Toward Greener Nanosynthesis

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Contents

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1. Introduction

During the past decade, scientists have developed techniques for synthesizing and characterizing many new materials with at least one dimension on the nanoscale, including nanoparticles, nanolayers, and nanotubes.[1] Still, the design and synthesis (or fabrication) of nanoscale materials with controlled properties is a significant and ongoing challenge within nanoscience and nanotechnology.

Nanoscience is still largely in the "discovery phase" wherein new materials are being synthesized (using any means available) on small scales (hundreds of milligrams or less) for testing specific physical properties. Typically, during this phase of development of a new technology area, researchers focus mainly on identifying new properties and applications. As a result, the examination of any unintended properties of the material (e.g., environmental or health hazards) or concerns about hazards or efficiencies of the production process is often deferred. Given the anticipated wide application and distribution of these materials in commerce, consideration of the materials design, processes, and applications that minimize hazard and waste will be essential as nanoscience discoveries transition to commercialized products of nanotechnology.

The nature of engineered nanomaterials and their proposed uses provides compelling reasons for the implementation of green chemistry in the development of the new materials and applications. The technology is early in development and expected to be widely applied and distributed. These materials are expected to (i) exhibit new size-based properties (both beneficial and detrimental) that are intermediate between molecular and particulate, (ii) incorporate a wide range of elemental and material compositions, including organics, inorganics, and hybrid structures, and (iii) possess a high degree of surface functionality. Assessment of the potential toxicological and environmental effects of nanoscale materials before they are accepted as mature technologies presents an opportunity to minimize putative negative consequences[2] from the outset and ultimately lead to the

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design of higher performance materials. Understanding the structure−function relationships that relate specifically to nanomaterials could lead to new "design rules" for producing benign, high-performance nanoscale substances.

Given that green chemistry has been employed successfully in the preparation of highly functionalized products (e.g., pharmaceuticals) that have a strong analogy to functionalized nanomaterials that have been proposed for a range of future applications, one would expect successful application of this approach for these nascent materials. Application of green chemistry to nanoscience should also prove beneficial in developing production-level commercial scale materials. The development of high-precision, low-waste

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methods of nanomanufacturing will be crucial to commercialization. In addition to providing enhanced research and development strategies, green chemistry offers an opportunity to improve public perception of nanoscience, as this approach is relatively easy to explain and can be used to convey a responsible attitude toward the development of this new technology. For these reasons, green chemistry can play a prominent role in guiding the development of nanotechnology to provide the maximum benefit of these products for society and the environment.

In this review, we explore the application of green chemistry principles to the field of nanoscience. We first define *green nanoscience*[3] and offer examples of the ways in which green chemistry has been, or can be, applied to the design of greener products, processes, and applications. Because the vast majority of the research in this area has, thus far, involved developing greener approaches and processes, this review will focus on nanosynthesis. We further focus the review on those methods that involve wet-chemical approaches to the production, functionalization, purification, and assembly of nanoparticle building blocks. The bulk of the materials covered within the review are ligand-functionalized inorganic nanoparticles, due to the fact that these have been the most prevalent in the literature to date. Throughout the review, we strive to examine how the application of green chemistry principles to nanoscience can guide technological progress within this emerging field. Because this is an emerging area of technology, we identify future research needs and directions throughout the review.

A number of outstanding reviews on the synthesis and assembly of functionalized nanoparticles have already been published.[4−7] This review does not intend to provide comprehensive coverage of these topics but will focus instead on the aspects of these processes that are most relevant to green chemistry. However, publications in nanoscience that identify the environmentally benign aspects of the work are

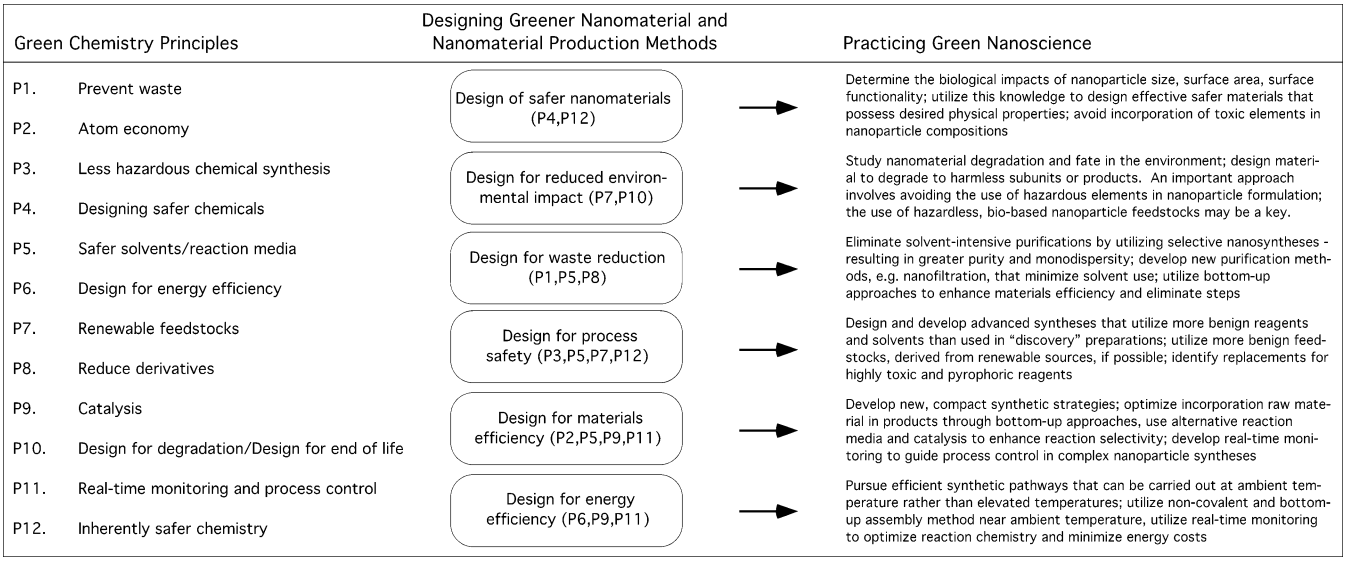


Figure 1. Translating the 12 green chemistry principles for application in the practice of green nanoscience. The principles are listed, in abbreviated form, along with the general approaches to designing greener nanomaterials and nanomaterial production methods and specific examples of how these approaches are being implemented in green nanoscience. Within the figure, P*X*, where $X = 1-12$, indicates the applicable green chemistry principle.

just starting to appear, so we have attempted to identify and highlight the examples from the literature that illustrate greener nanosynthesis concepts and techniques and that help inform the research needs within this emerging field.

1.1. Green Nanoscience

Green chemistry is "the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture, and application of chemical products".[8] The 12 principles of green chemistry (originally defined by Anastas and Warner[8] and summarized in Figure 1) have now been applied to the design of a wide range of chemical products and processes with the aims of minimizing chemical hazards to health and the environment, reducing waste, and preventing pollution. Application of these principles has reduced the use of hazardous reagents and solvents, improved the material and energy efficiency of chemical processes, and enhanced the design of products for end of life. Employing these principles toward nanoscience will facilitate the production and processing of inherently safer nanomaterials and nanostructured devices.

Green nanoscience/nanotechnology involves the application of green chemistry principles to the design of nanoscale products, the development of nanomaterial production methods, and the application of nanomaterials.[3] The approach aims to develop an understanding of the properties of nanomaterials, including those related to toxicity and ecotoxicity, and to design nanoscale materials that can be incorporated into high-performance products that pose little hazard to human health or the environment. It strives to discover synthesis/production methods that eliminate the need for harmful reagents and enhance the efficiency of these methods, while providing the necessary volume of pure material in an economically viable manner. It also provides proactive design schemes for assuring the nanomaterials produced are inherently safer by assessing the biological and ecological hazards in tandem with design. Finally, it seeks applications of nanoscience that maximize societal benefit while minimizing impact on the ecosystem. In this way, green nanoscience guides materials development, processing, and application design throughout the life cycle, starting with raw material selection through end-of-life.

1.2. Application of the Principles of Green Chemistry to Nanoscience

Nanoparticles or other nanomaterials that exhibit size-dependent properties are already finding application in products ranging from consumer healthcare products to high-performance composites.[9] In addition, a growing number of applications of nanoscience/nanotechnology are being developed that promise environmental benefit, including new catalysts for environmental remediation,[10] cheap and efficient photovoltaics,[11] thermoelectric materials for cooling without refrigerants,[12] lightweight (and thus energy-conserving) nanocomposite materials for vehicles,[13] miniaturized devices that reduce material consumption, and sensors that eliminate the need for (often) wasteful wet-chemical analyses. Nanoscale sensors[14] can also offer faster response times and lower detection limits, making on-site, real-time detection possible. New manufacturing strategies that are additive, rather than subtractive, such as functional group directed processes involving self-assembly, can reduce energy requirements and waste generation. The use of self-assembly methods also enables materials disassembly, incorporating a potential design for end-of-life. To realize new nanotechnologies that pose little harm to human health or the environment and to develop technologies that can be used to improve or protect the environment, it is desirable to design and use greener nanomaterials and develop greener nanoproduction methods.

