

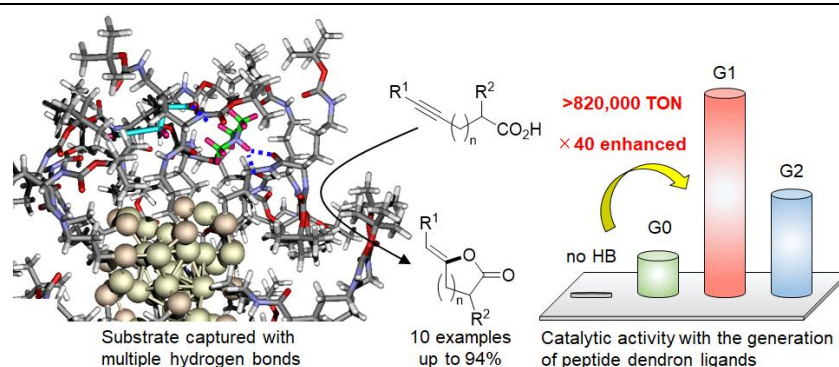
Accelerated Catalysis of Atomically Precise Thiolate-Protected Gold Nanocluster by Supramolecular Ligand Engineering

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ABSTRACT: We herein report the reaction acceleration effect of a supramolecular reaction field constructed of dendritic peptide thiolate ligands on Au₂₅ nanocluster toward catalytic cyclization of alkynoic acids. A remarkable reaction acceleration was achieved by peptide dendron thiolate ligands 40 times greater than simple alkyl thiolate ligands. Association experiments with ¹H NMR spectroscopy revealed that the unprecedented intermolecular hydrogen bonds between peptide dendron ligands and ammonium salts of alkynoic acid act the critical role for the reaction acceleration effect. High stability of the nanocluster catalyst bearing supramolecular reaction field was also represented by the turnover number over 820,000 in this catalytic reaction. Mechanistic investigations revealed the involvement of π -coordinated alkyne and following vinyl-Au intermediates. DFT calculations support the possible reaction pathway including both anionic and neutral form of nanocluster as the catalyst. Our finding demonstrates the usefulness of supramolecular ligand approach for metallic nanocluster catalysis, enabling an enhanced catalytic efficiency and selectivity towards various organic transformations.

Introduction

Ligand-protected gold nanoclusters (AuNCs) have gained considerable attention as a fascinating class of catalysts, because they are expected to show higher catalytic activity than conventional nanoparticle catalysts under the consideration of well-established size effect.¹ Thus, several types of AuNCs have been synthesized to date using various types of organic ligands, such as thiolate, phosphine, alkynyl, carbene, amidinate, and etc.² Although these ligands were conventionally used to control size and shape of AuNCs mainly by the steric effect, it was difficult to achieve both stability and reactivity of AuNC catalysts. To solve this issue the installation of functional moiety to organic ligands was focused to pave the way for accelerating the catalytic activity or improving the reaction selectivity with AuNCs. However, only limited approaches have been reported to date for the functionalized ligand-protected AuNC catalysts.^{3–5}

Li and Jin first reported the improvement of cross-coupling selectivity in Au₂₅ nanocluster-catalyzed biaryl coupling through the

intermolecular π - π interaction between 1-naphthylthiolate ligand and aryl iodide substrates (Figure 1a).³ Enantioselective Aldol condensation was achieved by Wang using proline as both protecting ligand for Au-Ag₈ nanocluster and co-acting organocatalyst.⁴ Non-coordinating pyridine moiety was installed by Li to the linker of bisphosphine ligand protecting Au₈ nanocluster, accelerating catalytic Michael addition as base cocatalyst (Figure 1b).⁵ We previously reported the first acceleration effect of photocatalytic reaction with AuNCs by the installation of dendritic peptide substituent to thiolate ligands, enabling the construction of hydrogen bonding supramolecular reaction field on the surface of Au₂₅ nanocluster, wherein photocatalytic oxidative cyclization of amino alcohol was accelerated through intermolecular interaction between peptide dendron ligands and substrates (Figure 1c).⁶ In this reaction, AuNCs act as a photosensitizer generating singlet oxygen without any direct reaction with substrates. Recently, we reported the Au₂₅NC-photocatalyzed cross-dehydrogenative coupling between amines

