Advances in Chiral Construction and Biochemical Applications of Chiral Gold Nanoparticles

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Abstract: Chiral gold nanoparticles (AuNPs) leverage nanoscale geometric asymmetry to amplify chirality-encoded functions, bridging molecular stereochemistry with plasmonic material properties. Their chirality arises from helical surface nanostructures or ligand-induced asymmetry, enabling strong chiroptical responses via plasmon-exciton coupling and circular dichroism enhancement. Bottom-up synthesis strategies—such as chiral ligand templating (e.g., cysteine, peptides) directing atomic lattice distortion, enantioselective growth on chiral seeds, and plasmon-guided self-assembly of achiral units into supramolecular helices—allow precise control over 3D chiral geometries. These architectures interact selectively with biomolecules through stereocomplementary interfaces, enhancing enantiomer discrimination (e.g., drug detection at ppm levels) and enabling chirality-dependent cellular uptake. In photomedicine, chiral AuNPs exploit plasmon-enhanced circularly polarized light absorption for targeted photothermal therapy and ROS generation, while their asymmetric catalytic sites promote stereoselective synthesis. However, challenges include weak interfacial chirality transfer, limited dynamic reconfiguration of chiral fields, and signal attenuation in biological environments. Advancing in situ chiral monitoring (e.g., chiral SERS) and adaptive chirality modulation via stimuli-responsive ligands could unlock applications like real-time chiral biomarker tracking and logic-gated nanomedicine. Integrating nanoscale chirality with quantum plasmonics further positions chiral AuNPs as multifunctional platforms for beyond-molecular stereochemical engineering.

1 INTRODUCTION

Chirality, a geometric property describing non-superimposable mirror-image configurations, manifests as left- and right-handed enantiomers. A striking example is the Chrysina gloriosa beetle, whose chiral exoskeleton exhibits polarization-dependent coloration—vivid under left-handed circularly polarized light but muted under right-handed polarization—demonstrating chirality-driven optical anisotropy. While early chirality research focused on biomacromolecules (proteins/DNA), advances in nanophotonics have enabled chiral engineering in inorganic systems. AuNPs overcome traditional limitations: Unlike biomolecules requiring millimolar concentrations for detectable circular dichroism, AuNPs amplify chiroptical signals 10^3–10^6-fold via localized surface plasmon resonance (LSPR) at 500–1200 nm wavelengths. This LSPR-enhanced chirality originates from asymmetric electron oscillations that magnify molecular asymmetry into macroscopic optical effects, achieving label-free chiral detection at sub-nanomolar levels, surpassing conventional spectroscopy by three orders of magnitude. To harness this plasmonic amplification, researchers now engineer programmable chiral architectures through innovative nanofabrication approaches.

By integrating chiral inducers (e.g., thiolated peptides, helical polymers) with synthetic strategies—including seed-mediated chiral growth, ligand-directed assembly, and plasmon-coupled superlattice engineering—researchers achieve precise control over AuNP chirality. These systems

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unlock transformative applications spanning enantioselective recognition through differential molecular adsorption, asymmetric photocatalysis mediated by spin-polarized hot carrier dynamics, and chirality-programmed tumor therapies that synergize circularly polarized light penetration with stereospecific immune modulation, each leveraging nanoscale chiral topology to manipulate light-matter interactions at subwavelength scales.

Recent advances in chiral AuNP synthesis have enabled precise control over geometric configurations and chiroptical properties through chiral inducers and innovative strategies like seed-mediated chiral growth, ligand-directed assembly, and plasmon-coupled superlattice engineering. These methods yield helical, twisted, or chiral-groove nanostructures with enhanced circular dichroism (g-factors: 0.1–0.3). Leveraging LSPR, chiral AuNPs amplify optical signals by 10^3–10^5-fold, surpassing traditional molecular chirality detection limits. Applications include enantioselective recognition via differential molecular adsorption, asymmetric photocatalysis with spin-polarized hot carriers (85% ee in CO_2 reduction), and chirality-dependent photothermal therapies, achieving >40% tumor ablation efficiency in vivo. These breakthroughs highlight chiral AuNPs as transformative tools in nanophotonics, catalysis, and biomedicine, bridging fundamental chirality studies to functional device engineering.