Nearly all of the principles of green chemistry can be readily applied to the design of nanoscale products, the development of nanosynthesis methods, and the application of nanomaterials (see Figure 1). In nearly every case, several of the principles can be applied simultaneously to drive the best design or solution. We will first discuss how the principles *guide* the design and application of nanoscale materials. Next, we describe how the principles *apply* to design, application, and production of nanoscale materials.

Principles of Greener Nanomaterial Design. Three of the 12 principles (as shown in Figure 1) relate directly to

nanomaterial design and the application of these materials toward nanodevices. These are principle 4 (Designing Safer Chemicals), principle 10 (Design for Degradation/Design for End of Life), and principle 12 (Inherent Safety). In some cases, self-assembled nanoscale systems might be disassembled for reuse in new devices. Application of principle 4 to product design involves considering the structural features of the nanomaterial (i.e., the size, shape, composition, and surface chemistry) that dictate its health hazards (e.g., toxicity) as well as its physical properties. In order to routinely implement this design approach, improved understanding of the structure−activity relationships for nanomaterials is needed. The rich structural diversity of nanomaterials provides significant opportunities to tune and optimize the physical and toxicological properties.

Although a significant body of research exists on environmental and health effects of ultrafine particles, there is still a lack of toxicological data regarding the effects of engineered nanomaterials on both human health and the environment. Ultrafine particle data show that materials such as silicates, asbestos fibers, and, to a lesser extent, carbon black and titanium dioxide can cause oxidative stress, induce pulmonary inflammation, trigger the release of cytokines, and induce signal transduction pathways.[15] "Nanoparticles" represent intentionally engineered products below 100 nm in diameter with carefully controlled sizes, shapes, and surface chemistries.[16] The unusual properties of nanoparticles (e.g., chemical, optical, or electronic) could lead to adverse biological effects that may be unique compared to larger compositions of the same material. Variations in particle size[17−19] and surface chemistry[15,18] can affect the degree of toxicity. For example, nanoparticles may generate free radicals that can adversely affect biological molecules. Significant differences may exist between the toxicities of nanoparticles and larger particles of the same chemical composition.[2,20] For instance, smaller nanoparticles are more likely to enter the circulatory system and travel throughout the body, lodging in distal organs.[2,15]

Methods developed to analyze toxicity of ultrafine particles may provide a starting point for determining toxicity of engineered nanoparticles, and comparisons can be made in terms of methods of injury (e.g., oxidative stress, inflammatory responses, signal transduction pathways, etc.). Traditional testing and screening strategies may be employed initially, leading to novel detection methods that account for the unique properties of nanoparticles. These include in vitro cellular assays[17,21,22] and biochemical analyses which probe the generation of reactive oxygen species and effects on enzymatic pathways. Using in vitro assays, the route of nanoparticle entry can be determined as well as biochemical effects (protein interactions, DNA damage, gene expression changes, or generation of reactive oxygen species). Genomics and proteomics can track oxidative stress, induction of signal transduction pathways, and apoptosis. Since susceptibility factors vary across a given population based on individual genetic makeup, risk assessment evaluation should accompany information provided by various assays and screens. In vivo studies are essential for identifying potential target organs, travel routes of nanoparticles within the body, or other phenotypic changes. Such studies could lead to reliable methods for tracking and quantifying nanoparticles in cells and whole animals.[23] Additionally, dose−response relationships, calculated using a variety of metrics including mass, number of nanoparticles, and surface area, provide a means of normalizing information gathered from individual toxicology studies. As an example, one study analyzed the cellular uptake of citrate-stabilized gold nanoparticles and found acute effects on cell proliferation, motility, and morphology. Unfortunately, only high concentrations were examined, so no definitive conclusions could be drawn on the toxicity of these nanoparticles,[21] exemplifying that dose−response studies are critical to accurate evaluation of nanoparticles.

Care must be taken in experimental design and analysis of engineered nanoparticles, since the diversity and complexity of nanoparticles can lead to altered toxicity. Drastically different methods may be used to produce similar products, but variations in methodology and reaction route often lead to differences in yields, purity, and side products. For example, carbon nanotubes are routinely mass-produced by at least four methods, leading to compositionally diverse products.[20,24] Thus, engineered nanoparticles should be well characterized, with known size and/or distribution, surface area, shape, solubility, purity, surface chemistry, and physical (e.g., crystal structure), electronic, or optical properties. Using these well-characterized nanomaterials will lead to more accurate assessments of biological and ultimately ecological impacts.

Principle 10 focuses on design related to the environmental impacts of nanomaterials. Here the design criteria aim to reduce harm to the environment from materials that may be released through their application or at the end of their product life. The approach is to design materials that rapidly degrade in the environment, producing innocuous degradation products. In order to implement principle 10, further understanding of the fate and transport of designed nanomaterials in the environment will be needed. Long-term effects of nanoparticles in the air, soil, and water are also important considerations in relation to human health because persistence in the environment is directly proportional to the amount of nanoparticles in use.[19,25] Environmental impacts of nanoparticles are usually considered in terms of toxicity or exposure,[19] but information garnered from the biological studies described above would complement our understanding of the corresponding environmental implications. For example, bioaccumulation in aquatic and terrestrial organisms will aid in developing models for environmental insult, as well as studies from whole animal analyses to in vitro experiments. Taxonomic and genetic susceptibility are also important considerations. Since chronic exposures often impact the environment in assessing ecological risk, long-term studies analyzing a range of sublethal doses should be included. A few studies have looked at the toxicological effects of engineered nanoparticles on fish, *Daphnia magna*, with mixed results.[20,26,27] However, very little is known to date concerning the ecotoxicity or chronic effects of nanomaterials.

Principle 12 addresses the inherent safety of the material being used. For example, nanomaterials that are incorporated into macroscale structures are less likely to be released into the workplace or environment. The high surface area of nanoparticles may lead to higher reactivities, explosions, or fires in large-scale production. Taken together, principles 4, 10, and 12 provide a robust framework for designing nanomaterials with reduced health, environmental, or safety concerns.

Principles of Greener Nanomaterial Production. Green chemistry provides a number of advantages in process development and manufacturing as well as product design.

Many preparations of the building blocks of nanotechnology involve hazardous chemicals, low material conversions, high energy requirements, and difficult, wasteful purifications; thus, there are multiple opportunities to develop greener processes for the manufacture of these materials. Many of the green chemistry principles apply readily to the synthesis or production of nanoscale materials.

Some progress toward greener nanosynthesis has already been made. For example, a more efficient and less hazardous synthesis of metal nanoparticles has been developed, producing greater amounts of particles, in less time, under milder conditions, while using less hazardous reagents than the traditional preparation.[28] Metal nanoparticles have been synthesized using intact organisms, such as living plants and microorganisms.[29] Microreactors have been used to synthesize nanoparticles in a rapid, continuous process, resulting in reduced waste, improved energy efficiency, and increased control of product properties.[30] In each of these processes, green chemistry principles have provided strategies for the development of synthetic methods that are more efficient, reduce waste, and have improved health and environmental impacts.

For the foreseeable future, green nanosynthesis will certainly be an iterative process. As greener methods are developed to provide the nanomaterials needed for testing or applications, the demand for enhanced, or more precise, functionality will often lead to new synthetic methods that require use of materials that are less green. Thus, another round of innovation will be required to meet the material needs while reducing hazards and environmental impact. Reducing the biological and ecological hazards can only be met through tandem testing during the "discovery" synthesis phase. At each stage of iteration, compromises may arise; thus, metrics will need to be developed to assess the relative greenness of the competing alternatives. In the long run, as green nanoscience becomes more developed, it should be possible to develop more benign discovery phase syntheses in the first iteration. An illustrative example that is described in more detail in the next section of this review involves the evolution of syntheses for gold nanoparticle production. The classic citrate reduction method is relatively green, involving the formation of gold nanoparticles in water; however, the resulting particles have limited stability and poorly defined surface functionality. To address these shortcomings, syntheses were developed that produced ligand-stabilized gold nanoparticles with well-defined surface chemistry and reactivity, but these preparations involve significantly more hazardous reagents and solvents. These methods are now being gradually improved through the application of the green chemistry principles as described in the next section.

One subset of these principles, *Prevent Waste* (P1), *Safer Solvents/Alternative Reaction Media* (P5), and *Reduce Derivatives* (P8), aims to reduce waste by designing methods that minimize the number of processing steps and the amount of ancillary material (solvents, processing aids) used to carry out those steps. An illustrative example of the application of this set of principles to nanomaterials production involves the fabrication of nanoscale features on a substrate such as a silicon wafer. The traditional strategy for producing these structures is a top-down approach that creates features through a lithographic process involving a significant number of deposition, patterning, etching, and cleaning steps that, in effect, remove material to produce nanoscale structures. This method employs many materials processing and cleaning steps that contribute to the waste stream. The vast majority of the materials used do not end up in the product, therefore resulting in low yields. Alternative greener approaches include additive or bottom-up processes, employing self-assembly reactions or "direct" write deposition to generate and interconnect the structures. Such alternatives eliminate many processing steps, thus minimizing material and solvent use.

Solvent use is of particular concern in the purification and size selection of nanomaterials. Current methods for purification of nanoparticle samples involve washing or extraction to remove impurities. This process typically requires liters of solvent per gram of nanoparticles and is not usually effective in removal of all the impurities. Size selection is essentially a form of purification that consumes solvents in extraction, fractional crystallization, or chromatographic methods used to separate the different sizes. Development of methods to reduce solvent use in purification and size selection remain essential areas of research in nanoscience.

