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# Stereoselective growth of small molecule patches on nanoparticles

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*KEYWORDS Patchy nanoparticles, self-assembly, ligand segregation, supramolecular chemistry, anisotropic structures*

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**ABSTRACT:** Patchy nanoparticles featuring tunable surface domains with spatial and chemical specificity are of fundamental interest, especially for creating three-dimensional (3D) colloidal molecules. Guided assembly and regioselective conjugation of polymers have been widely used to manipulate such topography on nanoparticles; however, the processes require pre-synthesized specialized polymer chains and elaborate assembly conditions. Here we show how small molecules can form 3D patches in aqueous environments in a single step. The patch features (e.g., size, number, conformation, and stereoselectivity) are modulated by a self-polymerizable aromatic dithiol and co-mixed ligands, which indicates an autonomous assembly mechanism involving covalent polymerization and supramolecular assembly. Moreover, this method is independent of the underlying nanoparticle material and dimension, offering an extremely streamlined and powerful toolset to design heterogeneous patches on the nanoscale.

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## ■ INTRODUCTION

Surface patterned colloids with anisotropic patches offer fascinating potential in photonics, electronics, biomedicine, and environmental applications as well as important insight into the building blocks of the natural world.[1-5] Current strategies for patchy architectures on micro- and macro-sized colloids include emulsion polymerization, microcontact printing, and glancing angle deposition,[6-9] but the ability to precisely deposit patches on a nanoparticle substrate has been elusive. Although self-assembled monolayer via the segregation of small molecules on nanoparticles can afford multiple "thin" patch modes,[10-12] it lacks high-fidelity morphology for further modification or assembling. Therefore, the design of three-dimensional (3D) patches on nanoparticles is envisioned to be a critical step for generating complex and programmable nanostructures towards emerging applications.

Until now, such 3D patchy nanosystems with topographic valence have mainly been obtained through the guided assembly and regioselective conjugation of polymers.[13-17] For example, amphiphilic poly(styrene)-b-poly(acrylic acid) in a binary solvent can assemble into an eccentric patch on a nanoparticle that is pre-modified with hydrophilic and hydrophobic ligands.[18-19] Alternatively, discrete polymer patches can be obtained on polymer-coated nanoparticles via a decrease in the solvent quality.[13, 20] These "grafting-to" approaches necessitate the synthesis of customized polymers and the delicate regulation of solvent systems to initiate the transformation of the polymeric chains into patches on the particles. A versatile "one-step" strategy that allows for stereoselective patches from small molecules has remained a challenge.[21-24] Inspired by biological systems that can direct the bottom-up synthesis of nano- and microscopic structures from simple molecules,[25-26] we hypothesized that soluble small molecules capable of both assembling onto nanoparticles and polymerizing into insoluble chains could be utilized to streamline and expand patch design with high-fidelity.

