetrical azobenzenes were typically carried out as follows. In a glovebox filled with an Ar gas, *n*-hexadecane (internal standard, 0.1 mmol), cyclohexanones (**1x**, 0.25 mmol), *N*,*N*-dimethylacetamide (DMA, 0.5 mL), hydrazine monohydrate (N₂H₄·H₂O, 0.25 mmol), and a Teflon-coated magnetic stir bar were successively added into a 6 mL vial. The solution was vigorously stirred at room temperature for 0.5 h. Then, 4A-MS (50 mg) was added into the vial. After reaction mixture was vigorously stirred at room temperature again for 0.5 h, the 4A-MS was filtered off and washed with DMA (0.5 mL). The filtrate was injected into a 20 mL Pyrex glass reactor containing another cyclohexanones (**1y**, 0.25 mmol) and a Teflon-coated magnetic stir bar, and the solution was vigorously stirred at room temperature for 2.4 h. Next, nitrobenzene (1.5 mmol), Au₇₁–Pd₂₉/Al₂O₃ (Pd: 3.0 mol% with respect to **1x**), and additional DMA (1 mL, with a total of 2 mL) were added into the reactor. Then, the reaction mixture was vigorously stirred at 130 °C. After the reaction was completed, the reaction mixture was diluted by chloroform and the catalyst was removed by simple filtration. The yields of products were determined by GC analysis. As for the isolation of the desired azobenzene products, the solution was evaporated to remove solvents. The crude products were subjected to column chromatography on silica gel (typically using *n*-hexane/chloroform as an eluent), giving the pure products. The products were identified by GC-MS and NMR (¹H and ¹³C) analyses.

Data availability

The data generated in this study are provided within the article and its Supplementary Information file. Correspondence and requests for materials should be addressed to K. Y. and T. Yatabe.

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Acknowledgements

This work was financially supported by JSPS KAKENHI Grant No. 21K14460, 22H04971, 24K17556, 24H01062 (Transformative Research Areas (A) JP21A204), and 24H02210 (Transformative Research Areas (A) JP24A202). This work was supported by JST, PRESTO Grant Number JPMJPR227A, Japan. This work is also based on results obtained from a JPNP20004 project subsidized by the New Energy and Industrial Technology Development Organization (NEDO). We appreciate Dr. Hironori Ofuchi (Japan Synchrotron Radiation Research Institute, SPring-8) for giving great support for XAFS measurements in BL14B2 (proposal no. 2023A1512). A part of this work was conducted at the Advanced Characterization Nanotechnology Platform of the University of Tokyo, supported by "Nanotechnology Platform" of the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan. We thank Ms. Mari Morita (The University of Tokyo) for her assistance with the HAADF-STEM and EDS analyses. The computation was performed using Research Center for Computational Science, Okazaki, Japan (Project: 23-IMS-C002). We also thank Prof. Toru Wakihara and Dr. Masanori Takemoto for the use of Rigaku SmartLab to measure XRD. We thank Mr. Haruumi Sakai for his help of TEM analyses.

Author contributions

T. Yatabe and K. Y. conceived and supervised the project. W.-C. L. performed most of the experiments and DFT calculations. T. Yabe performed the XAFS measurements and analysis. All authors contributed to data analysis and discussed the results. W.-C. L. and T. Yatabe wrote the manuscript with feedback from K. Y. and T. Yabe.

Competing interests

The authors declare no competing financial interests.