Another subset of the principles [*Atom Economy* (P2), *Catalysis* (P9), and *Real-time Monitoring* (P11)] aims to maximize materials efficiency, i.e., optimizing conversion of raw materials into desired products by enhancing reaction selectivity and efficiency. The concept of atom economy (P2) readily applies to wet-chemical nanomaterial preparations in the same fashion as for other synthetic transformations. However, the concept also applies to the fabrication of extended nanoscale structures that use bottom-up approaches such as self-assembly of molecules or nanoscale subunits into more complex structures. Because these approaches incorporate more of the raw materials in the product than corresponding top-down methods, they have higher atom economy. At the molecular level, however, an improved understanding of the mechanisms of nanomaterial production will be necessary to design processes that maximize atom economy. Catalysis (P9) can enhance materials conversion by enhancing the selectivity of reactions, thereby preventing the channeling of raw material into byproducts. The development of highly selective transformations that can be carried out in the presence of diverse, sensitive functionality is a continuing challenge in nanoscience, as it is in molecular reaction chemistry. Real-time monitoring (P11) of the production and transformation of nanomaterials, though in its infancy, will be one of the keys to enhancing materials conversion in the future. Data from this type of monitoring can be used to optimize reaction conditions (e.g., temperature, time, reactant concentration, solvent) in real time to maximize the yield of product and minimize side reactions.

Four of the principles, *Less Hazardous Reagents* (P3), *Safer Solvents/Alternative Reaction Media* (P5), *Renewable Feedstocks* (P7), and *Inherent Safety* (P12), can be employed to enhance the process safety or reduce the hazards associated with a process. This is an area of active investigation within nanoscience. Many of the "discovery phase" preparations of nanomaterials utilize hazardous reagents (P3, P12) or solvents (P5). There are already a few examples that illustrate the application and benefits of applying these principles to enhance process safety by developing alternatives for toxic and/or inherently hazardous reagents and replacing or reducing the use of hazardous solvents. This is a rich area for investigation, as the demand for larger volumes of nanomaterials increases and new methods for nanomaterial synthesis are developed. In some cases, the use of benign feedstocks derived from renewable sources (P7) may prove

a successful strategy for enhancing safety in nanomaterial production.

The last subset of the principles involves enhancing energy efficiency and includes *Design for energy efficiency (*P6), Catalysis (P9), and *Real-time Monitoring* (P11). Assembly reactions occur under mild conditions with a wide range of suitable materials and synthetic methods to choose from. Bottom-up assembly of nanodevices greatly reduces the number of processing steps, can be accomplished under very mild conditions, and could reduce the chances of particle contamination (reducing reliance on cleanrooms), all contributing to energy savings. In the event that higher temperatures are needed, as is currently the case for a number of nanoparticle preparations, the development of catalysts that can accelerate these reactions may be a useful strategy. Given the complexity of many nanoparticle preparation reactions (requiring simultaneous control of composition, dispersity, shape, and functionality), in most cases careful in situ monitoring of reaction conditions and progress (P11) will lead to energy savings as well as improved product characteristics.

This discussion thus far provides an overview of the broad applicability of the green chemistry principles to nanoscience. Each of the 12 principles provides guidance in the design of safer nanomaterials and greener production of these materials. The bulk of this review will describe the current status and ongoing challenges for greener synthesis and production of nanomaterials within the context of these defining principles.

2. Toward Greener Synthetic Methods for Functionalized Metal Nanoparticles

Many syntheses of nanoparticles have been developed in recent years, in an effort to produce structures that have a specific form and function relevant to a given application. The preparation of functionalized nanoparticles within a green context poses interrelated challenges in terms of maintaining product integrity (such as structure, shape and size dispersity, functionality, purity, and stability) while employing greener methods whenever possible. For example, control over particle size and dispersity may reduce purification requirements by eliminating the need for extensive separations, while the ability to control surface functionalization, intended to enhance particle stability and dictate surface chemistry, solubility, and the degree of particle interactions (see Figure 2), helps to better define the safety

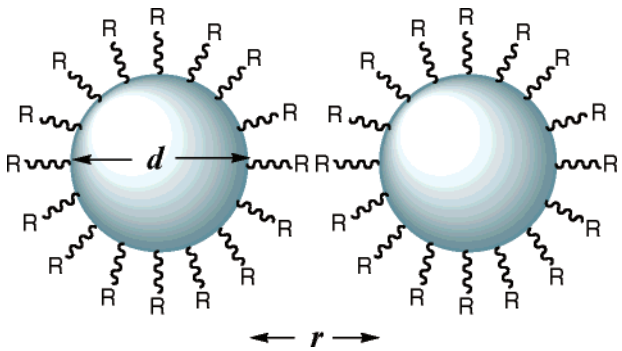


Figure 2. Key properties of nanomaterials. The overall size (*d*) and shape of the particle dictates the optical and electronic properties. A stabilizing shell composed of either covalently bound ligands (depicted above) or associated ions provides stability and solubility. Pendant functional groups define reactivity, while the length of the ligand shell determines the minimum interparticle spacing (*r*).

and reactivity of nanoparticles. Nanosynthesis methods are being refined such that they are convenient and scalable, whether it involves the direct synthesis of a functionalized material or the preparation of a versatile precursor particle whose surface properties can be easily modified to meet the demands of a given application.[5] While a tremendous body of knowledge related to nanosynthesis currently exists, the need for more advanced materials and techniques may bring nanosynthesis back to the discovery phase. Thus, we are presented with a unique opportunity to utilize green chemistry principles while acknowledging existing information, rather than simply retrofitting existing methods to meet greener standards.

To illustrate the status of green nanosynthesis as well as describe the challenges presented by the application of green chemistry to the field of nanoscience, we review the synthesis of noble metal nanomaterials, beginning first with citrate reductions of metal ions, followed by direct synthesis of ligand stabilized materials. Seeded growth approaches are discussed next, as they relate to both spherical and anisotropic particles. Emerging technologies in green nanosynthesis are reviewed, followed by sections describing modifications to nanomaterials that serve not only to impart new functionality but also to allow manipulation of the materials at the nanoscale. Not all of the practices and methods described would be characterized as "green". Indeed, many classic benchmark methods are described with the intent of providing a historical context for the implementation of green chemistry within nanoscience, while more recent reports offer incremental improvements to traditional practices, addressing process challenges, including reducing agent selection, avoiding surfactants, solvent choice, and improving yields, size distribution, and purity. It is by this gradual mechanism that the development of new methods to meet greener standards will occur: without compromise to the overall quality of the nanomaterial products, through continuous effort and revision, rather than as a single revolutionary event.

Direct synthesis involves nanoparticle preparation under conditions where the nanoparticles nucleate and grow, usually by the reduction of metal ions. Nanoparticles are often synthesized in the presence of a ligand or a stabilizer that can bind to the surface of the newly formed particle, offering stability, modifying surface reactivity and possibly arrest of further particle growth, thus offering increased control over nanoparticle size and polydispersity. It is critical that the ligand does not interfere with particle development in an undesirable manner (i.e., by preventing reduction of the metal ion precursor, or inducing the formation of misshaped particles). Typical ligands include phosphines, thiol, and amines, which may be organic or water soluble, depending on the pendant functionality.

2.1. Citrate Reductions

The reduction of gold salts by citrate anions was pioneered by Turkevich over half a century ago, yielding nearly monodisperse, water soluble gold clusters with diameters ranging from 7 to 100 nm.[31,32] Although the synthesis predates green chemistry principles by several decades, it is a rather benign procedure, as the reagents pose little hazard, the preparation does not rely on organic solvents, and few (if any) undesirable side products are generated in the course of the reaction. Revered for its simplicity, requiring only a gold salt (hydrogen tetrachloroaurate, $HAuCl_4$), trisodium citrate, and water, it remains one of the most reliable methods

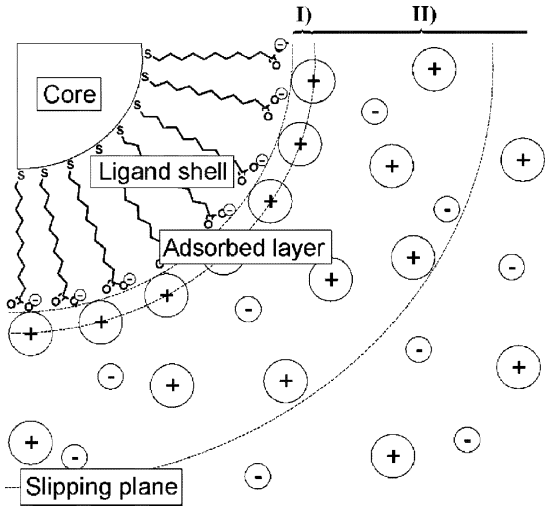


Figure 3. The electric double layer of nanoparticles in solution. The tightly bound Stern layer (or adsorbed layer) prevents aggregation by maintaining interparticle repulsion, while a graduated diffuse layer of ions provides compatibility between the dissolved nanomaterials and their solvent environment. (Reproduced with permission from Laaksonen, T.; Ahonen, P.; Johans, C.; Kontturi, K. *ChemPhysChem* **2006**, *7*, 2143, Figure 1. Copyright 2006 Wiley-VCH.)