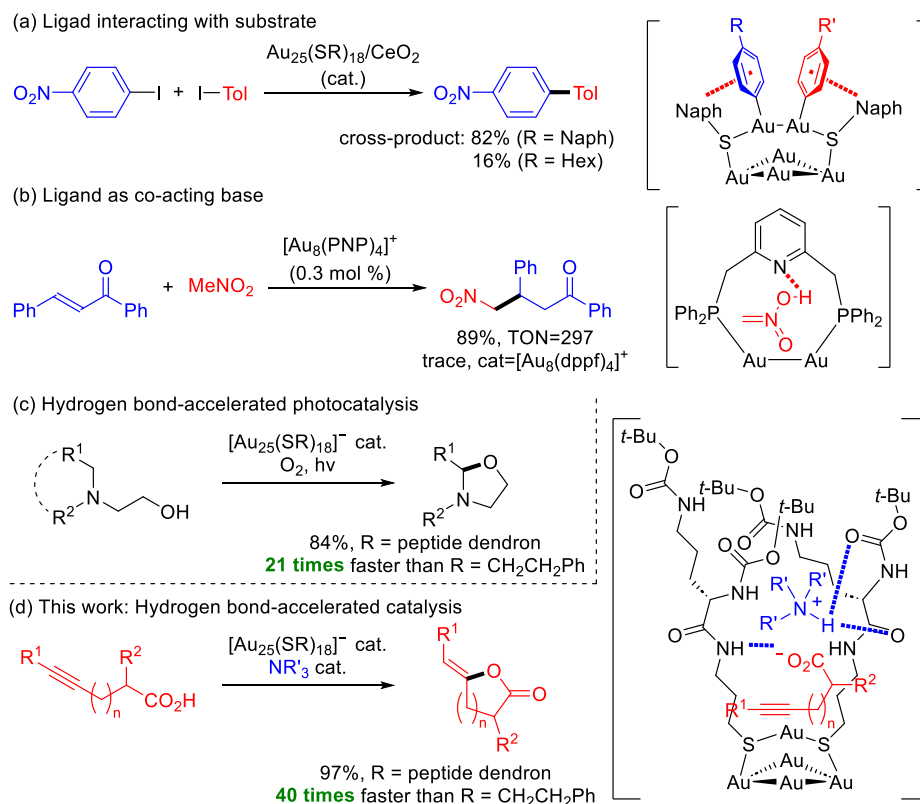


Figure 1. Reaction acceleration with intermolecular interaction between ligands and substrates in gold catalysis. (a) π - π stacking interaction. (b) Acid-base interaction. (c) Hydrogen bonds toward photocatalysis. (d) Hydrogen bonds for Lewis acid catalysis.

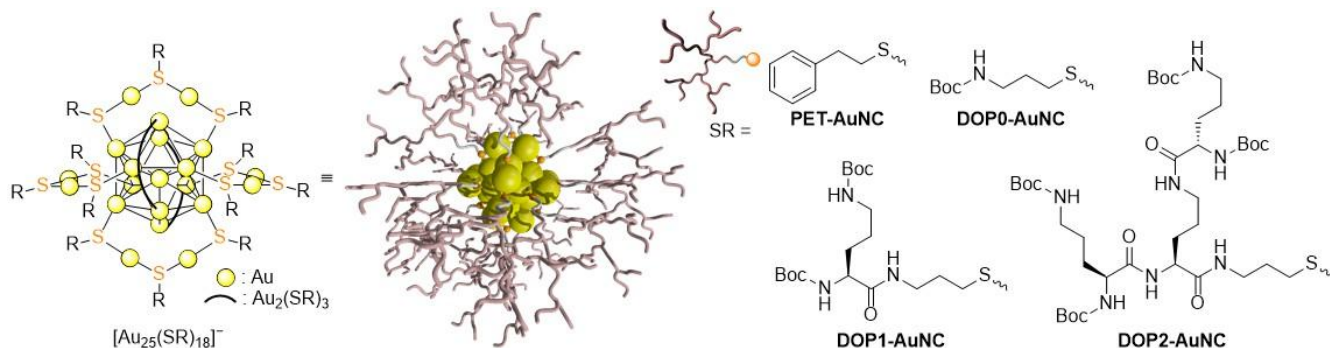


Figure 2. Molecular structure of AuNC catalysts.

and alkynes, in which the dendritic peptide ligands showed a slightly positive effect for the efficient catalytic turnover due to the detachment of dendritic peptide ligands via ligand exchange reaction with alkyne substrates.⁷ However, there is no report on the effect of supramolecular reaction field on AuNCs toward simple catalytic reaction without any photocatalytic process.

Herein, we report the effect of hydrogen bond-based supramolecular reaction field on AuNCs toward catalytic cyclization of alkynoic acids in the presence of tertiary amine co-catalyst (Figure 1d). A remarkable reaction acceleration effect was observed by dendritic peptide thiolate ligands with 40 times greater than simple alkyl thiols. Association experiments revealed the unprecedented hydrogen bonding behavior of dendritic peptide ligands on AuNCs toward in-situ formed ammonium salts through multiple hydrogen bonds like calixarenes.

Results and Discussion

Screening of reaction conditions

The study was begun with the screening of reaction conditions of catalytic cyclization of alkynoic acids using 4-pentynoic acid (**1a**) as the substrate. The alkynoic acid **1a** was efficiently cyclized to afford the corresponding exo-cyclized **2a** as the dominant product in 77% yield in the presence of the first-generation peptide dendron thiolate-protected Au₂₅ nanocluster **DOP1-AuNC** (where DOP_x represents dendritic ornithine peptide, and x denotes the dendron generation) with triethylamine in CDCl₃ (entry 1, Table 1). This reaction did not proceed without **DOP1-AuNC** (entry 2), clarifying the role of **DOP1-AuNC** as the catalyst for this reaction. When non-peptidyl 2-phenylethanethiolate-protected Au₂₅ nanocluster **PET-AuNC**⁸ was used as the catalyst, the product yield of **2a** was decreased to

Table 1. Screening of Reaction Conditions

entry	variation from standard condition	yield (%) ^a	<i>k</i> (×10 ⁻² h ⁻¹)
1	none	77	6.39
2	no cat	n.r.	-
3	PET-AuNC	5	0.16
4	DOP0-AuNC	40	1.43
5	DOP2-AuNC	56	3.31
6	Ph₃PAuCl (1.25 mol %) +DOP1-SH (0.9 mol %)	9	0.20
7	no NEt ₃	29	1.36
8	100 mol % NEt ₃	37	1.24
9	reaction at 25 °C	40	2.13

^a¹H NMR yield using 1,2,4,5-tetramethylbenzene as an internal standard.

5% (entry 3). To compare the catalytic activity of AuNC catalysts reaction rate constants were obtained from the pseudo first-order kinetics in the initial reaction steps (Figure S4). The obtained reaction rate constant of **DOP1-AuNC** was $6.39 \times 10^{-2} \text{ h}^{-1}$ which is 40 times higher than that of **PET-AuNC** with $0.16 \times 10^{-2} \text{ h}^{-1}$ (entries 1 and 3), indicating the remarkable reaction acceleration effect of supramolecular reaction field constructed of peptide dendron thiolates on AuNCs towards this catalytic reaction. To examine the effect of supramolecular reaction field 3-(Boc-amino)propanethiolate-protected ($x=0$, **DOP0-AuNC**) and the second-generation peptide dendron thiolate-protected Au₂₅ nanocluster **DOP2-AuNC** were also investigated as the catalyst. In the case of **DOP0-AuNC**, **2a** was obtained in 40% yield with reaction rate constant of $1.43 \times 10^{-2} \text{ h}^{-1}$, which is 9 times faster than **PET-AuNC**, but 4.5 times slower than **DOP1-AuNC**, indicating that the dendron unit with multiple hydrogen bonding sites is important to construct hydrogen bonding supramolecular reaction field (entry 4). Upon the usage of **DOP2-**