2 CHIRALITY SOURCES OF CHIRAL GOLD NANOPARTICLES

2.1 Ligand-Induced Chirality

Surface plasmon-coupled chiral enhancement has emerged as a transformative strategy for amplifying chiral signatures and shifting them into the visible spectral region. Studies have elucidated that intimate coupling between metal nanoparticles and chiral biomolecules enables UV chiral signatures to couple with LSPR frequencies (Zhang & Govorov, 2013). This phenomenon arises from "hotspot" regions between nanoparticles, which amplify local electric fields through plasmonic coupling. Building on this, Kneer et al. (2018) positioned DNA between gold/silver nanoparticles (spherical/rod-shaped) and used computational modeling to confirm that hotspot-mediated field enhancement in assemblies can amplify molecular chiral signals by orders of magnitude compared to single particles. The study highlighted how nanoparticle morphology and spacing modulate plasmonic coupling and chiral signal strength (Figure 1 a-b).

Zhang et al. (2023) reported chiral signal transfer from thiol molecules to gold nanorod assemblies by incorporating chiral thiol molecules into side-by-side assemblies of achiral gold nanorods. Their study revealed that while chiral thiol molecules played a critical role in generating chiral signals in the assemblies, the achiral CTAB ligands on gold nanorod surfaces also exerted significant influence. The formation of dense chiral ligand shells was found to facilitate efficient chiral transfer from adsorbed thiol molecules to the nanorod assemblies, enabling circular dichroism (CD) signal amplification. This work provided guidelines for chiral signal enhancement through manipulating achiral surface ligands.

Ligand-induced chirality represents a classic approach for transferring molecular chirality to the nanoscale and remains the most widely used method for constructing chiral nanoparticles. Such chiral nanomaterials have found extensive applications in chiral sensing, detection, and biomedical research. However, nanoparticles prepared with this method generally exhibit low anisotropy factors and pose challenges for characterization by electron microscopy, limiting mechanistic understanding of their chiral origination.

2.2 Colloidal Self-Assembly

Plasmonic CD signals in the visible range can be induced by coupling chiral small molecules with gold nanoparticles; however, this methodology encounters significant limitations. Specifically, the strategy demands both the well-ordered orientation of chiral ligands on nanoparticle surfaces and spectral overlap between molecular vibrations and plasmonic modes, which often results in suboptimal coupling efficiency and correspondingly weak CD responses. Hopefully, Chiral ligand-directed self-assembly yields rather enhanced CD-active chiral nanostructures.

In Fei's (2019) experiment of modifying AuNP colloidal solutions with NaC, due to the amphiphilic nature of NaC molecules, the NaC molecules adsorbed on the surface of gold nanoparticles can interact with those on the surface of adjacent nanoparticles through hydrophobic forces leading to the aggregation of nanoparticles. It is noteworthy that when the concentration of NaC is relatively high (24 mM), the generated AuNPs tend to be smaller. Sun et al. (2016) prepared a chiral gold nanohybrid dimer architecture. This dimeric system consists of two gold nano-ellipsoids: one functionalized with a telomerase primer and the other conjugated with linker-complementary DNA strands. These nanostructures self-assemble into a scissor-shaped configuration under linker DNA mediation. The resulting dimer exhibits robust chiral optical responses in the visible spectrum, enabling intracellular telomerase activity quantification (Figure 2a-b).

In addition, DNA Origami, proposed by Rothemund (2006), introduced a novel self-assembly approach. And Liu and Ding (2012) further developed adjustable helical structures by curving 2D DNA origami into nanotubes and positioning gold nanospheres (Figure 2c). Liu et al. (2016) created circular 3D assemblies by combining four curved DNA origami units, resulting in left/right-handed helices with 24 spirally arranged particles (Figure 2 d). These multi-unit constructs generated stronger CD responses than monomeric counterparts.

By transforming disordered ligand-NP systems into structured, highly active chiral plasmonic platforms, colloidal self-assembly paves the way for advanced applications in ultrasensitive sensing, nanophotonics, and beyond, where tunable and robust optical properties are critical.