of creating large gold nanoparticles. Upon addition to a refluxing solution of $HAuCl_4$, citrate plays the dual role of reductant and stabilizer, reducing Au(III) to colloidal gold clusters, where virtually all of the gold starting material is converted to product, demonstrating excellent atom economy. Excess citrate stabilizes the particles by forming a complex multilayered assembly of anions having various oxidation states, lending an overall negative charge to the surface, thus preventing aggregation. However, these solutions are very sensitive to changes in pH, the ionic strength of the medium, and the presence of other organic materials, thus complicating efforts to modify the surface chemistry by standard ligand exchange techniques. The stability of colloidal and nanoparticle solutions is attributed to the collective effects of van der Waals interactions, electrostatics, and steric forces.[33]

Citrate has proven to be a useful reagent in the synthesis of silver nanomaterials, in addition to gold. Pillai and Kamat investigated the role of citrate ions in the synthesis of spherical and anisotropic silver nanoparticles. Citrate reduction of gold ions leads to the formation of spherical particles, but the analogous reaction with silver ions (see Figure 4) can yield large silver particles (60−200 nm) having a wide range of morphologies, depending upon the reaction conditions, due to citrate's additional role as a complexing agent. The formation of citrate−silver complexes influences crystal growth and even facilitates photochemical reactions that convert spherical silver nanocrystals to triangular nanoprisms. Molar ratios of reagents that produce silver crystals in the size range of 50−100 nm produce much smaller nanocrystals (5−20 nm) if a different reducing agent is used, such as sodium borohydride, suggesting that citrate reductions follow a different mechanism. Studies comparing the impact of various concentrations of citrate ions in reactions where the molar amount of silver ion is held constant demonstrate that excess citrate ions dramatically slow the growth of silver nanoparticles. A series of pulse radiolysis experiments demonstrated that citrate ions complex with Ag^{2+} dimers in the early stages of the reaction, hindering seed formation while promoting slow growth of large nanocrystals. These results contrast sharply with the citrate reduction of gold ions, where increased molar ratios of citrate lead to smaller nanoparticles.[34]

Despite the benign nature of the citrate method, the need for greater stability and precise control over surface chemistry has driven researchers to explore alternative syntheses which may better suit these goals but cannot match the green merits of the citrate route. Later sections in the review will highlight methods which preserve or improve upon the green aspects of the synthesis of more complex materials, and recent efforts to control the surface chemistry of citrate-stabilized gold nanoparticles will be discussed.

2.2. Direct Synthesis of Ligand-Stabilized Nanoparticles

A wide range of materials can be generated by reducing metal ions in the presence of a capping agent, providing libraries of diverse materials useful for determining the structure−function relationships essential to understanding potential health and environmental impacts, aside from creating materials for targeted applications. The direct

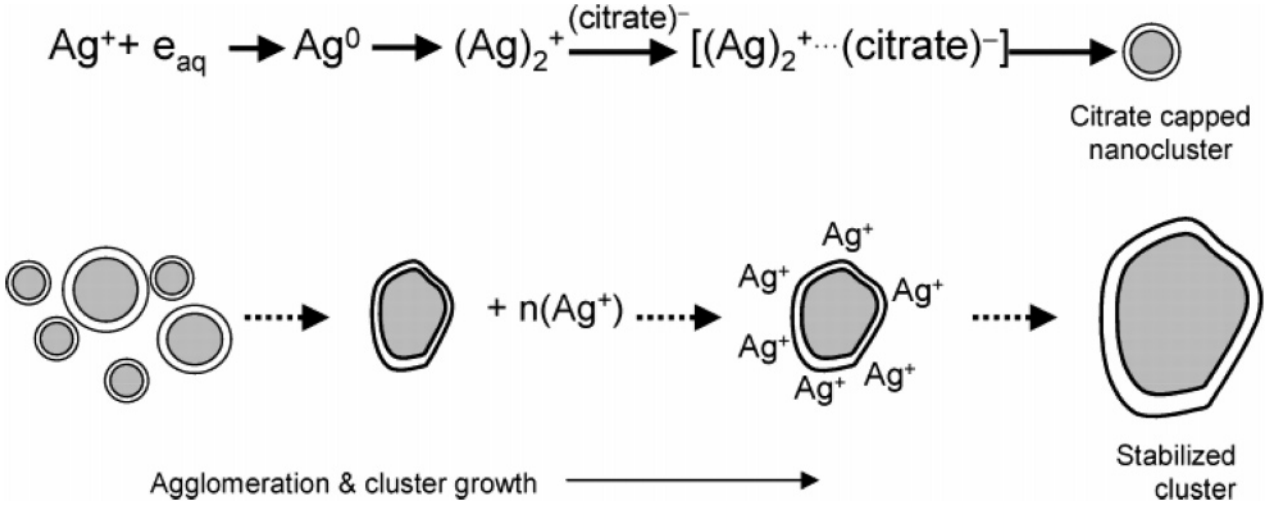


Figure 4. Large silver nanoparticles prepared by the citrate reduction route. Excess silver ions permit fusion of smaller particles into a large, stable cluster. Analogous reactions with citrate-stabilized gold nanoparticles have been shown to yield higher ordered structures, such as nanowires, from smaller "building block" particles. (Reprinted with permission from Pillai, Z. S.; Kamat, P. V. *J. Phys. Chem. B* **2004,** *108*, 945, Scheme 1. Copyright 2004 American Chemical Society.)

preparation of ligand-stabilized nanoparticles provides a simple route to functionalized materials, usually in a single step, one-pot procedure, imparting stability and chemical functionality to the nanoparticle products, often without the need for further modification. Current research challenges are focused on modifying solvents, reaction conditions, and reagents to access a target material, but one should not overlook the opportunity to incorporate greener methods by giving equal consideration to more benign reaction conditions (i.e., choosing safer solvents, avoiding biphasic conditions, and eliminating toxic surfactants), overall yield and atom economy, and the environmental fate of new nanoproducts. Additional attention toward controlling the average size, dispersity, and purity can further drive processing in a greener direction. The following sections describe the preparation of nanomaterials capped by various classes of ligands, including thiol, amines, and phosphines, highlighting green improvements that have emerged in recent years. Subsequent discussions will address the synthesis of more complex materials and emerging methods toward greener nanosynthesis.

2.2.1. Thiol-Stabilized Nanoparticles

The number of direct syntheses of thiol-stabilized nanoparticles has expanded in recent years since Brust reported the preparation of dodecanethiol-stabilized nanoparticles in 1994. The Brust synthesis provides ready access to functionalized nanomaterials with properties analogous to those of large molecules, as they are stable under ambient conditions and can exist in solvent-free forms, in contrast to the less stable citrate based materials. In this reaction, a gold salt (hydrogen tetrachloroaurate) is reduced by sodium borohydride in the presence of a capping agent, yielding particles having average core diameters in the range of 2−8 nm. This reaction was first developed within a biphasic context, taking advantage of phase transfer compounds to shuttle ionic reagents to an organic phase where particle nucleation, growth, and passivation occur. Subsequent variations of this procedure demonstrated the full scope of this reaction, substituting a wide range of thiols and varying the ratio of reagents in order to control the average diameter of the products. More recently, reports of water soluble nanoparticles prepared in this manner have further extended the utility of this procedure, and it remains the simplest direct synthesis of functionalized nanoparticles. The greatest limitation of the Brust preparation is that the stabilizing thiol ligands must be compatible with all of the reagents, including $NaBH_4$ and the phase transfer catalysts (if used, for a biphasic preparation of organic soluble particles), thus sidestepping adverse influences on the reaction chemistry. For example, the thiols must not be subject to any unwanted reduction of other functional groups that may be present on the ligand, and the thiol cannot interact with the phase transfer catalyst in such a way that leads to persistent reagent contamination or products that are inseparable from the reaction mixture. To this end, Brust-type reactions have been performed in other solvents such as water and THF, permitting a single phase synthesis of organic soluble gold nanoparticles while eliminating the need for phase transfer reagents.

Here, we will describe modifications to this classic method of synthesizing monolayer-protected clusters, noting refinements offered from Brust and others. Emphasis has been placed on modifications in either design or process that represent improvements within the context of green nanosynthesis, by improving size control and dispersity, utilizing safer solvents, or avoiding surfactants by adapting reactions for a single phase context. Methods that enhance monodispersity are inherently greener, since solvent consumption due to size separation efforts is avoided. Biphasic methods requiring phase transfer reagents are valued for obtaining high-quality materials with narrow size distributions, while greener, single phase methods sometimes fail to yield products of equal merit, underscoring the need for continued research efforts within this highly developed class of nanosynthesis.

In 2000, Chen and Murray et al. addressed specific issues of particle growth and monodispersity issues in the preparation of hexanethiol protected gold nanoparticles, monitoring size evolution of the clusters over the course of 125 h. Core diameters reached a maximum of 3.0 nm at 60 h, and particle growth occurs only if the nanoparticles remain in situ, while toluene solutions of isolated, purified nanoparticles are stable in solution for extended periods.[35] A stable Au_{38} compound was isolated by a slightly different method, using a reduced temperature adaptation of the Brust synthesis where the biphasic reduction of $HAuCl_4$ was carried out at 0 °C in the presence of a phenylethanethiol passivating ligand. Reduced reaction temperatures impact nanoparticle growth without significantly slowing nucleation and passivation events, thus leading to a product enriched in smaller particles.[36] Jiminez and Murray et al. detailed the synthesis of a Au_{38} compound having a narrow size dispersity. Either by reducing the reaction temperature to −78 °C or by running the reaction at ice temperature with a hyperexcess (300-fold, relative to Au) of thiol, nanoparticle growth is arrested, enriching the products with Au_{38} clusters.[37] The above cases highlight the importance of controlling competing particle nucleation and growth processes in order to limit the size dispersity of nanosynthesis products.