AuNC as the catalyst, 56% yield of **2a** was obtained with the *k* with $3.31 \times 10^{-2} \text{ h}^{-1}$, which is 2 times slower than **DOP1-AuNC**, suggesting that too many hydrogen bonding sites slower the reaction turnover due to the inter-dendron hydrogen bonding equilibrium tending to the closed form, as observed in the previous report (entry 5).⁶ The effect of the hydrogen bonding supramolecular reaction field was also investigated with the mixture of 25 times Ph₃PAuCl and 18 times peptide dendron thiol, **DOP1-SH**, corresponding to the formula of **DOP1-AuNC**. In this case, much lower product yield of 9% and much slower reaction rate of $0.20 \times 10^{-2} \text{ h}^{-1}$ was obtained (entry 6). Although the surface-exposed Au atoms in **DOP1-AuNC** is 12, **DOP1-AuNC** showed faster reaction rate than free Au complex, revealing the reaction acceleration in the hydrogen-bonded supramolecular reaction field on Au₂₅ NC surface. Without the addition of triethylamine the reaction didn't proceed smoothly, resulting in 29% yield of **2a** (entry 7). With the addition of 100 mol % of triethylamine no significant improvement was observed for the product yield and the reaction rate (entry 8, further screening of the amount of base, see Figure S5). Lower reaction temperature also slowed down the reaction rate (entry 9), thus 45 °C was chosen as the optimal reaction temperature (Table S1).

The screening of reaction solvents was also investigated using deuterated acetone, toluene, acetonitrile, methanol, dimethyl sulfoxide, and tetrahydrofuran as the solvent (Figure 3a). Among the all solvents investigated chloroform showed the highest reaction rate, followed by toluene, acetonitrile, THF, acetone, MeOH, DMF, and DMSO. This order is strongly related to the hydrogen bonding property of solvents.⁹ The less hydrogen bonding acceptor nature of solvents accelerates the reaction more, strongly suggesting the key role of intermolecular hydrogen bonds between peptide dendron ligands and substrates (Figures 3b, c, and d).

Organic base additives were also screened using DBU, Et₃N, DABCO, *N*-methylmorpholine, imidazole, lutidine, and *N,N*-dimethylaniline (Figure 3e). All base additives gave 37 to 86% yield of **2a**,

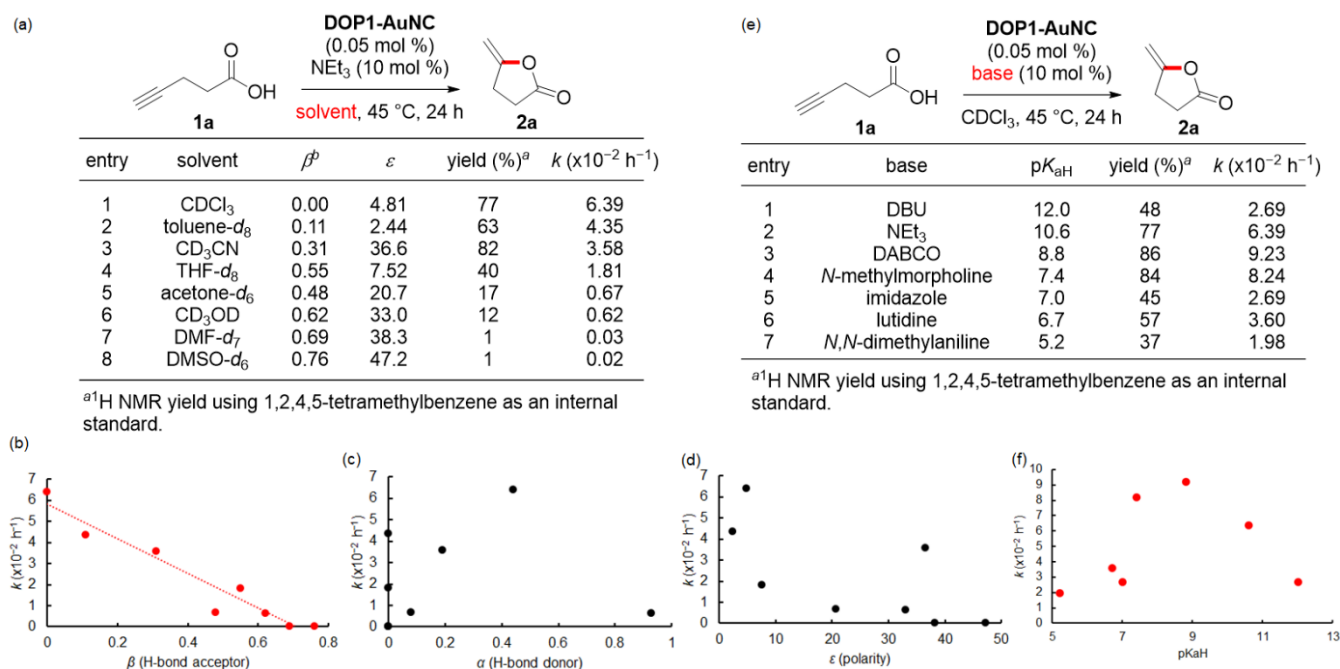


Figure 3. (a) Screening of solvents. Plots for reaction rate vs (b) β , (c) α , and (d) ϵ values of solvents. (e) Screening of organic bases. (f) Plot for reaction rate vs pK_{aH} of organic bases.

but the reaction rate is significantly affected by the base. With increasing pK_{aH} from 5.2 of *N,N*-dimethylaniline to 6.7 of lutidine, 7.0 of imidazole, greater reaction rate constant is observed to be 1.98, 3.60, and $2.69 \times 10^2 \text{ h}^{-1}$, respectively (entries 5–7). The higher reaction rate of 6.39, 9.23, and $8.24 \times 10^2 \text{ h}^{-1}$ are observed from triethylamine, DABCO, and *N*-methylmorpholine (entries 2–4). In the case of DBU with pK_{aH} of 12.0, the reaction rate was decreased to 2.69 (entry 1). These results clarify that the base additive acts an important role relating to the rate determining step in the catalytic cycle, and the middle pK_{aH} range from 7 to 11 is key to the smooth catalytic turnover (Figure 3f). From these base screening results, common and inexpensive Et_3N was chosen as the optimal base additive for the further investigation.

