Au$_{25}$ Clusters as Electron-Transfer Catalysts Induced the Intramolecular Cascade Reaction of 2-nitrobenzonitrile

Hanbao Chong$^1$, Peng Li$^1$, Shuxin Wang$^1$, Fangyu Fu$^1$, Ji Xiang$^1$, Manzhou Zhu$^1$ & Yadong Li$^2$

$^1$College of Chemistry and Chemical Engineering Anhui University, Hefei, 230601 (P. R. China), $^2$Department of Chemistry Tsinghua University, Beijing, 100084 (P. R. China).

Design of atomically precise metal nanocluster catalysts is of great importance in understanding the essence of the catalytic reactions at the atomic level. Here, for the first time, Au$_{25}$ nanoclusters were employed as electron transfer catalysts to induce an intramolecular cascade reaction at ambient conditions and gave rise to high conversion (87%) and selectivity (96%). Electron spin-resonance spectra indeed confirmed the consecutive electron transfer process and the formation of N radical. UV-vis absorption spectra also verified Au$_{25}$ was intact after the catalytic circle. Our research may open up wide opportunities for extensive organic reactions catalyzed by Au$_{25}$.

Atomically precise Au nanoclusters (NCs) serving as effective catalysts have been widely explored for a variety of organic reactions, such as the oxidation, hydrogenation, C-C coupling reactions and even C-H activation. Among them, as homogeneous or heterogeneous catalysts, Au$_{25}$ NCs have attracted particular attention due to their precise number of atoms and stable structure, which is important to understand the catalytic mechanism at the atomic and molecular level. To our knowledge, there are three stable charge states for Au$_{25}$ NCs. It is notable that the charge states have been further confirmed by the corresponding single-crystal structures. Besides, the three different states are reciprocally transformed by oxidation and reduction. Our previous results also indicated the single electron of Au$_{25}$ was capable to be transferred to organic molecule. Notably, Au$_{25}$ NCs employed as ET mediators, which provide electrons or deliver electrons, may offer novel insights into the mechanism of Au-catalyzed chemical reactions and the correlation between structure and catalytic property. The electron transfer (ET) reactions of the Au$_{25}$ NCs have been discussed by nuclear magnetic resonance, electrochemistry and thermochemical calculations. However, to date, there are no reports of Au$_{25}$ NCs functioning as ET catalysts in solution-phase organic reactions. Herein, we first demonstrate the ET catalysis of Au$_{25}$ in intramolecular cascade reaction of 2-nitrobenzonitrile, from which 2-amino-1-benzamide (a precursor of significant pharmaceuticals) is produced with high yield.

Results
The synthesis protocol of Au$_{25}$(SR)$_{18}$TOA$^+$ (abbreviation as Au$_{25}$+, SR = SCH$_2$CH$_2$Ph) was referred to the previous literature. The ultraviolet-visible (UV-vis) spectrum of the obtained NCs is shown in Supplementary Fig. S1. The composition of the as-prepared NCs is further verified by matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF-MS, see Supplementary Fig. S2). In this work, the intramolecular cascade reaction of 2-nitrobenzonitrile (abbreviated as 1a) for 2-amino-1-benzamide (2a) was investigated using Au$_{25}$ as ET catalysts (See Fig. 1).