Larger (5−8 nm) gold clusters can be prepared in biphasic water/toluene systems.[38] Brust explored a range of biocompatible moieties by using derivatives of thioalkylated polyethylene glycol ligands to impart water soluble ligand shells to 5−8 nm tetraoctyammonium bromide (TOAB)-stabilized particles. To access more versatile surface chemistries, a range of target ligands featuring carboxylate, amino, and monohydroxy pendant groups (attached to the terminus of the polyethylene glycol portion of the ligand) were prepared for use in ligand exchange reactions.[39] Although the ligands used in these reactions present biocompatible moieties, special care must be taken to ensure that all traces of TOAB are removed from the system prior to use in biological applications.

To generate nanomaterials featuring biocompatible surfaces, Kanaras and Brust used a thioalkylated ligand (monohydroxy(1-mercaptoundec-11-yl)tetraethylene glycol) to introduce a stable, neutral, water soluble functionality to gold nanoparticles by both ligand exchange and direct synthesis routes (see Figure 5).[38] This work was inspired by Foos' report of water soluble gold nanoparticles capped with short chain thiolated polyethylene glycol ligands that were capable of place exchange reactions and by the work of Murray, who demonstrated the synthesis of gold clusters in the presence of thiolated PEG. By successfully incorporating water soluble functional groups, these reports inspired researchers to consider new ligands, solvents, and reaction conditions that permit synthesis within a single phase context.

Development of a single phase adaptation of the Brust method of nanoparticle synthesis was motivated by a desire

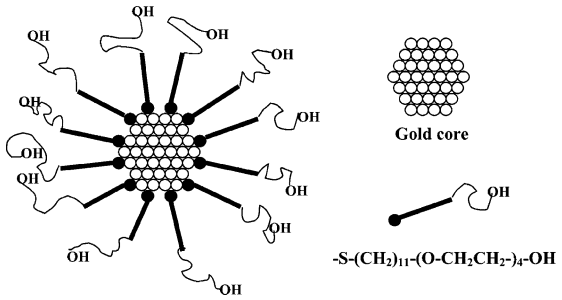


Figure 5. Tetraethylene glycol terminates a C_{11} alkylthiol ligand, which offers the combined advantages of water solubility and the high surface coverage characteristic of an alkylthiol capping ligand. (Reprinted with permission from Kanaras, A. G.; Kamounah, F. S.; Schaumburg, K.; Kiely, C. J.; Brust, M. *Chem. Commun.* **2002**, *20*, 2294, Figure 1. Copyright 2002 Royal Society of Chemistry.)

to eliminate issues posed by the use of phase transfer reagents, including cytotoxicity and the potential for persistent contamination. In the course of such developments, many of the single phase procedures became much greener as well, sometimes eliminating organic solvents, improving atom economy, and using milder reaction conditions. Quite often the products are benign enough for use in biological applications, especially in the case of certain aqueous procedures. Most single phase adaptations of the Brust method yield products with larger average diameters than those produced by the original biphasic procedure, which poses a challenge to researchers targeting smaller functionalized nanoparticles prepared by greener routes. It is believed that variations in product morphology may be attributed to the difference in the ordering of the capping agents in highly polar aqueous environments. Thus, possible solutions may include the use of capping agents that present additional order to aqueous phases (such as those containing hydrogen-bonding moieties) or the substitution of somewhat less polar solvents in lieu of water. The following section highlights some examples of cleaner, more efficient single phase Brust-type syntheses of metal nanoparticles, concluding with some reports of alternative procedures that are likely to open up a new area of innovation in nanosynthesis.

In 1999, Murray et al. reported water soluble clusters with an average diameter of 1.8 nm, synthesized in a single aqueous phase using a method adapted from Brust, where $HAuCl_4$ was reduced by $NaBH_4$ in the presence of tiopronin (*N*-2-mercaptopropionylglycine). This report focused on the viability of these water soluble nanoparticles as precursors for both ligand exchange and postsynthetic modification via amide coupling reactions.[40] In the same year, Chen and Kimura reported the synthesis of nanoparticles ranging in size from 1.0 to 3.4 nm by $NaBH_4$ reduction of $HAuCl_4$ in the presence of mercaptosuccinic acid, using methanol as a solvent. Although size evolution of the nanoparticle products in solution became apparent over time, the dried nanoparticle powders were stable and completely redispersible in water. Such nanoparticles could be used to construct various nanostructures by taking advantage of hydrogen bonding or electrostatic interactions controlled by the pendant carboxylate groups.[41]

In 2003, a single phase nanoparticle procedure was developed by Pengo, using ligands having common features to those used in the biphasic synthesis of Brust and Twigg. Water soluble nanoparticles with core sizes ranging from 1.5 to 4.2 nm were synthesized in a single water/methanol phase, using an amphiphilic thiol featuring a hydrophobic mercaptoheptane portion and a hydrophilic triethylene glycol monomethyl ether unit linked together by a central secondary amide. The rate of $NaBH_4$ addition impacted the average core size and monodispersity, especially if the ratio of gold to thiol was high. The rate of Au reduction corresponds to the initial borohydride concentration: if a reducing agent is added rapidly, small nanoparticles form rapidly and sequester much of the thiols, leaving little capping agent to stabilize (and arrest the growth of) larger nanoparticles.[42] Such issues are not encountered in the traditional biphasic Brust synthesis, since the rate of $NaBH_4$ addition is controlled by the phase transfer process at the interface.

A unique approach to water soluble nanoparticles was presented by Selvakannan, where aqueous $HAuCl_4$ is reduced by $NaBH_4$ in the absence of any potentially toxic stabilizers or phase transfer reagents, yielding 6.5 nm bare gold clusters.[43] The amino acid lysine was added to the solution as a capping agent, rather than a thiol. NMR studies suggest that lysine binds to the bare gold clusters via the α-amino group, leading to reversible pH dependent properties attributed to the pendant carboxyl and amino moieties, aggregating at pH = 10 and redispersing at lower pH values. TEM images of these aggregates are shown in Figure 6.

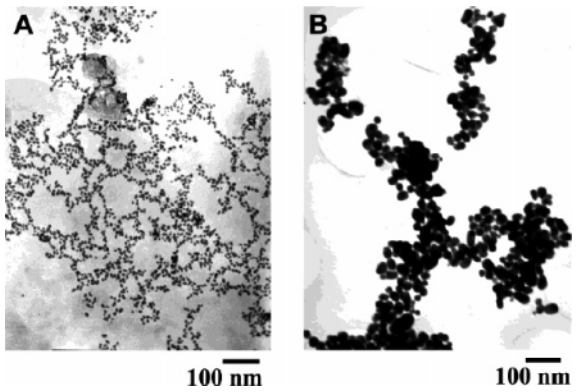


Figure 6. Lysine-capped gold nanoparticles feature inherently pH-sensitive pendant groups, which may be manipulated to control the degree of interparticle interaction. (Left) Particles at pH = 3. (Right) Particles at pH = 10. (Reprinted with permission from Selvakannan, P. R.; Mandal, S.; Phadtare, S.; Pasricha, R.; Sastry, M. *Langmuir* **2003,** *19*, 3545, Figure 5. Copyright 2003 American Chemical Society.)

Fabris designed thiolated ligands with various numbers of peptide moieties for use in aqueous Brust procedures, finding that capping agents with greater degrees of conformational constraint (imparted by hydrogen bonding interactions among the peptides) yield smaller nanoparticles, reconciling the difference in core sizes provided by biphasic and single phase methods.[44] Beyond offering more control over the average core size of the products, the presence of hydrogen-bonding peptides increases the overall stability of the particles, evidenced by resistance to cyanide etching.[45] Conformational constraint appears to be key to the trend reported by Fabris, while Higashi discovered an opposing trend: that increased numbers of helical peptide moieties within a thiol capping agent lead to larger particles.[46] However, in Higashi's case, the peptides of neighboring thiols on a nanoparticle probably do not strongly interact with each other (as in Fabris' study) due to their particular conformational arrangement.