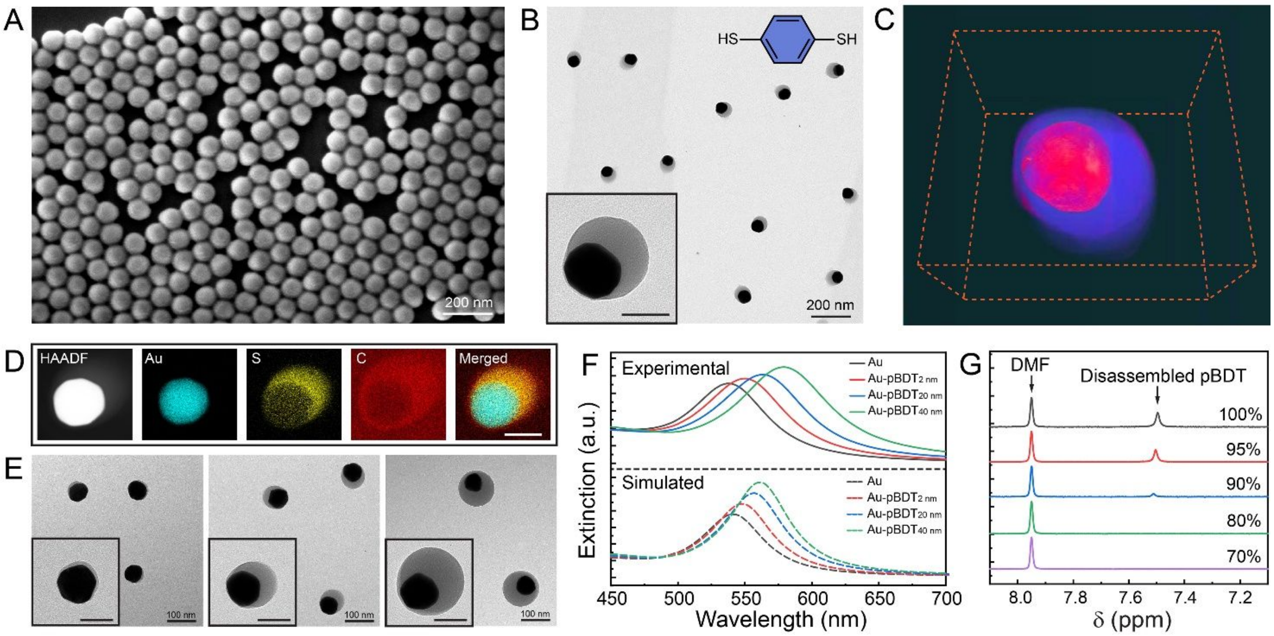

**Fig. 1. Patchy nanoparticles synthesized from small molecules (i.e., BDT).** (**A** and **B**) Scanning electron microscopy (SEM) and TEM images of the patchy Au-pBDT Janus nanoparticles. (**C**) Electron tomography reconstruction image of Au-pBDT nanoparticles: Au core (red) and pBDT patch (blue). (**D**) EDX elemental mapping of Au-pBDT nanoparticles. (**E**) Patchy Au-pBDT Janus nanoparticles with different patch size, i.e., 2 nm, 20 nm, and 40 nm after increasing the concentration of BDT. Inset scale bars (**B**, **D**, and **E**) are 50 nm. (**F**) Experimental (solid lines) and simulated (dash lines) extinction of AuNPs and Au-pBDT nanoparticles. (**G**) $^1$H NMR of pBDT in $(CD_3)_2SO$-$D_2O$ two-component solvent with different volume ratios of $(CD_3)_2SO$ from 70% (bottom) to 100% (top).

Here we validate a small molecule-based strategy to synthesize 3D stereoselective patches on nanoparticles of different sizes, shapes, and compositions in aqueous environment. The size of the patch can be easily modulated by varying the amount of benzene-1,4-dithiol (BDT), which can bind to metal surfaces via thiol-mediated chemistry, self-polymerize into polymerized BDT (pBDT) via disulfide bonds, and form finite-sized supramolecular patches via π–π interactions on nanoparticles without any external stimuli. Experiments and molecular dynamics (MD) simulations corroborate that the spatial distribution of patches on nanoparticles is determined by ligand segregation of modulating ligands (e.g., thiol-carrying small molecules and non-thiol aromatic dyes) and are agnostic to the nanoparticle surface curvature. Eccentric to concentric designs as well as linear through octahedral structures were easily prepared. An autonomous assembly mechanism is proposed to underpin this new type of stereoselective patch: The attractive intermolecular forces amongst pBDT and their preferential binding to the nanoparticle surface are counteracted by the electrostatic repulsion between individual pBDT patches. The resulting patchy nanoparticles present greater opportunities for designing customized colloidal molecules and other complex superstructures.

## ■ RESULTS AND DISCUSSION

To evaluate this approach, we first employed gold nanoparticles (AuNPs, 60 nm) as an example (fig. S1). The AuNPs stabilized by sodium dodecyl sulfate (SDS) were dispersed in bicine buffer (10 mM pH 8.5) followed by the addition of BDT. The thiol moiety of BDT allowed the replacement of the original SDS on the AuNPs' surface due to the favorable gold-sulfur bonds. Meanwhile, BDT molecules polymerize into pBDT via disulfide bridges,[27] and the hydrophobic backbone of pBDT induces the progressive assembly of pBDT complexes on the surface of AuNPs via π–π interactions with pre-absorbed BDT and/or pBDT (figs. S2 and S3).[28-30] The pBDT-patched AuNPs (Au-pBDT) have a narrow size distribution with no obvious aggregates of pBDT in solution (Fig. 1A and fig. S4). Transmission electron microscopy (TEM) and 3D electron tomography reconstruction reveals the anisotropic growth of pBDT patches on AuNPs producing Janus nanoparticles (Fig. 1B and C and movie S1). Energy-dispersive X-ray spectroscopy (EDX) mapping further confirms the patch is composed of C and S indicating the BDT-based patch formulation (Fig. 1D). The patch size can be easily tuned from 2 nm to more than 40 nm by adjusting the concentration of BDT molecules (Fig. 1E). It is notable that the AuNPs in this study act as substates for patch attachment without showing potential catalytic effects on the polymerization. This is validated by the formation of similar pBDT nanoparticles without adding AuNPs (fig. S4). The anisotropic patch resulted in a polarization-dependent enhancement of an electromagnetic field (figs. S5 and S6) and a redshift in the localized surface plasmon resonance of the Janus nanoparticle (Fig. 1F) as validated by experiments and simulations.[31]