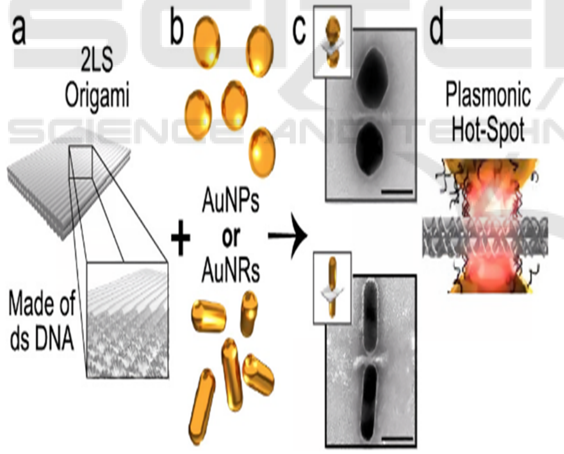

Figure 1: (Color online) Chiral induction by ligands. (a) An origami sheet composed of multiple parallel b-type DNAs; (b) DNA-functionalized gold nanospheres or nanorods; (c) TEM images of dimer structures of gold nanospheres or nanorods; (d) Schematic representation of a "hot spot" region between two nanoparticles generating a strong electric field (Kneer et al., 2018).

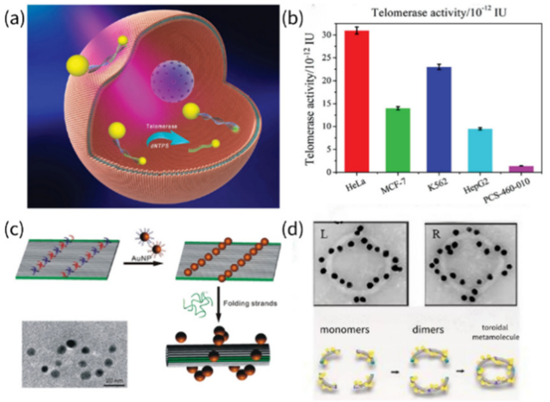

Figure 2: (Color online) Chiral induction of AuNPs by self-assembly. (a) Schematic of intracellular quantitative detection of telomerase using gold heterodimers. (b) Corresponding data of telomerase activity measured in various cells with this nanoplatform. (Sun et al., 2016) (c) DNA origami nanoparticle helices. (Liu and Ding, 2012) (d) TEM diagram of the ring structure of left and right-handed nanoparticles. (Liu et al., 2016)

2.3 Intrinsic Chiral Crystal Structure

Despite significant advancements in chiral gold nanomaterials through coupling and self-assembly strategies, persistent challenges—including inadequate chiral induction and structural instability, particularly in complex DNA-templated protocols—necessitate alternative approaches. Direct synthesis of inherently chiral AuNPs with precisely controlled morphologies has emerged as a critical frontier to address these limitations.

Innovative work by Wang et al. (2014) revealed that asymmetric chiral cores can exist in gold clusters, distinct from symmetric cores stabilized by chiral ligand shells. Using a tetradentate organophosphorus ligand (PP3), they synthesized chiral Au20 nanoclusters via direct reduction. Structural analysis revealed the Au20 core comprises two subclusters: an icosahedral Au13 (orange spheres) and a Y-shaped Au7 (green spheres) in Figure 3 (a). The helical arrangement of the Y-shaped Au7 subcluster imparts C3 symmetry to the entire Au20 core, providing definitive structural evidence for inherently chiral gold clusters. The multidentate phosphine ligands enhance cluster stability through chelation, opening a path to design gold clusters with purely inorganic chiral cores for applications in catalysis and sensing.

Lee et al. (2018) demonstrated another breakthrough by fabricating chiral propeller-shaped gold nanoparticles (with g-factors ≈ 0.2) using glutathione-mediated growth on octahedral seeds (Figure 3 b-c). The particle's slit-rich architecture generates intense electromagnetic coupling between adjacent nanosheets, amplifying CD responses. This strategy induces helical morphologies in nanoparticles, presenting a scalable method for 3D chiral structures with high optical activity.

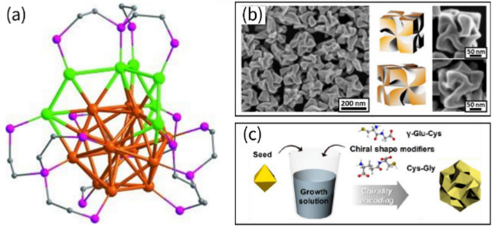

Figure 3: (Color online) AuNPs with structural chirality. (Wang et al., 2014) (a) Au20 model: The purple spheres are phosphorus atoms, and the gray spheres are carbon atoms. (b-c) SEM images and geometric models. (Lee et al., 2018).