In 2004, Rowe and Matzger reported a single phase synthesis of gold nanoparticles in tetrahydrofuran using metal

to ligand ratios similar to those of the Brust route, yielding products indistinguishable from those of the biphasic Brust method. While the methods described in this report are not particularly green, the importance of eliminating phase transfer reagents was highlighted during evaluation of the products. Since small nanoparticles are often synthesized with electrical applications in mind, it is imperative that unnecessary ionic species are removed from the products. The materials obtained by this route were compared to those of the Brust method, and it was found that the charge transport properties of the Brust products were dominated by ionic conduction, overshadowing the tunneling-based behaviors expected of gold nanoparticles.[47]

Besides eliminating issues of contamination associated with biphasic reactions, single phase procedures can provide a facile route to synthesizing water soluble nanoparticles that can act as useful, modifiable precursor materials for use in biologically relevant applications. For example, Latham and Williams recently developed a unique ligand, trifluoroethylester−polyethylene glycol−thiol, which may be used for direct synthesis, ligand exchange, and postsynthetic modification approaches to functionalized nanomaterials (see Figure 7). Direct synthesis of gold clusters via the modified

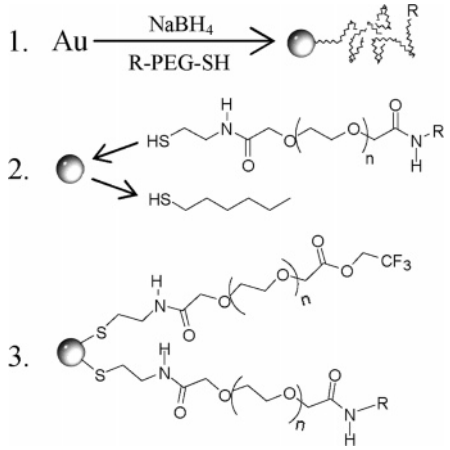


Figure 7. The versatile trifluoroethylester−PEG−thiol ligand may serve multiple roles, acting as (1) a capping agent for direct synthesis, (2) an incoming ligand for place exchange reactions on preformed particles, and (3) an ideal candidate for postsynthesis coupling reactions, due to the labile CF_3 protecting group. (Reprinted with permission from Latham, A. H.; Williams, M. E. *Langmuir* **2006,** *22*, 4319, Scheme 1. Copyright 2006 American Chemical Society.)

Brust route leads to particles having average core diameters of 3−4 nm. Ligands used in direct synthesis may be modified via the trifluoroethyl ester moiety prior to particle formation, which reacts with amines to form amides in the absence of coupling agents, or it may be hydrolyzed in water to yield a pendant carboxylic acid. Coupling reactions of the ligand with primary amines prior to its use in direct synthesis afford a diverse range of pendant functionalities, including butane, pyridine, amino, and biotin. The ligands are capable of participating in exchange reactions with alkanethiol-protected particles. The trifluoroethylester group remains intact after direct synthesis of nanoparticles or after a ligand exchange reaction (if anhydrous conditions are maintained), offering multiple opportunities to introduce other functional groups or small biomolecules to the surface of the nanoparticle. This ligand has also been used to impart similar chemistries to FePt nanoparticles, which are gaining prominence as MRI imaging agents.[48]

At this point, all discussion has been focused on gold nanoparticles, but further insight can be derived from similar treatments of platinum, lending greater understanding to the preparation of other noble metal materials. For example, Yang and Too et al. described the multiple roles of $NaBH_4$ in nanosynthesis, demonstrating its additional capability as a stabilizing agent. Platinum nanoparticles were synthesized in the aqueous phase by $NaBH_4$ reduction of a Pt(IV) precursor. The authors proposed that excess BH_4^- anions hinder transfer to the organic phase by acting as stabilizing agents that hinder the binding of alkanethiols. To confirm this hypothesis, platinum nanoparticles were prepared with a 4-fold stoichiometric excess of $NaBH_4$ and indeed could not be transferred to an alkanethiol/toluene solution unless concentrated HCl was added to the platinum sol in order to accelerate the decomposition of BH_4^- anions. In light of these results, the authors modified their procedure such that the platinum nanoparticles could be transferred to the organic phase immediately upon formation, without the use of a phase transfer reagent, resulting in nanoparticles with an average core size of 2.6 ± 0.4 nm.[49]

Like other methods of preparing gold nanomaterials, weaker reducing agents may be substituted for sodium borohydride. Eklund and Cliffel prepared organic and water soluble platinum nanoparticles for use as catalytic reagents. Organic soluble particles were synthesized by reducing $HAuCl_4$ with lithium triethylborohydride (LiTEBH) in the presence of alkanethiols suspended in THF. Aqueous platinum nanoparticles were prepared in an analogous manner with water soluble thiols, substituting $NaBH_4$ for LiTEBH and using water as a solvent.[50] Most recently, the microwave-assisted preparation of platinum nanoparticle catalysts was reported, using only aqueous sugar solutions as a support medium. In this procedure, numerous green challenges were met, including the elimination of organic solvents, surfactants, and strong reducing agents, while demonstrating excellent atom economy.[51]

The Brust method of nanoparticle synthesis can be used to generate amine-stabilized nanoparticles by simply substituting an appropriate amine for the thiol. Such particles may provide a route to larger (5−15 nm) materials capable of participating in ligand exchange reactions, since amines are more labile ligands than thiols.

Amine-stabilized particles were first prepared by Leff using a method analogous to that of Brust, substituting a primary amine for alkanethiol. Larger nanoparticles having diameters up to 7 nm can be accessed by this method, although dispersity broadens at the upper limit of the size range. If harsh reducing agents (i.e., $NaBH_4$) are replaced by weaker reagents, or completely omitted from the procedure, even larger noble metal nanoparticles may be obtained, as primary amines are strong enough reducing agents to nucleate and grow particles. Jana and Peng further extended the Brust analogy, synthesizing noble metal nanoparticles in a single organic phase from $AuCl_3$ (or another organic soluble metal cation), tetrabutylammonium borohydride (TBAB), and either fatty acids or aliphatic amines. Organic soluble articles between 1.5 and 7.0 nm were obtained without the use of surfactants, depending on the amount of capping agent used.[52]

Hiramatsu and Osterloh found that borohydride reducing agents are unnecessary for the synthesis of nanomaterials in larger size regimes. Gold and silver amine-stabilized particles with core diameter ranges of 6−21 nm for gold and 8−32

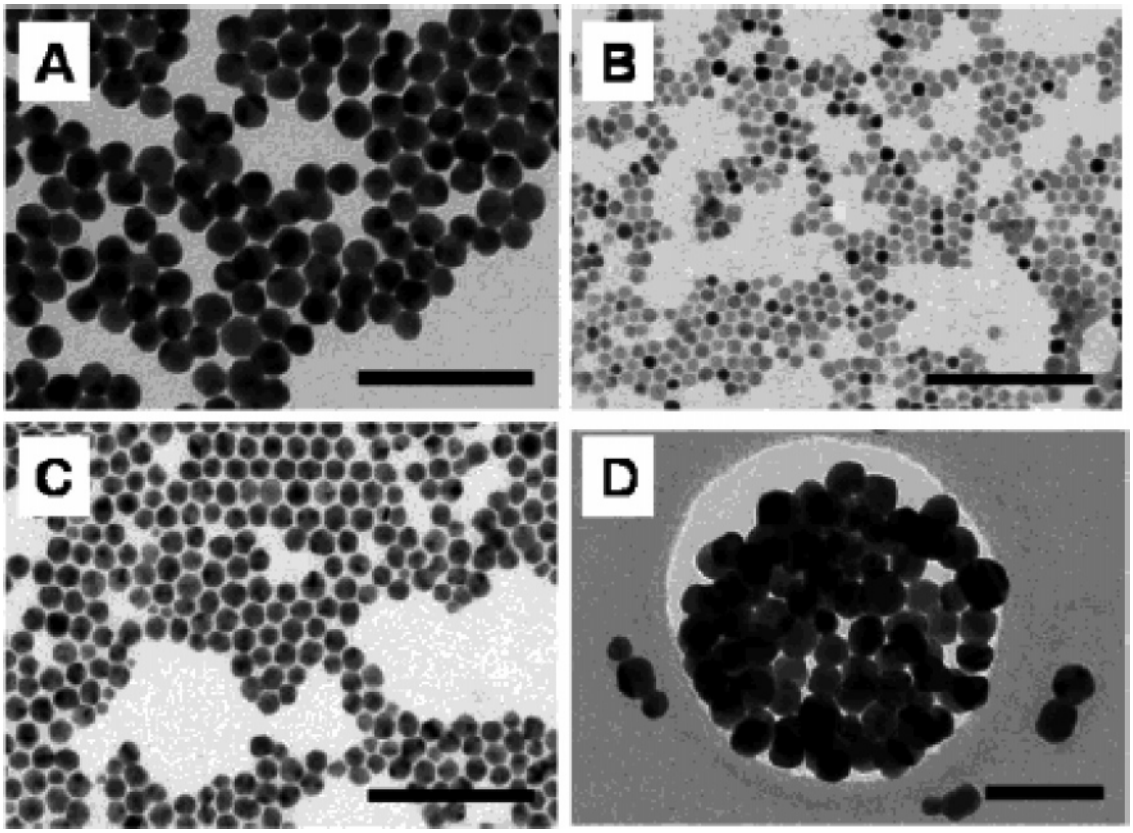


Figure 8. Nanoparticles prepared by refluxing gold or silver precursors with oleylamine: (A) 21 nm gold; (B) 9 nm Ag; (C) 12 nm Ag; (D) 32 nm Ag. Scale bars indicate 100 nm. (Reprinted with permission from Hiramatsu, H.; Osterloh, F. E. *Chem. Mater.* **2004**, *16*, 2509, Figure 1. Copyright 2004 American Chemical Society.)