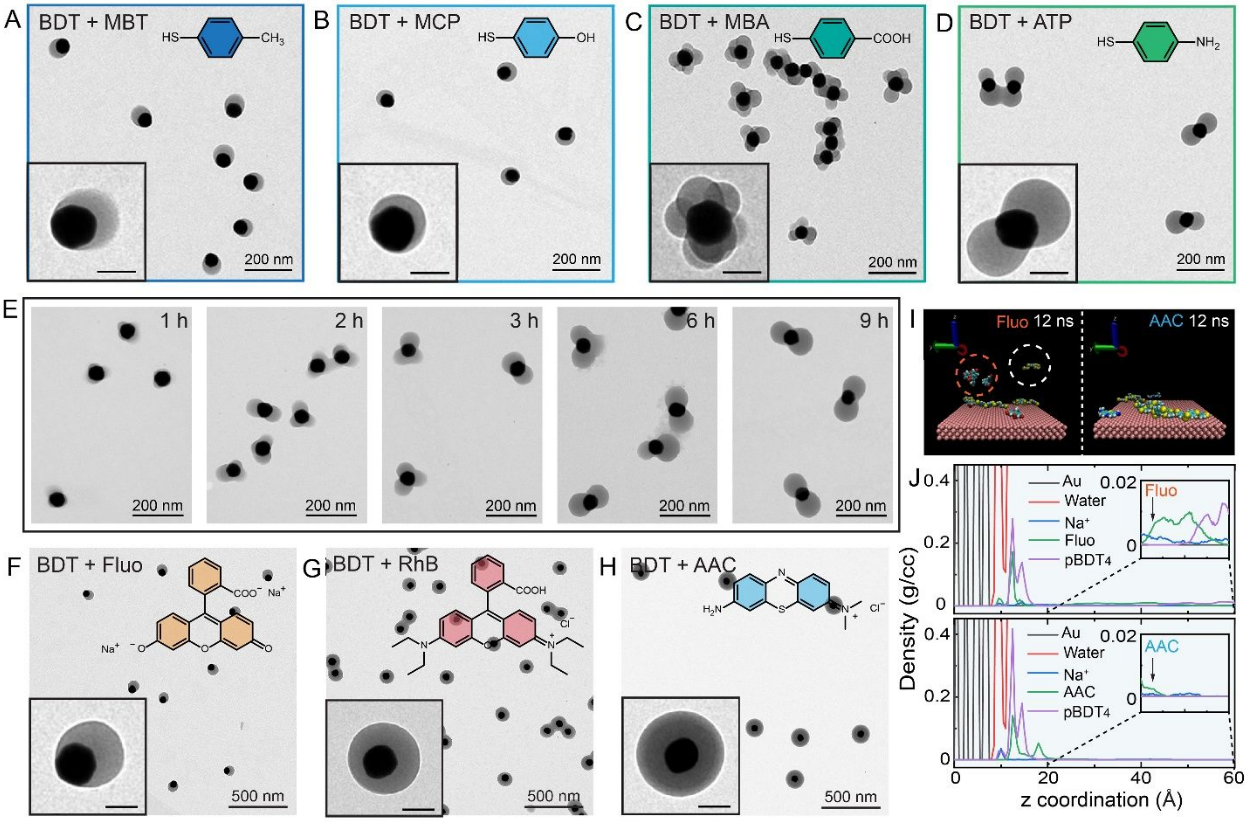

**Fig. 2. Stereoselective tuning of the patch geometry.** (**A**-**D**) TEM images of the patchy nanoparticles upon the addition of thiol-carrying molecules. Inset TEM images are the close-up image of representative patchy nanoparticles in each scenario; scale bars are 50 nm. (**E**) Dynamic transition of patch configuration in ATP-guided assembly. (**F**-**H**) TEM images of Au-pBDT nanoparticles obtained by adding different dyes. Inset scale bars are 50 nm. (**I**) The MD snapshot of the tetramer-BDT ($pBDT_4$), and Fluo or AAC on Au substrate (001) at 12 ns at 323K, 1 atm. Water molecules are not shown for clarity. The white circle highlights the free pBDT in the solution and the orange circle highlights the free Fluo molecules. (**J**) The mass density-profiles from equilibrium MD simulations. Insets are a magnification of the profile 2 nm from the surface.