Scope of substrate

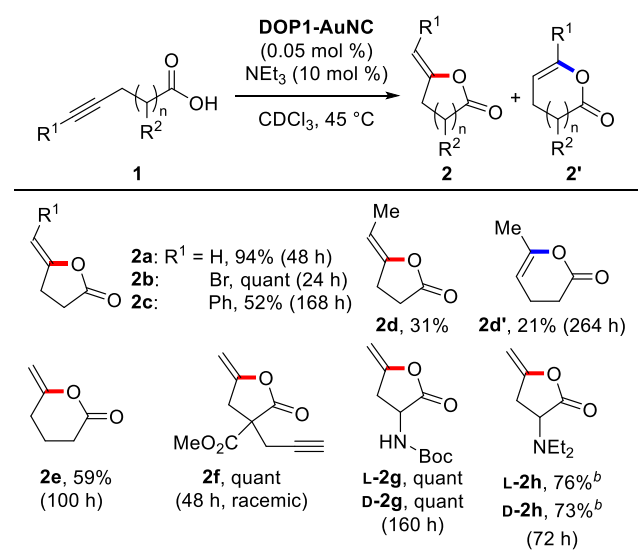
Using the optimized reaction conditions, the scope of substrates was investigated (Table 2). First, the chain length dependence was investigated using terminal alkynoic acids. Both 4-pentynoic acid (**1a**) and 5-hexynoic acid (**1e**) with C5 and C6 chains were smoothly cyclized to afford the corresponding exo-cyclized product **2a** and **2e** in 94 and 59% yield, respectively. In contrast, no cyclization reaction proceeded with C4 and C7 acids, as similar to the conventional transition metal-catalyzed reactions.¹⁰ Internal alkynes bearing methyl, bromo, and phenyl substituents on alkyne termini of 4-pentynoic acid also participated in the reaction to afford cyclized products. The smooth cyclization reaction was achieved by internal alkynes bearing electron deficient substituents, such as bromo and phenyl groups, producing exo-cyclized product **2b** and **2c** regioselectively in quantitative and 52% yield, respectively. In contrast, electron-rich alkyne with terminal methyl substituent gave a mixture of exo-cyclized product **2d** and endo-cyclized product **2d'** in 31 and 21% yields, respectively. These reactivity and selectivity correspond to those with conventional transition metal catalysts.¹⁰ The effect of the supramolecular reaction field was investigated by desymmetrization and

amino acid substrates. The desymmetrization substrate, methyl 2,2-dipropargylmalonate was cyclized to afford the exo-cyclized product **2d** in quantitative, which was confirmed to be a racemic product by chiral HPLC analysis (Figure S6). Two types of *L*-/*D*-propargylglycine substrate bearing Boc or diethyl substituents on the amino groups showed almost the same reaction rate (Figures S7 and S8) and product yield between enantiomers, indicating no kinetic resolution took place in this reaction system. These results suggest that intermolecular interaction between chiral peptide dendrons and alkynoic acid substrates don't affect the enantio-induction, as similar to previous observations.^{6,7}

Hydrogen bonding with peptide dendron ligands

To investigate the reaction acceleration effect association experiments between peptide dendron ligands and alkynoic acids were carried out using ^1H NMR. In this experiment, **1a** and triethylamine were mixed in 1:1 ratio to form an ammonium salt in the mixture solution (Figure 4a). With the increasing concentration of co-existing acetyl-protected 1st generation peptide dendron thiolate ligand **DOP1-SAc** from 0 to 100 mM, methylene protons neighboring to nitrogen atom of the ammonium salt shows upfield shift of 0.019 ppm, indicating that the equilibrium between free amine and ammonium salt shifted to the free amine side due to the weak basic nature of **DOP1-SAc** (Figure 4b). In contrast, when 1.39 mM of **DOP1-AuNC** was mixed instead of **DOP1-SAc**, the methylene protons of ammonium salt showed downfield shift with 0.027 ppm. The contrasting behavior suggests the feature of peptide dendron ligands on the surface of AuNC constructing a supramolecular hydrogen bonding field encapsulating ammonium salts through multiple hydrogen bonds. The similar host-guest property was previously reported with the crownether bearing multiple hydrogen bonding sites towards ammonium salts.¹¹ When only **1a** was mixed with **DOP1-SAc** or

Table 2. Scope of Substrate



^a ^1H NMR yield using 1,1,2,2-tetrachloroethane as an internal standard.

^bNo NEt_3 was added.