nm (Figure 8) for silver were synthesized in a simple scalable preparation where either $HAuCl_4$ or silver acetate was refluxed with oleylamine in an organic solvent. Other reducing agents are not necessary, since amines are capable of reducing gold, forming nitriles upon further oxidation. In the case of gold, core size was controlled by regulating the gold to amine ratio, although it is acknowledged that samples with good monodispersity (less than 10%) were achieved only if a minimum of 65 equiv of amine (relative to gold) was used. Silver nanoparticles were formed by refluxing silver acetate with oleylamine in a variety of organic solvents. The particle size is determined primarily by the reflux temperature associated with each solvent: hexanes (bp: 69 °C) yield 8.5 nm particles, while the use of toluene (bp: 110 °C) and 1,2-dichlorobenzene (bp: 181 °C) results in 12.7 and 32.3 nm particles, respectively.[53]

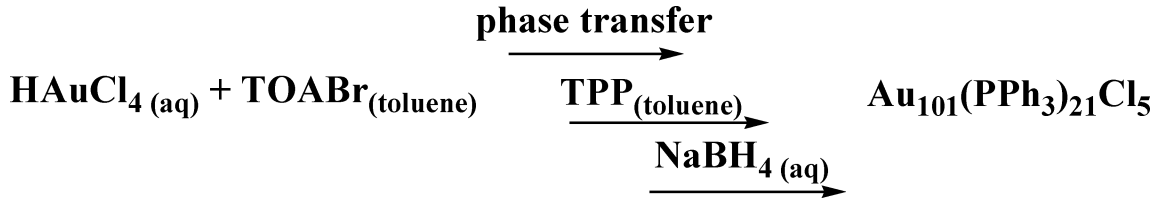
Aslam and Dravid et al. reported a similar method of generating water soluble gold nanoparticles that eliminates harsh reducing agents and organic solvents, while demonstrating greatly improved atom economy. $HAuCl_4$ is reduced by oleylamine in water, creating nanoparticles that are water soluble despite the apparent mismatch in polarity between the solvent and the stabilizing ligand. Gold is used in excess over the amine, perhaps leading to products with mixed ligand shells whose stability is bolstered by chloride complexes. The products of this reaction have core sizes of 9.5 to 75 nm, and the greatest monodispersity is achieved for particles at the lower end of the size range, where a 10:1 ratio of gold to amine is used. Lesser amounts of amines lead to particles with very wide polydispersities.[54]

2.2.2. Phosphine-Stabilized Nanoparticles

The Brust method of nanoparticle synthesis is a valuable technique for preparing thiol-stabilized nanoparticles, where functional groups are limited only by the compatibility of thiols. However, the identification of a unique set of reaction conditions is often required for the preparation of each functionalized target, and it is often difficult to access smaller nanomaterials by this route. An approach pioneered in our laboratories involves producing a nanoparticle precursor having a temporary stabilizing ligand shell, amenable to ligand exchange reactions with an incoming molecule that has the desired chemical functionality. By optimizing the preparation of a common precursor (synthon), one can generate libraries of diverse nanoparticles that bear pendant functional groups, thus introducing the desired chemical functionality to the surface of the particle. Although this procedure requires two steps and employs triphenylphosphine as a temporary stabilizing group, this synthon approach has permitted greater control of nanoparticle size, dispersity, and functionality. The tradeoff made is the use of an additional step to avoid the inefficiencies and waste-generating purification steps inherent in developing a specific preparation for each direct synthesis.

While somewhat unstable, as-synthesized triphenylphosphine-stabilized nanoparticles are valued for their ready participation in ligand exchange reactions (which will be discussed in later sections of this review covering nanoparticle functionalization and exchange reactions). The earliest reported syntheses of such particles by Schmid provided the benchmark method for preparing high-quality, small gold nanoparticles.[55−57] $AuCl(PPh_3)$ is prepared from $HAuCl_4$,

Scheme 1. Biphasic Synthesis of 1.4 nm Triphenylphosphine-Stabilized Gold Nanoparticles



suspended in warm benzene, and reduced by a stream of diborane gas, presenting significant health and explosion hazards. Despite the hazards involved, this method remained the most reliable large-scale preparation of phosphine-stabilized gold nanoparticles for nearly two decades.

In 1997, Hutchison et al. presented a convenient, safer, and scalable synthesis (Scheme 1) that yields high-quality 1.4 nm triphenylphosphine-stabilized gold nanoparticles through a much greener route that eliminates the use of diborane gas (>40 L of diborane/g of nanoparticle) and benzene (>1000 g of benzene/g of nanoparticle). This biphasic synthesis involves the use of a phase transfer reagent (TOAB) to facilitate the transfer of chloroaurate ions from an aqueous solution to an organic phase (toluene) containing triphenylphosphine. Reduction is carried out using aqueous $NaBH_4$ delivered to the organic phase via complexation with TOAB. There is still opportunity to further green this preparation. Substitutions of $NaBH_4$ for diborane and of toluene for benzene are clearly beneficial; however, it would be preferable to avoid using TOAB and find a yet greener solvent. In addition, the purification of these particles still requires solvent washes. If membrane filtration methods suitable for use with organic solvents could be developed to replaced solvent washes as the purification step, the preparation could be made even less wasteful.

The triphenylphosphine-stabilized nanoparticles may be stored as a powder under cold, dry conditions until they are needed for ligand exchange reactions.[58] Besides being greener and safer, this synthesis also features a great improvement in yield, providing 500 mg of purified nanoparticles from 1 g of $HAuCl_4$, compared to 150 mg of product from Schmid's method. The products of both preparations yield nanoparticles of equal core diameter, monodispersity, and reactivity. The nanoparticles from Hutchison's preparation have been functionalized by a wide range of ligands through ligand exchange reactions, yielding a diverse library of functional nano "building blocks" ideal for use in the bottom-up assembly of new nanostructures, all from a versatile gold nanoparticle precursor.

2.3. Seeded Growth and Shape Control of Nanoparticles

In the pursuit of nanoscale materials featuring optical properties, nanoparticles having core diameters exceeding 5 nm can be grown from smaller seed particles through the epitaxial addition of metal atoms. Delivered to the surface of the seed particle in a partially reduced form, supplemental amounts of a metal salt can be reduced in a surface-catalyzed reaction with a mild reducing agent, transforming a solution of small particles to larger colloids. Whether the goal is to grow large spherical particles or nanorods, the use of well-defined seeds is critical to obtaining products with narrow size dispersity. Other reagents such as surfactants may be present as a component of the nanoparticle growth solution, acting in the capacity of a directing agent that promotes the formation of anisotropic materials, or simply as surface passivants and stabilizing agents. Growth of such materials from monodisperse seeds allows the researcher to employ milder reaction conditions for the synthesis of materials, and the wide range of weaker reducing agents capable of reducing metal ions in a growth solution offers increased possibilities for designing greener syntheses. Larger nanomaterials are especially valued for their optical properties, useful for surface-enhanced Raman scattering, imaging, sensing, and waveguiding applications, where the optical absorption arising from the surface plasmons (see Figure 9) of noble metal materials is key.

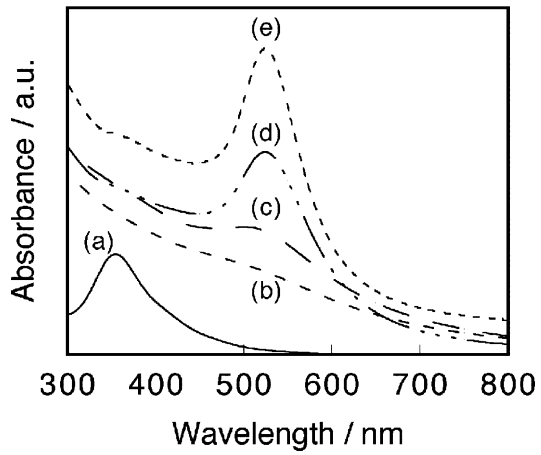


Figure 9. UV−vis absorption spectra of gold nanoparticles corresponding to (a) 1.5 nm, (b) 3.4 nm, (c) 5.4 nm, (d) 6.8 nm, and (e) 8.7 nm. Absorptions due to interactions with surface plasmons feature extinction coefficients that increase with particle size, making particles with average diameters >8 nm appropriate for optical applications. (Reprinted with permission from Shimizu, T.; Teranishi, T.; Hasegawa, S.; Miyake, M. *J. Phys. Chem. B* **2003**, *107*, 2719, Figure 1. Copyright 2003 American Chemical Society.)

The synthesis of larger spherical nanoparticles from smaller seed materials is reviewed, as is the formation of anisotropic nanorod materials. (A complete analysis of seeded growth methods is beyond the scope of this review, but an excellent review of gold nanorods was recently offered by Perez-Juste and co-workers.[4]) A special focus has been placed on studies intended to elucidate the individual roles of nanoparticle seeds, reducing agents, and additives, with respect to their impact on the morphology of the final products. The information garnered from these studies has ultimately contributed to a better understanding of the surface chemistry of these materials, which should in turn lead to targeted functionalization methods that will enable their utility in solution-based sensing applications and beyond. Next, shape controlled methods that provide access to more exotic materials are discussed, followed by selective etching techniques (see section 2.3.4) which can be used to give new life to nanomaterials by transforming their shape. Gaining access to larger particles through growth techniques provides

a secondary use for small gold clusters (which serve as seeds), while etching techniques can be especially helpful for transforming larger spherical and rodlike structures back to smaller particles. Ultimately, the application of these recycling measures prolongs the useful lifetime of a nanomaterial, reducing the amount of products entering the waste stream.