The chemical composition of the nanoparticles was examined next. Fourier-transform infrared spectroscopy results show a loss in the $\upsilon_{S-H}$ stretching mode upon disulfide bridging and subsequent patch formation (fig. S7). Janus nanoparticles in deuterium oxide ($D_2O$) exhibit no detectable nuclear magnetic resonance (NMR) signal in the aromatic region due to the densely-packed π−π stacking of pBDT (fig. S7C).[32] In contrast, the intensity of an aromatic proton peak increased with increasing volume ratio of deuterated dimethyl sulfoxide, i.e., $(CD_3)_2SO$ (Fig. 1G). This result validates the supramolecular nature of the patches, which can disassemble in organic solvent such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) (figs. S8 and S9). Moreover, the supramolecular patch is heat-resistant (e.g., 90 °C for 3 h) and remains intact at high ionic strengths (e.g., 100 mM NaCl or PBS) and extreme pH (pH 2 or 13) (figs. S9 and S10) further confirming their colloidal stability in diverse aqueous conditions.

To study the solution conditions for creating this Janus nanostructure, we investigated the roles of the reactant concentration as well as pH, buffer, surface stabilizer, temperature, and reaction time. The results show that varying the concentration of AuNPs, BDT, or SDS only changes the size of the pBDT patch but not its asymmetrical growth pattern (Fig. 1E, figs. S11 and S12, and table S1). The basic pH (e.g., from pH 7 to > 12) facilitates the formation of the patch while acidic media cause aggregation of the nanoparticles and a low yield of Janus nanoparticles (fig. S13). This is likely due to the low solubility of BDT monomers in acid environments.[33]

The tertiary amine of bicine may interact with gold substrates, and thus we investigate this possible effect using a primary amine-containing buffer (i.e., TRIS buffer) and amine-free media (i.e., NaOH solution). The results show that the amino groups have no contribution to the final morphology due to their weak binding with gold (fig. S14). Other surface ligands (i.e., sodium citrate and sodium dodecylbenzenesulfonate) and reaction temperatures (i.e., 50 °C) can still produce Janus structures (figs. S15 and S16). The time interval between the addition of BDT and Au was investigated showing that Janus nanoparticles of similar patch dimension were obtained within a 1-h window after adding BDT (figs. S17 and S18). Collectively, this approach offers a robust way to synthesize patchy Janus nanoparticles.