Cyclic voltammograms of 1a and Au$_{25}$ in 0.1 M Bu$_4$NClO$_4$/CH$_2$Cl$_2$ solution are shown in Fig. 2 and Supplementary Table S1. It is obvious that half-wave potential of 1a is positive than that of Au$_{25}$, suggesting 1a is capable to grab the electron from Au$_{25}$. In the ET mediated system, Au$_{25}$ is susceptible to the substrate (1a) and easily oxidized into Au$_{25}$$. Meanwhile, N free radicals can be formed after 1a getting electrons from Au$_{25}$ clusters, proceeding with an intramolecular cascade reaction. Additionally, while treated with NaBH$_4$, Au$_{25}$ could be reduced back to Au$_{25}$, indicating Au$_{25}$ functioned as an electron bridge and excess NaBH$_4$ provided continual electron source. The electron transfer reactions are presented as follows (Fig. 3), which are indeed established by our investigation.
To achieve the essential understanding, UV-vis and electron spin-resonance (ESR) spectra were initially employed to investigate the electron transfer process. The distinguished UV-vis absorption characters of $\text{Au}_{25}^-$ ($z = -1, 0$) can indeed serve as spectroscopic fingerprints and be capable for ready determination of the negative and neutral states. When increased amounts of $1\alpha$ were added to $\text{Au}_{25}^-$ in tetrahydrofuran, the UV-vis spectra showed obvious changes, in contrast to pure $\text{Au}_{25}^-$. As shown in Fig. 4a, the shoulder peak at 800 nm, the fine spectral peak of $\text{Au}_{25}^-$, successively declined and eventually disappeared. Simultaneously, a new shoulder dominated at ~620 nm emerged and gradually enhanced, indicating the progressive formation of $\text{Au}_{25}^0$ from $\text{Au}_{25}^-$. On the other hand, after excess addition of sodium borohydride, the 800 nm absorption shoulder arose again (Fig. 4b), suggesting the recovery of $\text{Au}_{25}^-$. The above spectroscopic evidence confirmed that $\text{Au}_{25}^-$ was an electron mediator and it kept delivering electrons from NaBH$_4$ to substrate. After a circle, a molecule of $1\alpha$ gained an electron from $\text{Au}_{25}^-$ to form a radical anion and further converted into 2-aminoazobenzamide. More significantly, we achieved ESR data to further confirm the occurrence of the initial ET process. Pure $\text{Au}_{25}^-$ shows no signal while the mixture of $\text{Au}_{25}^-$ and $1\alpha$ displays a triplet peaks, suggesting the formation of N radical (Fig. 4c). In addition, more complicated radical was formed with the addition of NaBH$_4$ (Supplementary Fig. S3), indicating the N radical proceeded with further reaction.

To get a deep insight into the catalytic reaction, a range of control experiments were carried out, the conversion was determined by GC. The catalytic reduction was operated in THF at 20 °C for 2 h. $\text{Au}_{25}^-$ could achieve high conversion (87%) and selectivity (96%) (Entry 10, table 1), which was considered as highly efficient at ambient condition. For comparison, a range of functionalities like nitro, amino, nitrile groups were introduced to assess the electronic effects. Comparing with $1\alpha$, solo-functionalized nitrobenzene was reduced to azoxybenzene in relatively low yield in the presence of $\text{Au}_{25}^-$ (Entry 1, table 1). It is worth mentioning that no reductive or additive product of cyanobenzene was detected even through the prolonged reaction time, neither did the substituted cyanobenzene with an electron-donating group or an electron-withdrawing group.

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Similar theories were previously reported by Baker’s yeast catalysis to form a five-member heteroring (the nitrile group at ortho position was reduced, they were supposed to follow one of the three paths. Given the whole reaction route (see Supplementary Fig. S7): (1) 2-aminobenzonitrile (4a; Supplementary Fig. S7) acted as intermediate; (2) a five-member ring intermediate was formed; (3) nitrile group was reduced at the beginning (5a; Supplementary Fig. S7). The transforming process was supposed to follow one of the three paths. Given the whole reaction was conducted in strong reducing environment (excessive NaBH4 present), oxidative addition to form carbonyl bond from 4a to 2a, or from 1a to 5a was clearly impossible, which meant both path 1 and 3 were implausible. Hence, path 2 was considered to be the plausible route. The two-step reaction proceeded as an intramolecular cascade reaction. As nitro group was sensitive to the catalyst, after the nitrile group at ortho position was reduced, they were supposed to form a five-member heteroring (3a; Supplementary Fig. S7). Similar theories were previously reported by Baker’s yeast catalysis and transition metal catalysis.