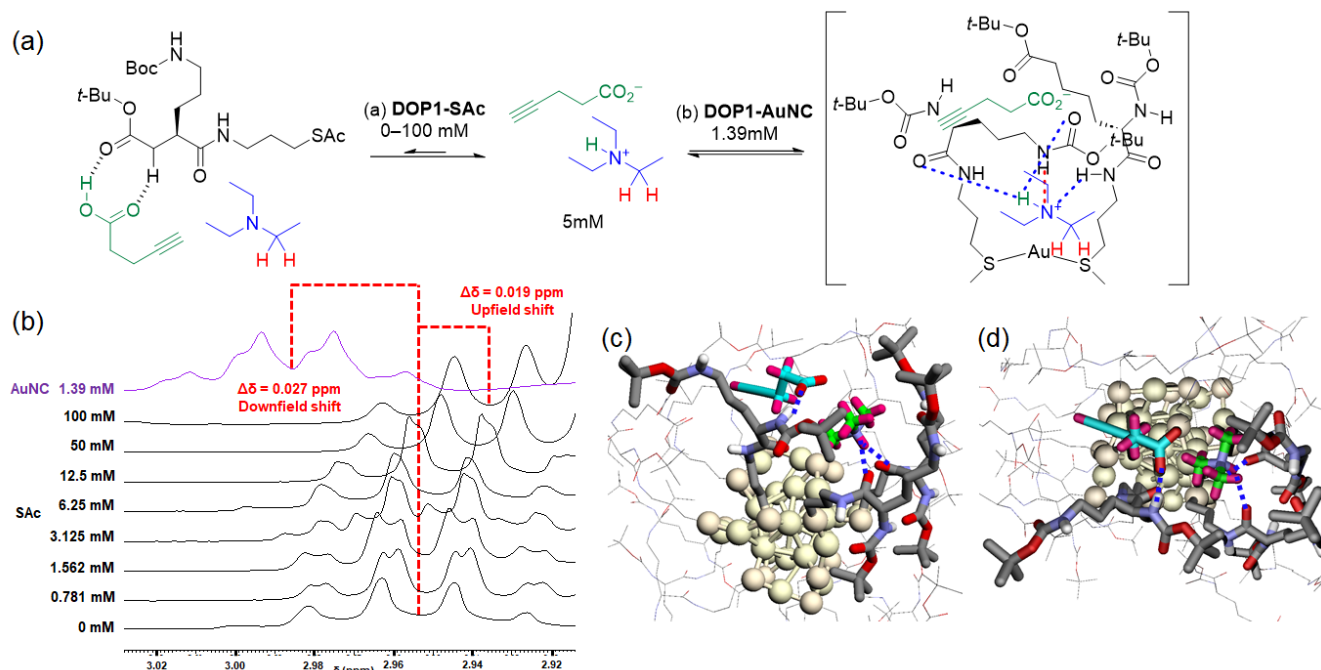


Figure 4. (a) Schematic illustration for association experiments between in situ formed ammonium salt and **DOP1-Sac** or **DOP1-AuNC**. (b) Magnified ^1H NMR spectra of methylene protons of triethylamine with variety concentration of **DOP1-Sac** and 1.39 mM of **DOP1-AuNC**. (c) Side and (d) top views of molecular mechanics-optimized structure of **DOP1-AuNC** encapsulating ammonium salt through multiple hydrogen bonds. Color code, Au: pale yellow, S: pale orange, C: gray, light blue, and green, N: cyan, O, red, H: white and magenta.

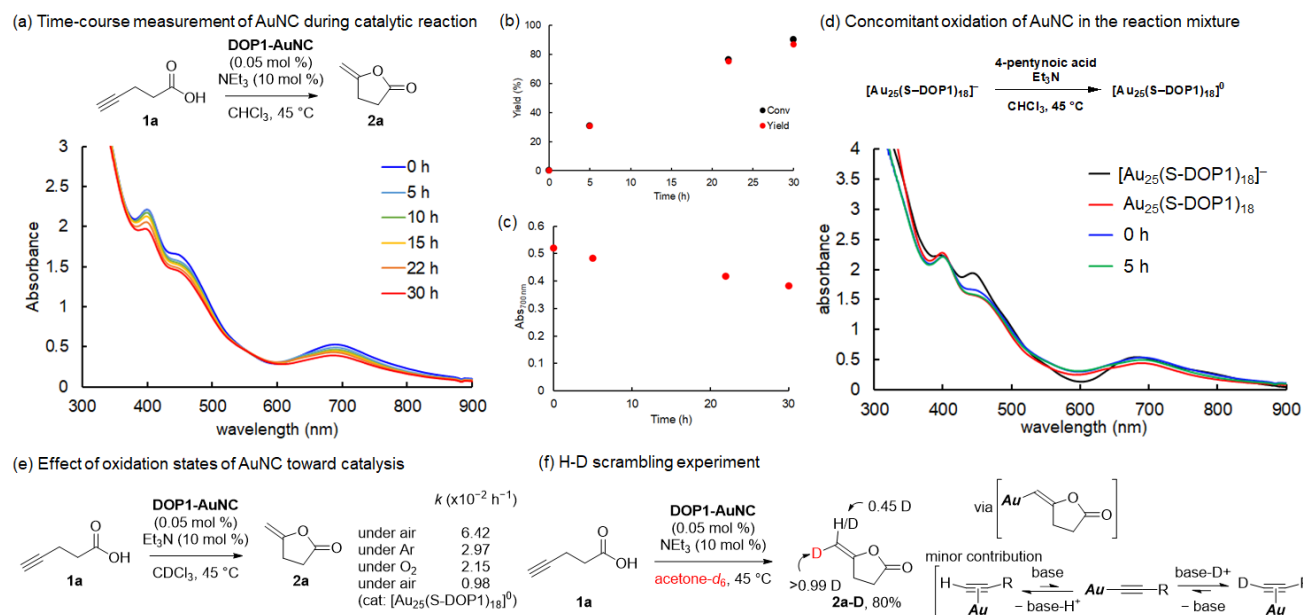


Figure 5. Mechanistic investigations. (a) Time-course absorption spectral change of AuNC in the reaction solution. (b) Time-course reaction profile by ^1H NMR measurement. (c) Absorbance change at 700 nm. (d) Absorption spectra of **DOP1-AuNC** (black line), **DOP1-AuNC** with **1a** and Et_3N in air (blue line), **DOP1-AuNC** with 2000 equiv. of **1a** and Et_3N under argon (green line), and neutral Au_{25}NC (red line). (e) The effect of oxidation state of Au_{25}NC . (f) H-D scrambling experiment using **1a** in acetone- d_6 .