Tables

N ₂ H ₄ ·H ₂ O + <i>t</i> -E (0.25 mmol)	0.5 mmol) 0.5 mmol)	t-Bu catalyst (Pd: 0.5 mol acceptor (1.5 mmol DMA (2 mL) 130 °C, 20 h Ar (1 atm)	^{1%)})→ t-Bu	N _N t-Bu 3a 4	u NH ₂ t-Bu la	5a
Entre		Hydrogen acceptor	Yield (%)			
Entry	Catalyst		2a	3a	4 a	5a
1	Pd/Al ₂ O ₃	none	<1	<1	31	49
2	Pd/Al ₂ O ₃	cyclooctene	3	<1	48	2
3	Pd/Al ₂ O ₃	styrene	83	<1	<1	<1
4	Pd/Al ₂ O ₃	nitrobenzene	58	<1	2	<1
5	$Au_{71} - Pd_{29}/Al_2O_3$	none	<1	<1	19	53
6	$Au_{71} - Pd_{29} / Al_2O_3$	cyclooctene	17	<1	26	7
7	Au ₇₁ -Pd ₂₉ /Al ₂ O ₃	styrene	3	<1	39	<1
8	$Au_{71} - Pd_{29} / Al_2O_3$	nitrobenzene	<1	70	9	<1
9^b	Au ₇₇ -Pd ₂₃ /Al ₂ O ₃	nitrobenzene	<1	44	5	<1
10^{b}	Au ₇₁ -Pd ₂₉ /Al ₂ O ₃	nitrobenzene	<1	65	6	<1
11^{b}	$Au_{59}\!-\!Pd_{41}/Al_2O_3$	nitrobenzene	2	29	5	<1
12^{b}	Au45-Pd55/Al2O3	nitrobenzene	44	2	1	<1
13 ^b	Pd/Al ₂ O ₃	nitrobenzene	85	<1	<1	<1
$14^{b,c}$	Au/Al ₂ O ₃	nitrobenzene	82	<1	<1	<1
15 ^{<i>b,c</i>}	$Au/Al_2O_3 + Pd/Al_2O_3$	nitrobenzene	9	8	2	<1

Table 1: Catalyst effects on the dehydrogenative aromatisation to azobenzene 3a.^a

^{*a*}Conditions: First step, **1a** (0.5 mmol), N₂H₄·H₂O (0.25 mmol), DMA (1 mL), 90°C, Ar (1 atm), 3 h. Second step, catalyst (Pd: 0.5 mol% to **1a**), hydrogen acceptor (0 or 1.5 mmol), DMA (2 mL), 130°C, Ar (1 atm), 20 h. GC yields are shown based on **1a**. ^{*b*}Second step, 3 h. ^{*c*}Au amount was consistent with that of Au₇₁–Pd₂₉/Al₂O₃ (Au: 1.2 mol% to **1a**).

DMA (2 mL) 130 °C, 3 h 6c Ar (1 atm) 3c 4c	NHa
6c Ar (1 atm) 3c 4c	
(0.25 mmol)	

Table 2: Catalyst effects on the reaction of 1,2-diphenylhydrazine (6c).^{*a*}

Enter	Catalyst	Hudrogen accenter	Yield (%)		
Linuy		Hydrogen acceptor	3c	4c	
1	Pd/Al ₂ O ₃	none	46	43	
2	Pd/Al ₂ O ₃	4-nitrotoluene	56	37	
3	$Au_{71} - Pd_{29}/Al_2O_3$	none	46	50	
4^b	$Au_{71} - Pd_{29}/Al_2O_3$	4-nitrotoluene	92	8	
5 ^c	Au/Al ₂ O ₃	none	47	50	
6 ^{<i>b,c</i>}	Au/Al ₂ O ₃	4-nitrotoluene	97	3	
7^d	Al ₂ O ₃	none	3	<1	
8^d	Al ₂ O ₃	4-nitrotoluene	13	<1	
9	Au ₇₁ -Pd ₂₉ /Al ₂ O ₃	2,2,2-trifluoroacetophenone	52	46	
10	Au ₇₁ -Pd ₂₉ /Al ₂ O ₃	styrene	44	49	
11	Au ₇₁ -Pd ₂₉ /Al ₂ O ₃	ethynylbenzene	56	36	
12 ^c	Au/Al ₂ O ₃	2,2,2-trifluoroacetophenone	53	47	
13 ^c	Au/Al ₂ O ₃	styrene	44	51	
14 ^c	Au/Al ₂ O ₃	ethynylbenzene	41	28	

^{*a*}Conditions: **6c** (0.25 mmol), catalyst (Pd: 1 mol%), hydrogen acceptor (0 or 1.5 mmol), DMA (2 mL), 130°C, Ar (1 atm), 3 h. GC yields are shown based on **6c**. ^{*b*}10 min. ^{*c*}Au: 2.5 mol%. ^{*d*}Al₂O₃ (44 mg). NMR yields are shown.