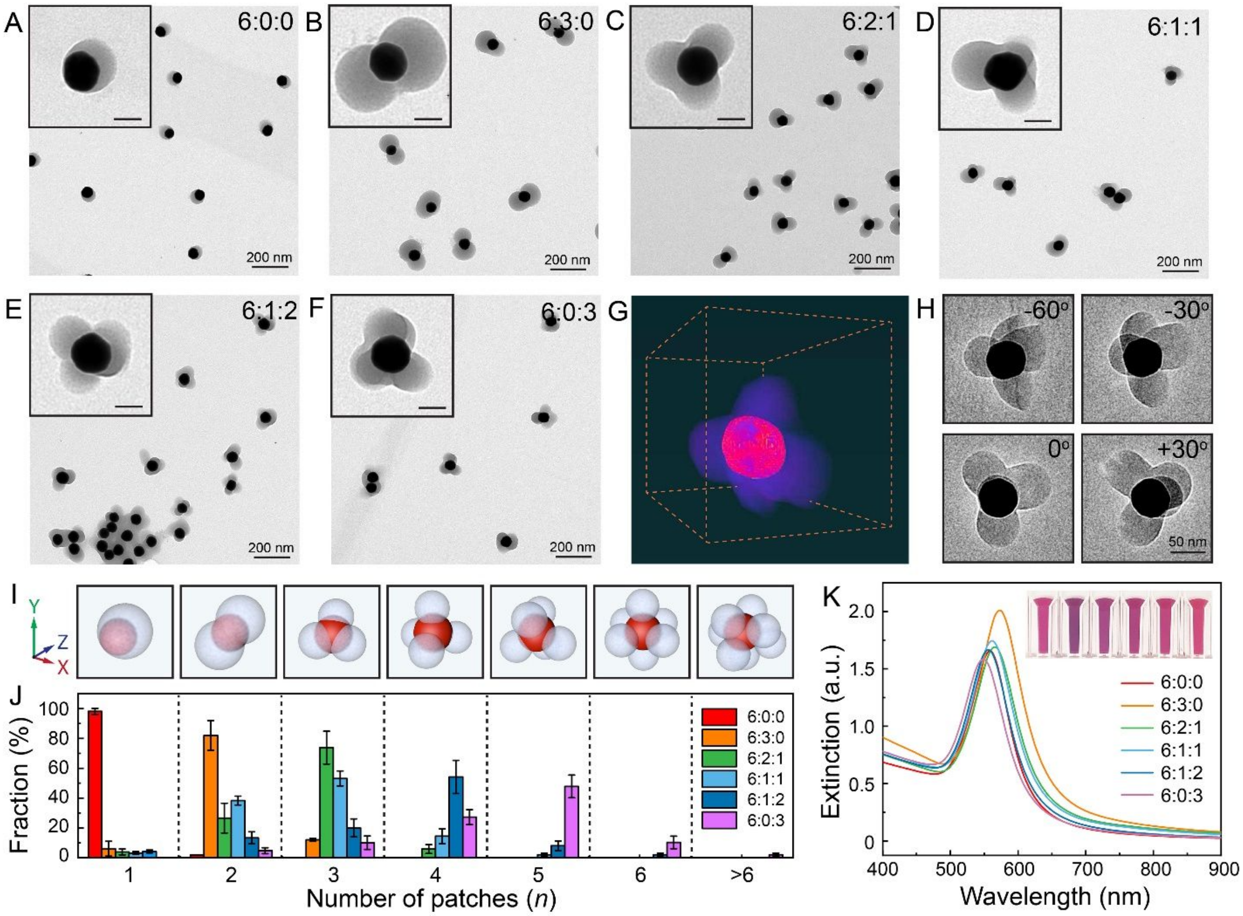

**Fig. 3. Modulating the number of patches using a ternary system.** (**A**-**F**) TEM images of Au-pBDT patchy nanoparticles by adjusting the ratio of ATP and MBA. The molar ratio of BDT:ATP:MBA is 6:0:0 (**A**), 6:3:0 (**B**), 6:2:1 (**C**), 6:1:1 (**D**), 6:1:2 (**E**), and 6:0:3 (**F**). Inset: scale bar is 50 nm. (**G**, **H**) 3D electron tomography reconstruction of a tetrahedral Au-pBDT nanoparticle and corresponding TEM images at different tilting angles. (**I**) Schematic illustration of different patchy nanoparticles. (**J**) Population distribution of nanoparticles with different patch numbers in each stoichiometric ratio. The error bars represent the standard deviations: 50 particles were analyzed, and each experiment was run in triplicate. (**K**) UV–vis spectra and photography of Au-pBDT patchy nanoparticles with differing ligand ratios.

Previous atomistic simulations suggested that the competing binding and mobility of multiple thiol-carrying small molecules on a gold surface can induce ligand segregation.[12, 34] Therefore, we speculated that introducing a second thiol can alter the ligand distribution and change the symmetry of the pBDT patch patterns. Four BDT analogues were chosen: 4-methylbenzenethiol (MBT), 4-mercaptophenol (MCP), 4-mercaptobenzoic acid (MBA), and 4-aminothiophenol (ATP) (Fig. 2A-D). These molecules alone do not produce obvious patches on the surface of the AuNPs (fig. S19). Surprisingly, the 3D morphology of the patches changes drastically from Janus to a dimer or octahedral conformation when the AuNPs were incubated with ATP or MBA for 10 min before adding BDT, respectively (the molar ratio of BDT to the second thiol-carrying molecule is 6:1). In contrast, the addition of MBT or MCP does not change the patch morphology and retains the Janus structure (Fig. 2A-D and fig. S20). We reason that the small ligand pattern on AuNPs varies according to the charge and polarity of the additional thiol molecules, which subsequently dictates the 3D configuration of the assembled pBDT patches.