DOP1-AuNC, such a significant shift was not observed (Figure S11). These results strongly suggest that the hydrogen bonding between in-situ formed ammonium salts and peptide dendron ligands on AuNC is the driving force for the enhanced catalytic cyclization of alkynoic acids. Based on these results, the multiple hydrogen bonding between **DOP1-AuNC** and ammonium salt was investigated using theoretical calculation. Molecular mechanics-based

structural optimization also indicates the formation of multiple hydrogen bonds between **DOP1-AuNC** and ammonium salt (Figures 4c, d, and S16). Two hydrogen bonds are formed between ammonium proton and two amide $\text{C}=\text{O}$ moieties of the neighboring two thiolate ligands. The other hydrogen bond is formed between carboxylate anion and amide $\text{N}-\text{H}$ moiety of another thiolate ligand. The well accordance of the experimental results and computational

simulation strongly suggests that the formation of multiple hydrogen bonds is the driving force to accelerate the current catalytic reaction.

Mechanistic study

To gain insight into the reaction mechanism, the time-course measurement of AuNC during the catalytic reaction was performed. The catalytic reaction solution of 0.1 mmol of **1a** in the presence of 10 mol % of Et₃N and 0.05 mol % of DOP1-AuNC was prepared and time-course absorption spectra were recorded at 45 °C (Figure S5a). With the similar reaction condition, 90% of **1a** was consumed and 87% of **2a** was produced after 30 h reaction (Figure S5b). In this reaction profile, no induction period was observed, suggesting Au₂₅NC acts as the active catalytic intermediate without structural change. During the course of the catalytic reaction the characteristic absorption bands of Au₂₅NC at 400, 450, and 680 nm were gradually decreased, but no significant change was observed in the spectral shape, indicating most of the catalyst retained the original Au₂₅NC form. From the absorbance at 700 nm, 73% of Au₂₅NC was retained intact after 30 h catalytic reaction (Figure S5c). The high stability of Au₂₅NC was further confirmed by the catalytic reaction with the catalyst loading of 1.0 mol ppm (Figure S12). The reaction turnover continued over 2,500 h and final yield of **2a** was reached to 82%, indicating the high stability of Au₂₅NC catalyst over 820,000 turnover number.

Most importantly, just after mixing **1a** and Et₃N, absorption spectrum of DOP1-AuNC was changed, in which absorption shoulder at 800 nm was disappeared and absorbance at 440 nm was decreased, suggesting the formation of oxidized neutral form of Au₂₅NC (Figure S5d).¹² The similar oxidation occurred without Et₃N, but didn't occur under argon atmosphere (Figure S13), indicating that the co-existence of acid and oxygen is the key for the spontaneous oxidation of [Au₂₅]⁻ to [Au₂₅]⁰, as similar to the recent report on proton-coupled electron transfer from [Au₂₅]⁻ to oxygen.¹³ To clarify the active catalytic intermediate [Au₂₅]⁰ was synthesized by the photoinduced oxidation reaction¹² (Figure S2) and its catalytic activity was compared with DOP1-AuNC (Figure S5e). The isolated [Au₂₅]⁰ cluster showed a slightly lower, but a comparable catalytic activity in air to

that of the original anionic form used as the precatalyst. In addition, even when the catalytic reaction with [Au₂₅]⁻ was performed under argon and oxygen atmosphere, the comparable catalytic activity was also observed. These results suggest that both [Au₂₅]⁻ and [Au₂₅]⁰ act as the active catalytic intermediate in this reaction.

H-D scrambling was observed when the catalytic reaction of **1a** was carried out in acetone-*d*₆ (Figure S5f). The obtained product **2a-D** shows the complete D-incorporation to vinyl position trans to oxygen together with moderate D-incorporation to cis-position. The complete D-incorporation indicates the existence of vinyl-Au intermediate generated from exo-cyclization of pi-coordinated terminal alkyne, which is finally protonated by D-exchanged ammonium salt to afford the D-incorporated alkylidene lactone products. The moderate D-incorporation to cis-position suggests the formation of the alkynyl-Au intermediate via the deprotonation of terminal alkynyl proton as a minor side reaction.

DFT calculation

The reaction pathway was investigated by DFT calculation under the consideration of both possibility of [Au₂₅]⁻ and [Au₂₅]⁰ as the catalytically active intermediates (Figure 6). The organic base screening indicated the participation of the base in the catalytic cycle, thus the reaction pathway including the base was investigated. The calculation was carried out with **1a**, Me₃N, and [Au₂₅(SMe)₁₈] as the model system. In the case of in-situ formed [Au₂₅]⁰, the coordination of hydrogen-bonded **1a** to the surface Au atom on the Au₂(SR)₃ staple stabilizes the intermediate **B** from the starting **A** with 34.3 kcal/mol. Through the transition state **TS_{BC}** with the activation energy of 18.2 kcal/mol, the Au-S bond in the staple is cleaved and the ammonium cation-hydrogen-bonded vinyl-Au-tethered AuNC intermediate **C** is produced. The ammonium cation detaches from the lactonyl oxygen to afford the non-hydrogen-bonded intermediate **D**. Finally, the protonation to the vinyl-Au site with the ammonium cation produces the alkylidene lactone product **2a** and regenerate [Au₂₅]⁰ intermediate with the activation energy of 1.4 kcal/mol. In the case of [Au₂₅]⁻, all intermediates show just a slightly higher energy than those in the pathway with [Au₂₅]⁰, corresponding to the possible participation both of [Au₂₅]⁻ and [Au₂₅]⁰ in the catalytic