3 ADVANCES IN THE APPLICATION OF CHIRAL AUNPS

3.1 Enantiomer Recognition

Conventional molecular chirality exhibits suboptimal signal intensity in the visible spectral region, hindering its practical implementation in chiral sensing applications. However, the synergistic combination of chiral molecules with plasmonic AuNPs generates enhanced chiral signals in the visible range, which are highly responsive to geometric variations of nanoparticles and environmental changes. This property enables development of ultrasensitive chiral biosensors.

Kang's group (2010) fabricated an electrochemical sensor using penicillamine-functionalized AuNPs (Pen-AuNPs) for enantioselective recognition of 3,4-dihydroxyphenylalanine (DONP). Small-sized Pen-Au NPs with a single enantiomeric ligand only promote the redox reaction of one enantiomer of DONP. The study also found that the size of Pen-Au NPs affects their enantioselectivity performance. Specifically, smaller Pen-Au NPs show better selectivity for L- and D-DOPA.

Tang et al. (2025) utilized L-cysteine-functionalized AuNPs as colorimetric probes for rapid R/S-phenylalaninol and R/S-ibuprofen detection, which could develop into purity detection so as to ensure drug therapeutic effects while limiting side effects. And it is assumed that when chiral AuNPs recognize enantiomers, non-covalent interactions induce energy resonance transfer on the surface of nanomaterials, leading to their aggregation and color changes. Li et al. (2022) synthesized helical gold nanoparticles with intrinsic chirality and constructed a chiral sensor for discriminating L-tyrosine from D-tyrosine. Notably, differential pulse voltammetry revealed nearly sixfold differences in peak currents between tyrosine enantiomers, enabling accurate determination of enantiomeric purity and composition. The chiral electrode developed also enabled quantification of L-tyrosine in pharmaceutical capsules, opening new avenues for chiral enantiomer recognition in biomedical and pharmaceutical fields.

3.2 Asymmetric Catalysis

Chiral metallic nanomaterials exhibit unique size-dependent optical and catalytic properties distinct from molecular-scale chirality, offering transformative opportunities in asymmetric organic synthesis.

Cui (2015) advanced chiral nanocatalysis by incorporating a cytosine-derived amphiphilic ligand (C_8H_4Cyt) into AuNP systems. These chiral AuNPs displayed superior catalytic activity for p-nitrophenol reduction by sodium borohydride at $\geqslant 30$ °C, outperforming conventional AuNPs in both stability and recyclability. The chiral architecture mitigated aggregation, maintaining activity even after long-term storage. Notably, larger chiral nanomaterials experienced less activity due to decreased accessible reaction sites, highlighting needs of finer AuNPs producing method in plasmonic catalysis.

Tan and colleagues (2022) made use of chiral Au@CdS core-shell nanostructures for asymmetric photocatalytic water splitting while from Negrín-Montecelo group (2022), chiral Au and TiO_2 combination irradiated with polarization-matched circularly polarized light (CPL) exhibit approximately 2.9-fold higher catalytic efficiency compared to mismatched polarization conditions, demonstrating strong selectivity for enantiomeric interactions. (Figure 4a-b).

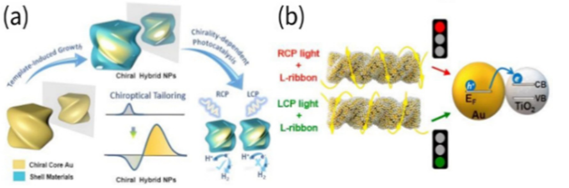

Figure 4: (a) Chirality-dependent hydrogen production efficiency in water splitting. (Tan et al., 2022) (b) Au and TiO2 for chiral photocatalytic applications. (Negrín-Montecelo et al., 2022)

3.3 Tumor Photothermal Therapy

Accumulating evidence highlights the profound impact of chirality on nanomaterial performance in biological systems. In tumor phototherapy using chiral noble-metal nanostructures, Gao et al. (2017) engineered DNA-templated self-assembled gold core-shell satellite nanostructures (Figure 5). Under circularly polarized light irradiation, these constructs exhibited enhanced reactive oxygen species (ROS) generation (roughly two-fold higher than linear polarization), underscoring chirality's role in optimizing photodynamic therapy. Additionally, chiral architecture modulates nanomaterial biocompatibility and downstream signaling pathways, overcoming challenges in cancer treatment. Xu et al. (2022) synthesized AuNPs with record-high g-factors (0.4), demonstrating chiral-dependent immune activation: left-handed NPs induced stronger dendritic cell maturation and pro-inflammatory cytokine expression compared to right-handed counterparts. This disparity arises from differential binding affinity to G-protein-coupled receptors and accelerated endocytosis rates for left-handed NPs.