To gain further insight into the assembly process, we investigated the dynamic transition of patch configuration in a BDT-ATP system. A three-patch architecture was dominant at the beginning (< 2 h) of the reaction while two linear patches were eventually formed (Fig. 2E and fig. S21). It is likely that the electrostatic repulsion between different patches on the confined Au surface increases as patches grow larger and therefore limits their further growth (fig. S22). To overcome this, the existing small patches dissociate and reorganize into a lager patch to lower the tension among neighbor patches. This dynamic patch formation suggests an autonomous assembly mechanism that balances surface binding affinity, π–π interactions among pBDT molecules, and electrostatic repulsion of the polymeric patches (fig. S22C). The resulting patch structures can be maintained at room temperature for more than three months (fig. S23).

Furthermore, the localization of the Au core in patches can be progressively modulated from eccentric to concentric via non-thiol aromatic dye additives (Fig. 2F-H and fig. S24). While negatively charged fluorescein sodium (Fluo) largely remains the Janus morphology (i.e.,

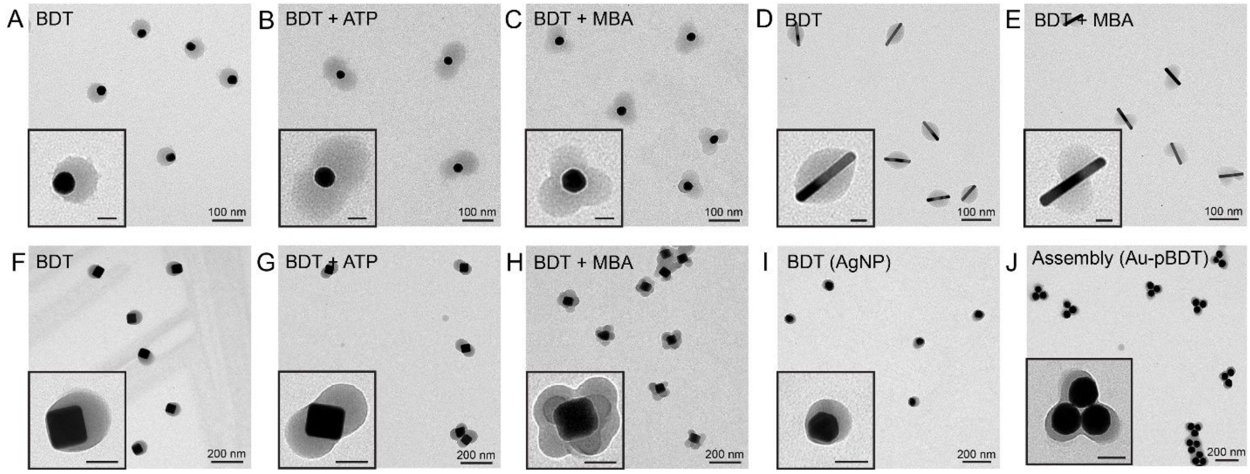

**Fig. 4. Generality of BDT-mediated patch design.** (**A**-**C**) TEM images of tunable patches on 20 nm AuNPs. (**D** and **E**) TEM images of tunable patches on AuNRs. Insets in (**A**-**E**): scale bars are 20 nm. (**F**-**H**) TEM images of tunable patches on 60 nm AuNCs. (**I**) TEM images of patches on AgNPs. (**J**) Trimer-shaped hierarchical assembly with Au-pBDT. Insets in (**F**-**J**): scale bars are 50 nm.

eccentric) (Fig. 2F), zwitterionic rhodamine B (RhB) at a similar concentration can make AuNPs entirely engulfed in a slightly-off centered patch (Fig. 2G). This particle became even more symmetric when a positively charged dye (i.e., azure A chloride, AAC) was used (Fig. 2H). We confirmed above that the amino groups do not modulate the gold interface in this system (fig. S14), and thus the charge of the dye is expected to be the key influence on the patch morphology. MD simulations further suggest that the positively charged AAC tends to form complexes with pBDT due to the electrostatic attraction, and therefore reduce the interfacial energy between Au and pBDT for rapid and conformal deposition (Fig. 2I and J, figs. S25-S30, and tables S2-S6).