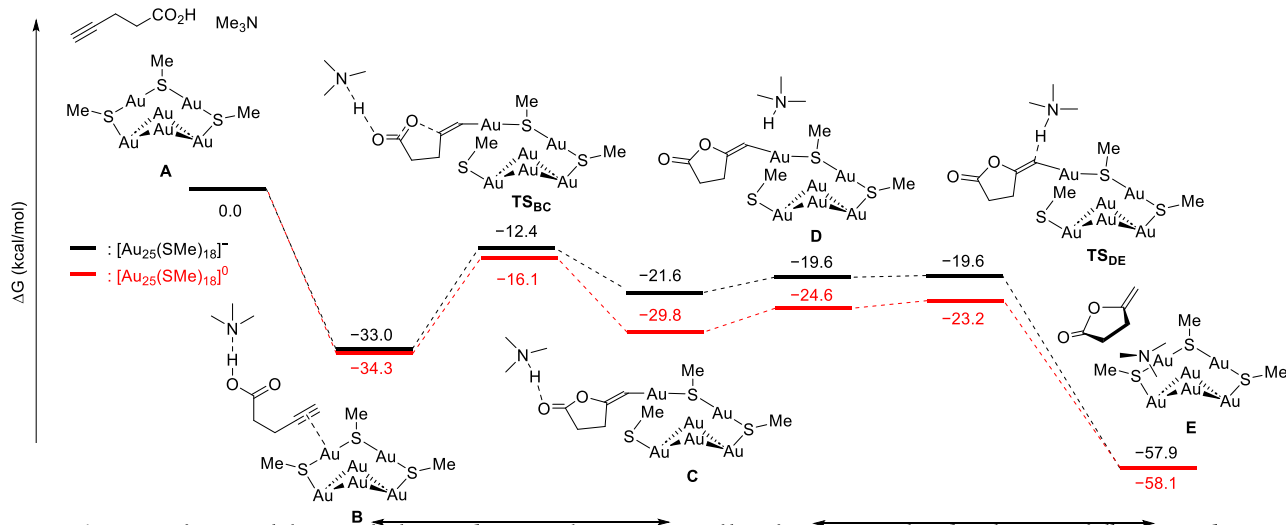


Figure 6. Density functional theory calculations depicting the reaction profiles of Au₂₅NC-catalyzed cyclization of alkynoic acids. Partial molecular structure of AuNCs are shown for clarity.

cycle. In both reaction pathways, the transition states of the cyclization step show the highest energy levels, indicating that the cyclization step is the potent rate-determining step. The energy barrier of the cyclization step is considered to depend the Lewis acidity of the pi-coordinated Au atoms.¹⁰ The Lewis acidity of staple Au atoms of $[\text{Au}_{25}]^-$ and $[\text{Au}_{25}]^0$ was estimated by the calculation of NBO charges, indicating the averaged values of 0.314 for $[\text{Au}_{25}]^-$ and 0.328 for $[\text{Au}_{25}]^0$, respectively (Table S2). The less difference in NBO charge can be ascribed to the delocalization of the net charge onto the whole nanocluster molecules containing 25 Au atoms. This results supports the possible participation both of $[\text{Au}_{25}]^-$ and $[\text{Au}_{25}]^0$ in this catalytic reaction. Although the DFT calculation with simple model system suggests the cyclization step as the rate-determining step, the screening of base additive indicates the protonation step as the real rate-determining step (Figure 3e). As indicated by the association experiments, ammonium cation is hydrogen-bonded with peptide dendron ligands. Due to the hydrogen bonds between ligands and ammonium cation the energy barrier of protonation step is considered to be higher than the cyclization step in the real catalytic system bearing peptide dendron ligands.

Proposed mechanism

Based on the experimental and computational results a plausible reaction mechanism was proposed (Figure 7). The anionic Au_{25}NC precatalyst **A** is simultaneously oxidized in the presence of alkynoic acid **1**, amine, and oxygen to afford the neutral nanocluster **B** encapsulating ammonium salt through multiple hydrogen bonds between peptide dendron ligands and ammonium salts. In the equilibrium, the encapsulated alkynoate anion coordinates to the staple Au atom through the pi-coordination of alkynyl moiety to generate pi-coordinated intermediate **C**. The following intramolecular cyclization of

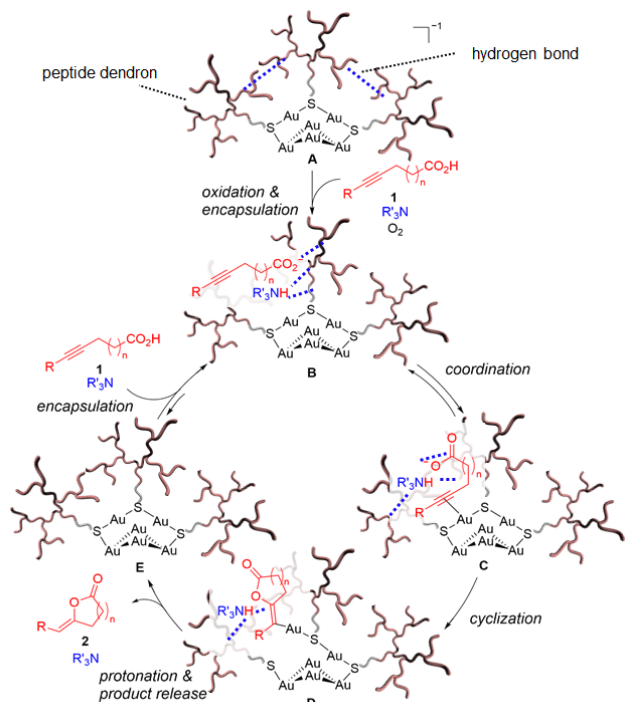


Figure 7. Proposed mechanism with a part of AuNC for clarity.

the activated alkynoate proceeds to give the intermediate **D** bearing vinyl–Au bonding structure. The protonation of the vinyl–Au species with the encapsulated ammonium cation provides and releases the alkylidene lactone product **2** and amine co-catalyst, generating a guest-free nanocluster **E**. Finally, the alkynoic acid **1** and amine co-catalyst are encapsulated to the hydrogen bonding supramolecular reaction field as the ammonium salt, regenerating the catalytically active intermediate **B** to close the catalytic cycle. The similar catalytic cycle is also possible under argon atmosphere utilizing the anionic nanocluster as the catalytically active intermediate.