In the realm of chiral materials, a larger g-factor implies less energy dissipation of light energy, signifying a greater capacity for controlling light polarization. As depicted in Figure 6, the chiral Au Helicoids nanoparticles prepared by Weng (2023) possess a wide-ranging optical absorption spanning from 550 to 1100 nm and a relatively elevated g-factor. When excited by 808-nm near-infrared CPL, the photothermal efficiency of the chiral Au helicoid nanoparticles demonstrates a distinct chiral disparity. And the disparity primarily stems from HeLa cells' higher endocytosis efficiency for L-Au Helicoids nanoparticles compared to D-Au Helicoids nanoparticles. In contrast to traditional photothermal therapy, which frequently inflicts damage on healthy cells due to the employment of high-power lasers or prolonged radiation, chiral photothermal therapy can manifest efficient light-conversion properties and selective light-absorption characteristics within the near-infrared region. This can substantially minimize the damage to normal cells (with a cell survival rate of around 90.00%) and enhance the inactivation efficiency of cancer cells (94.95%), which means it can be harnessed as a secure photothermal conversion agent for the research on the photothermal inactivation of tumor cells.

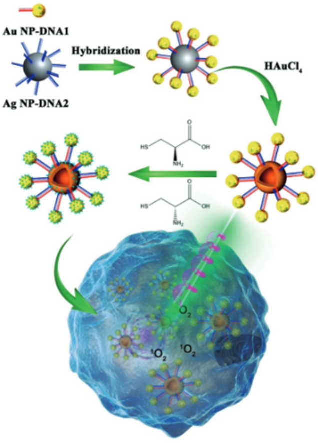

Figure 5: (Color online) Schematic diagram of self-assembled shell satellite nanostructures as chiral photodynamic therapeutic agents. (Gao et al., 2017)

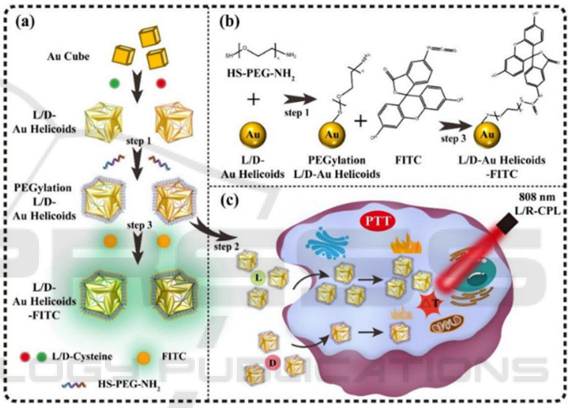

Figure 6: (Color online) Schematic diagram of surface modification of L-/D-Au Helicoids nanoparticles and their photothermal effects under CPL excitation at 808nm. (Weng, 2023)

4 CONCLUSION

This review systematically evaluates the synthetic strategies and emerging applications of AuNPs. Chiral architectures in AuNPs can arise from template-directed growth (e.g., helical seed-mediated synthesis), molecular imprinting with chiral ligands, or supramolecular self-assembly. These design principles enable advanced applications in stereoselective sensing, asymmetric catalysis, and synergistic photothermal cancer therapy.

Notwithstanding significant progress in chiral AuNP synthesis and bioanalytical applications, critical challenges persist. Current methods for producing AuNPs with uniform chiral configurations and robust chiroptical activity remain inefficient and scalable, while most plasmonic responses occur in the visible spectrum, limiting deep-tissue penetration in biomedicine. Additionally, comprehensive biocompatibility assessments—encompassing long-term stability, toxicity profiles, and clearance mechanisms—are underdeveloped. In vitro models often fail to recapitulate in vivo complexities, necessitating sophisticated in vivo studies to characterize size/shape-dependent biodistribution and enantioselective biological effects.

To address these challenges, future research should focus on developing Chiral AuNPs with enhanced near-infrared (NIR) chiroptical activity, advancing surface functionalization for non-toxicity and targeted specificity, elucidating cellular uptake mechanisms, and fostering interdisciplinary collaboration to bridge fundamental synthesis with translational precision medicine applications. Despite these hurdles, the dynamic field of Chiral AuNP research continues to hold immense potential for breakthroughs in biochemical research and clinical practice.

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All the authors contributed equally and their names were listed in alphabetical order.

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