As showed in Fig. 5, the possible reaction mechanism was speculated to disclose the process. The single electron was first transferred from Au25* to 1a with the formation of N radical. Importantly, this electron transfer step and the formation of N radical were supported by ESR spectra. Then, the radical could be readily transformed into the intermediate of 2-(hydroxyamino) benzonitrile. Before the final product (2a) was eventually formed, a five-member heterocyclic intermediate emerged to grab another electron from Au25. Meanwhile, one molecule of water was generated after a circle which could be involved in the intramolecular cascade reaction. Notably, solo-functionalized and para-substituted substrates were not capable to attain the active intermediate five-member ring. When reacted with NaBH4, Au25* could be reduced to Au25, suggesting Au25 served as the ET mediator and NaBH4 provided consequent electron source. UV-vis spectra also confirmed the circle of catalytic species. After the reaction reached a chemical equilibrium, the mixture was centrifugated to test the supernate for UV-vis spectrum and MALDI-TOF-MS. Typical absorption bands centered at 670 nm and 450 nm were observed (See Supplementary Fig. S8). Besides, molecular ion peak of 7391 (See Supplementary Fig. S9) further verified that the Au25 remained after catalyzing the intramolecular cascade reaction, which was consistent with our hypothesis.

### Discussion

In summary, we have demonstrated an intramolecular cascade reaction catalyzed by Au25* which served as electron mediators. It was worth noting that this reaction achieved high conversion (87%) and selectivity (96%) with Au25* NCs as ET catalysts at ambient conditions. Furthermore, the catalytic mechanism was systematically investigated. Au25* shifted between Au25 and Au25* in order to ensure the intermolecular electron flow. Excess NaBH4 provided hydrogen source and kept Au25 at negative state. More importantly, the catalytic species Au25* was proved to be still existed after the reaction finished, which meant it could be recycled and recycled. It is believed that our research may open up wide opportunities for ET catalysis of Au25 in extensive organic reactions.

### Methods

**General experimental detail.** All the chemicals and reagents are commercially available. TLC plates (Merck Silica Gel 60 F254) were used for analytical TLC and Merck Kieselgel 200–300 was used for preparative column chromatography. 1H NMR spectra were acquired on a Brucker AM 400 operating at 400 MHz. 13C NMR spectra were acquired on a Brucker AM 400 operating at 100 MHz. Conversion and selectivity was measured with Shimadzu GC 2010 plus. UV tests were conducted with a Hewlett-Packard (HP) 8453 diode array spectrophotometer. TEM images were obtained by JEM 2100. Room temperature electron spin resonance (ESR) was conducted on JEOL JES-FA200 EPR spectrometer (300 K, 9048 MHz, X-band). Cyclic voltametric measurements (CV) were performed on an electrochemical workstation (CHI 660D) at a scan rate of 0.05 V·s⁻¹ under ambient conditions.
Preparation of \( \text{Au}_{25}(\text{SCH}_2\text{CH}_2\text{Ph})_{18} \). Briefly, \( \text{HAuCl}_4 \cdot 3\text{H}_2\text{O} \) dissolved in deionized water along with \( \text{TOAB} \) dissolved in toluene, were combined in a 25 mL tri-neck round bottom flask. After stirring for ~15 min, the aqueous phase was excluded by syringe. The toluene solution was protected with \( \text{N}_2 \) and cooled down in an ice bath. Hereafter, \( \text{PhCH}_2\text{CH}_2\text{SH} \) was added with a very low speed. 1 h later, the stirring speed was adjusted to fast stirring; an aqueous solution of \( \text{NaBH}_4 \) was quickly added all at once. The synthesis proceeded overnight. The final product was purified by precipitation with acetonitrile three times.

Typical procedure of reduction reaction. 0.2 g 2-nitrobenzonitrile (1.35 mmol), 0.102 g \( \text{NaBH}_4 \) (2.7 mmol) and 2 mg catalyst was added into 10 mL of THF in round-bottom flask. The mixture was stirred for 2 h at room temperature before being evaporated to dryness under vacuum. The crude product was dissolved in 8 mL methylene dichloride and washed by 3 mL deionized water. Finally the pure product was obtained by column chromatography.

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Author contributions

H.C. conducted most of the experiments, collected the data, and wrote the paper. S.W., F.F. and J.X. synthesized and characterized the \( \text{Au}_{13}(\text{SR})_{14} \) \( \text{NCs} \), M.Z., P.L. and Y.L. conceived the experiments and wrote the paper. All authors analyzed the data and discussed the results.

Additional information

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