Conclusion

In conclusion, we have demonstrated the accelerated catalysis of gold nanocluster toward catalytic cyclization of alkynoic acid by the supramolecular ligand engineering approach using peptide dendron thiolate as the multiply hydrogen bonding ligands. The ligand-based supramolecular reaction field accelerated the cyclization reaction rate 40 times greater than that with non-peptidyl alkyl thiolate ligands. The driving force for the reaction acceleration was identified to originate from the unprecedented hydrogen bonding between the in-situ formed ammonium salt and the supramolecular reaction field constructed with peptide dendron ligands on AuNC. Mechanistic investigations indicated the high stability of the AuNC catalyst in this reaction over the turnover number of 820,000 and revealed the reaction intermediates involving pi-coordination of alkynes to the staple Au atoms and vinyl–Au intermediates. The DFT calculation supported the experimental observations for the participation both of $[\text{Au}_{25}]^-$ and $[\text{Au}_{25}]^0$ nanocluster as the catalyst. Our results disclose the usefulness of supramolecular ligand engineering approach for the catalytic applications of metallic nanoclusters. The acceleration of catalytic reactions within the supramolecular reaction field can be finely tuned through careful ligand design, as well as by controlling the size and shape of the nanocluster core. This approach offers a rational pathway for developing highly active and selective nanocluster catalysts.

MATERIALS AND METHODS

Materials. Materials were purchased from Wako, Tokyo Chemical Industry Co., Ltd., Nakalai tesque, Inc., and other commercial suppliers, and were used without further purification, unless otherwise noted. Ethanol (EtOH), sodium borohydride (NaBH_4), toluene, potassium carbonate (K_2CO_3), 1,2,4,5-tetramethylbenzene, 1,4-diazabicyclo[2.2.2]octane (DABCO), 2,6-lutidine, *N,N*-dimethylaniline, acetonitrile- d_3 , and tetrahydrofuran (THF) were purchased from Wako. Methanol (MeOH), distilled water (H_2O), *N*-methylmorpholine, and triethylamine (NEt_3) were purchased from Nakalai tesque. Tetrachloroauric(III) acid tetrahydrate ($\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$) was purchased from TANAKA KIKINZOKU KOGYO K. K. 3-Butynoic acid, 6-hexynoic acid, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), tetrahydrofuran (THF)- d_8 , and dimethylsulfoxide (DMSO)- d_6 were purchased from Sigma-Aldrich. 2-Phenylethyl mercaptan ($\text{PhCH}_2\text{CH}_2\text{SH}$), imidazole, and tetraoctylammonium bromide (TOAB) were purchased from TCI. Chloroform (CHCl_3) and ethyl acetate (EtOAc) were purchased from Kishida Chemical Co., Ltd. Chloroform- d and *N,N*-dimethylformamide (DMF)- d_7 were purchased from Cambridge Isotope Laboratories, Inc. Toluene- d_8 , methanol- d_4 , and acetone- d_6 were

purchased from Eurisotop. **DOP1-SH**, **DOP1-SAc**, **DOP1-AuNC**, and **DOP2-AuNC** were synthesized according to the previously reported method.⁶ **PET-AuNC**,¹⁴ and chloro(dimethylsulfide)gold (I) (Me_2SAuCl)¹⁵ were synthesized according to the literature method. 2-(methoxycarbonyl)-2-(2-propynyl)-4-pentynoic acid (**1f**) was synthesized according to the literature method.¹⁶

Synthesis of DOP0-AuNC. This compound was synthesized by a modified procedure based on the previously reported method.⁷ To a solution of *tert*-butyl *N*-(3-mercaptopropyl)carbamate (191 mg, 1.00 mmol) in chloroform (50.0 mL), Me_2SAuCl (296 mg, 1.00 mmol) was added under an argon atmosphere in the dark. After stirring for 10 min, NEt_3 (168 μL , 1.20 mmol) was added, accompanied by the observation of white smoke. After the additional stirring for 30 min, a solution of NaBH_4 (30.5 mg, 0.81 mmol) in ethanol (10.0 mL) was added dropwise under vigorous stirring. The reaction mixture was then allowed to stir at room temperature for 6 days. The solvent was evaporated, and the obtained residue was purified using silica gel flash column chromatography (gradient elution from $\text{CHCl}_3/\text{MeOH} = 100/0$ to 95/5). The main fraction was further treated with approximately 100 equivalents of NaOH in MeOH . After the addition of CHCl_3 and water, the organic phase was separated. The organic layer was further washed by water, Brine, and dried over Na_2SO_4 . The obtained residue was purified by preparative thin layer chromatography using $\text{CHCl}_3/\text{MeOH} = 95:5$ as the eluent, yielding **DOP0-AuNC** as a brown solid (7.5 mg, 2%).

Synthesis of neutral $\text{Au}_{25}(\text{S-DOP1})_{18}$ by photooxidation of anionic $\text{Au}_{25}(\text{S-DOP1})_{18}$. A 0.3 mM chloroform solution of anionic $\text{Au}_{25}(\text{S-DOP1})_{18}$ (**DOP1-AuNC**, 10 mg, 0.8 μmol) was irradiated with 680 nm light under oxygen atmosphere at rt. After 48 h irradiation with time-course monitoring by UV-Vis absorption spectrum and TLC (Figure S1), the crude mixture was purified by SiO_2 column chromatography to afford neutral nanocluster $\text{Au}_{25}(\text{S-DOP1})_{18}$ as a brown solid (7.5 mg, 75%).

General procedure for catalytic cyclization of alkynoic acids. NMR tube was charged with alkynoic acids (0.1 mmol), amines (0.01 mmol), gold nanocluster (50 nmol), and 1,2,4,5-tetramethylbenzene (0.1 mmol). To the NMR tube CDCl_3 was added as a solvent (700 μL). The NMR tube coated by aluminum foil and heated at 45 $^\circ\text{C}$. The reaction process was monitored by ^1H NMR measurement on a JEOL ECS-400NR.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge via the Internet at <http://pubs.acs.org>. Experimental details and supplementary data (PDF)

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