Control over the number of patches is an important topic especially for investigating colloidal nanoparticles with valence and directional bonding.[35-36] Since tuning the concentration of the second thiol-carrying molecules did not considerably change the patch morphology (fig. S20), we employed a ternary system to achieve this goal in which a combination of BDT, ATP and MBA were used in tandem. The number of patches obtained per nanoparticle is proportional to the ratio of MBA to ATP (Fig. 3A-F). For example, TEM and 3D tomography reconstruction images clearly showed a tetrahedral structure of patchy Au-pBDT nanoparticles obtained with a stoichiometric ratio of 6:1:2 (i.e., BDT:ATP:MBA) (Fig. 3G and H, and movie S2). All of the products show good monodispersity and the trends of varying ratios for different patch number are further summarized in (Fig. 3I and J, and fig. S31). For example, 82% of Au-pBDT nanoparticles had two patches at a molar ratio of 6:3:0 and 52% of the nanoparticles had four patches at 6:1:2. UV–vis spectra confirm that there is negligible aggregation in the products indicating the high yield of the patchy nanoparticles (Fig. 3K).

The versatility of this patterning strategy was explored for diverse nanoparticles with different sizes, shapes, and compositions. We created similar Janus-, dimer-, and tripod-like patches on 20 nm AuNPs (Fig. 4A-C and fig. S32). Stereoselective patches were also obtained on gold nanorods (AuNRs) and gold nanocubes (AuNCs) (Fig. 4D-H and figs. S33 and S34). Considering that they all have different surface curvatures and crystal facets but result in the similar patch structure (fig. S35),[37-38] we infer that these structural parameters do not play an important role in this method, which is in stark contrast with previous studies.[13] Indeed, the pBDT approach was also applicable to silver nanoparticles (AgNPs) (Fig. 4I and fig. S36) underscoring its utility with a variety of metal nanoparticles. The resulting patchy nanoparticles can be further utilized as building blocks for hierarchical self-assembly (Fig. 4J). We ascribe this unique template-free assembly to a steric interlock mechanism, which can direct the patchy nanoparticles into staggered conformation.[6]

## ■ CONCLUSIONS

We note that previous work has focused on a “grafting-to” strategy while our work demonstrates a “grafting-from” concept harnessing autonomous covalent and supramolecular assembly of BDT molecules. Importantly, off-target patches are very rare due to the thiol-mediated growth: All growth is exquisitely controlled to the nanoparticle surface eliminating the need for elaborate purification. The synthesis is performed in aqueous conditions and forms patches on multiple nanoparticle geometries underscoring its versatility. This method described here is primarily mediated by surface binding of BDT/pBDT via thiol-mediated chemistry. Therefore, the extension of this strategy to other non-metallic particle systems (e.g., polymer and silica) is currently limited and may require additional surface engineering.[39] This aim would be worthy of more efforts and is currently on-going in our group. Combined with available bioorthogonal chemistry and biological recognition (e.g., antigen-antibody interaction, DNA hybridization), we envision that this tunable high-valence patchy nanoparticle will be indispensable in the design of intricate superstructures and further our understanding of bottom-up assembly in natural systems.

## ■ EXPERIMENTAL SECTION

**Synthesis of 60 nm AuNPs.** AuNPs of 60 nm in diameter were prepared using a seeded growth method. For the preparation, AuNPs (seeds) with a diameter of 20 nm were first synthesized. Then, the AuNPs of 20 nm in diameter were used to synthesize AuNPs of 60 nm in diameter. Briefly, 50 mL water was added into a 100 mL round-bottom flask. Then, 2 mL of the seed solution (20 nm AuNPs) and 200 µL of 0.2 M $NH_2OH{\cdot}HCl$ were added to this flask consecutively. Then, 3 mL of 0.1 wt.% $HAuCl_4$ was added dropwise to the solution under vigorous stirring followed by reaction for 30 min at room temperature. A gradual color change from light red to dark red was observed. Finally, the concentration of sodium citrate was adjusted to 1 mM. After reacting for another 2 h, the nanoparticle dispersion was stored at 4 °C for further use.

**Synthesis of Au-pBDT patchy nanoparticles with 60 nm AuNPs.** For a typical synthesis of Au-pBDT nanoparticles, 50 µL of 60 nm AuNPs and 100 µL of 0.5wt% sodium dodecyl sulfate (SDS) were added to 2 mL bicine buffer (pH 8.5, 10 mM). After vigorous stirring for 10 min, 60 µL BDT solution (2 mg $mL^{-1}$ in DMF) was added to the above solution. The reaction was stirred for 20 h. Then, the resulting patchy nanoparticles were purified by centrifugation (1600 *g*, 10 min) to remove the supernatant. The pellets were resuspended in water for future use.

**Synthesis of patchy nanoparticles with a second thiol-carrying molecules.** To induce the surface ligand segregation on AuNPs, a second thiol-carrying molecule was added into the systems: 4-methylbenzenethiol (MBT), 4-mercaptophenol (MCP), 4-mercaptobenzoic acid (MBA), or 4-aminothiophenol (ATP). To validate if those mono-thiol molecules will form patches, 50 µL of AuNPs were added into 2.0 mL bicine buffer with 100 µL 0.5 wt% SDS. After stirring for 10 min, 60 µL of the thiol-carrying molecules were added dropwise. The concentration for each stock solution were 1.75 mg $mL^{-1}$ (MBT) 1.74 mg $mL^{-1}$ (MCP), 2.14 mg $mL^{-1}$ (MBA), and 1.76 mg $mL^{-1}$ (ATP), respectively. The products were collected by centrifugation (1600 *g*, 10 min) after 20 h, and measured by UV-vis spectrometer and TEM.

The binary ligand systems were then employed to modulate the ligand segregation. In a typical synthesis, 50 µL of AuNPs were first added to 0.35 mL water followed by 100 µL 0.5 wt% SDS solution. After stirring for 10 min, different amounts of thiol-carrying molecules in DMF (i.e., 1.75 mg $mL^{-1}$ (MBT), 1.74 mg $mL^{-1}$ (MCP), 2.14 mg $mL^{-1}$ (MBA), or 2.14 mg $mL^{-1}$ (ATP)) were added into the above solution. After gentle stirring for 10 min, 60 µL BDT solution (2 mg $mL^{-1}$ in DMF) was added. After another 5 min of gentle mixing, 1.5 mL bicine buffer (pH 8.5, 10 mM) was added dropwise. The reaction was stirred for 20 h. The resulting patchy AuNPs were then purified by centrifugation (1500 *g*, 10 min) to remove the supernatants. The pBDT-patched AuNPs were resuspended in water for future use. The volume of added thiol-carrying molecules solution was adjusted (i.e., 10 µL, 30 µL, and 60 µL) to investigate the effect of concentration of second ligand for the final patchy morphology.

**Synthesis of patchy nanoparticles (60 nm AuNPs) in a ternary system.** To modulate the number of patches on single AuNP, we concurrently introduced two thiol-carrying molecules (i.e., MBA and ATP) in the system because ATP can induce two patches and MBA can induce more than 5 patches on AuNPs. In a typical synthesis, 50 µL of AuNPs were first added to 0.35 mL water followed by 100 µL 0.5 wt% SDS solution. The mixture was stirred for 10 min. Meanwhile, MBA (2.14 mg $mL^{-1}$) and ATP (1.76 mg $mL^{-1}$) were mixed first to prepare the mixed ligand solution (30 µL). The mixed ligand solution was then added dropwise into the AuNP solution. After gentle stirring for 10 min, 60 µL BDT solution (2 mg $mL^{-1}$ in DMF) was added. After another 5 min, 1.5 mL bicine buffer (pH 8.5, 10 mM) was added dropwise. The reaction was stirred for 20 h. The resulting patchy AuNPs were then purified by centrifugation (1500 *g*, 10 min) to remove the supernatants. The pBDT-patched AuNPs were resuspended in water for future use. We also compared the results with patchy nanoparticles prepared from 60 µL mixed ligand solution (data not shown here), and we found that using 30 µL mixed ligand solution can produce uniform morphology and less free pBDT nanoparticles in the solution. The average number of the patches on individual nanoparticles were summarized based the TEM images of 50 nanoparticles, and the final results were calculated in triplicate batches of particles.

## ASSOCIATED CONTENT

**Supporting Information**. Detailed experimental procedures for different patchy nanoparticles, characterization of patchy nanoparticles, detailed simulation results, and movies of 3D electron tomography reconstruction. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interests.

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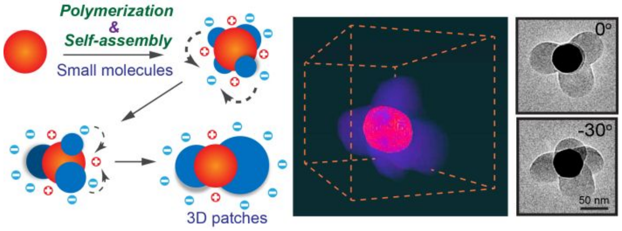
Polymerization
&
Self-assembly
Small molecules
3D patches
0°
-30°
50 nm