2.3.1. Spherical Particles

Seeded growth of nanoparticles utilizes a growth solution composed of a weak reducing agent, a gold salt, and possibly a surfactant. Small nanoparticle "seeds" are known to exhibit surface selective catalytic properties, and the use of high-quality materials allows the researcher to gain additional control over subsequent reactions, whether it involves growth to a larger material or other catalytic applications. The choice of reducing agent was once thought to be the most critical factor in preventing secondary nucleation within a growth solution. Reducing agents such as citrate, some organic acids, and hydroxylamine catalyze the reduction of metal ions at metal surfaces yet do not contribute to additional nucleation events, since the seed particles themselves act as nucleation centers. Central to seeded growth is the selection of monodisperse, well-defined seed particles. Sodium citrate has been used most extensively in this manner to yield particles having average diameters of 20−100 nm,[31] although a significant population of gold rods forms with iterative growth. Hydroxylamine is thermodynamically capable of reducing Au^{3+} to the bulk metal, but the rate of this reaction is negligible. Brown and Natan reported the growth of gold nanoparticles with core diameters ranging from 30 to 100 nm from existing smaller particles prepared by the single step citrate route, utilizing the surface-catalyzed reduction of Au^{3+} by hydroxylamine.[59] The growth of the particles was monitored by visible spectroscopy (see Figure 10). The average diameters of the products were governed by the diameter of the seed nanoparticles and the amount of Au^{3+} present in the growth solution. The further utility of this method was demonstrated by exposing a monolayer of nanoparticles assembled on a solid substrate to hydroxylamine/$HAuCl_4$ growth solutions, resulting in the growth of the fixed particles, thereby affording a simple method for decreasing interparticle spacing within a nanoparticle array.

In a follow-up study by Brown, Walter, and Natan,[60] it was noted that the reduction of Au^{3+} is greatly catalyzed on any surface, and thus other (stronger) reducing agents could be used in seeded growth methods. Growth conditions consisting of the addition of a boiling mixture of citrate to a boiling solution of either 2.4 or 12 nm nanoparticle seeds and Au^{3+} were used to develop the seed particles into larger structures, even though it is well-known that such solutions promote particle nucleation. However, since the rate of reduction at the surface of the seeds greatly exceeds the reduction rate of metal ions in the growth solution, the seed nanoparticles grow at the expense of nucleating new particles.

Jana and Murphy et al. were able to grow nanoparticles having diameters ranging from 5 to 40 nm with narrow polydispersity from 3.5 nm seeds, using stock solutions of $HAuCl_4$ and a surfactant, cetyltrimethylammonium bromide (CTAB), as a growth medium. The reduction of Au^{3+} was carried out by ascorbic acid. The authors found that an iterative approach to nanoparticle growth, where seed particles are repeatedly exposed to fresh aliquots of growth solutions, yields products of greater monodispersity in terms of both size and shape. The presence of CTAB added stability to the nanoparticle solutions and aided subsequent functionalization by alkanethiols.

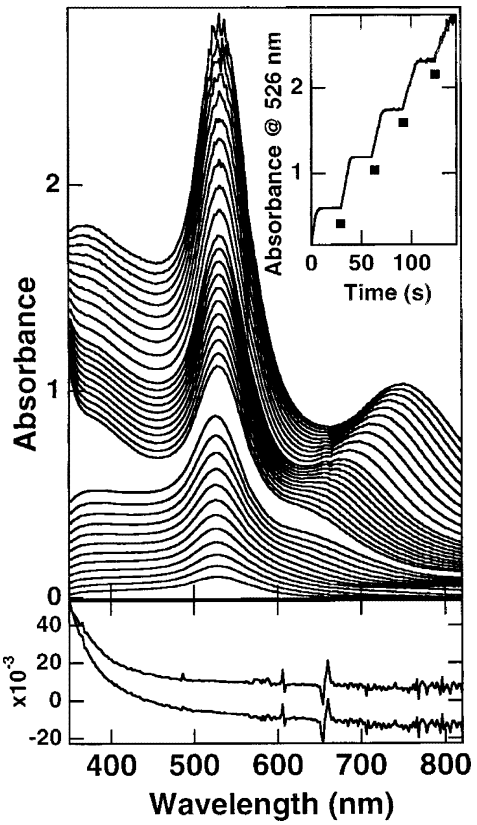


Figure 10. Preformed gold nanoparticle seeds are capable of catalyzing further reduction of gold salts at their surfaces in the presence of a mild reducing agent such as hydroxylamine. The reaction between 12 nm gold seeds and a growth solution of $HAuCl_4$ was followed *in situ* by UV−vis, showing increased intensity of the surface plasmon band (530 nm) as well as the appearance of higher order multipole plasmon activity (700−750 nm) indicative of larger gold nanoparticles. (Reprinted with permission from Brown, K. R.; Natan, M. J. *Langmuir* **1998**, *14*, 726, Figure 1. Copyright 1998 American Chemical Society.)

The preparation of seeds intended for use in nanoparticle growth procedures need not be by the citrate reduction route. Sau et al. reported the photochemical preparation of seed particles with core diameters ranging from 5 to 20 nm. Various aqueous solutions of $HAuCl_4$ were reduced to gold colloids by a photochemically activated reaction with a polymeric stabilizing agent, Triton X-100 (poly(oxyethylene)isooctylphenyl ether). Nanoparticle growth was initiated by the ascorbic acid-catalyzed reduction of surface-adsorbed Au(III) ions, reaching final core sizes ranging from 20 to 110 nm, depending upon the size of the seed particles and the amount of gold ions present in the growth medium.[61]

2.3.2. Anisotropic Particles and Nanorods

Anisotropic metal nanoparticles feature unique optical properties which have generated interest in applications related to surface-enhanced Raman scattering, single molecule detection, surface-enhanced fluorescence, biological imaging, and scanning optical microscopy techniques, among many others.[4,7,62] Anisotropic materials possess multiple surface plasmon bands with tunable positions (see, for example, Figure 11) based on the overall size of the particle

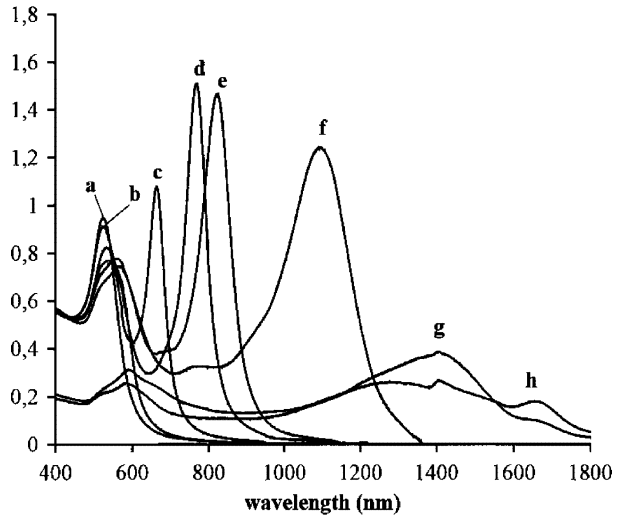


Figure 11. The aspect ratio of gold nanorods may be tuned by controlling the ratio of gold seeds to growth solution. The extinction spectra a−h result from increasingly reduced amounts of seed particles, which effectively increases the amount of growth solution available for addition to individual particles. (Reprinted with permission from Jana, N. R.; Gearheart, L.; Murphy, C. J. *Adv. Mater.* **2001**, *13*, 1389, Figure 1. Copyright 2001 Wiley Interscience.)

and the aspect ratio (length divided by width, in the case of nanorods). Additionally, anisotropic materials feature enhanced electric fields at the tips of the structure,[7] making them especially well-suited for many of the applications listed here.

While understanding of growth mechanisms has accumulated, several challenges remain toward shifting the synthesis and application of these materials toward a greener context. It has been acknowledged that mild conditions may be used for seeded growth approaches, yet maximization of yields of anisotropic materials relative to spherical byproducts remains a significant challenge, despite increased mechanistic understanding. The replacement of surfactants with other shape-directing agents would greatly improve the green merits of seeded growth while broadening the range of utility for these materials, enabling their use in applications where low toxicity is a priority. The following contributions offer insight into both the growth mechanisms and the unique surface chemistry of anisotropic particles, setting the stage for future refinements in the functionalization and application of these materials.

Formation of nanorods relies on coordination chemistry between the surface of the seed particle and additives such as surfactants, passivants, chelating agents, or polymers which hinder the growth of certain crystal faces, promoting an overall lengthening of the seed particle as the metal ions of a growth solution are reduced at the exposed faces.[4] Besides presenting a useful synthetic route toward the preparation of reduced-symmetry materials, such approaches may offer a simple means of creating ordered arrays of nanorods if placement of the gold seeds is controlled.[63,64]

The mechanism by which growing particles break symmetry and favor growth in a particular direction has been the topic of much speculation, as the formation of reduced symmetry materials occurs under a wide range of circumstances. Although nanorods can form spontaneously under conditions intended to favor growth of symmetric colloids, it is understood that surfactants may act in a capacity beyond that of mere passivants, directing epitaxial growth of a particular crystal face by hindering the growth of others. However, a number of preparations of shape-controlled materials have been reported where symmetry breaking of a growing seed particle is not considered the key step in the growth mechanism (see section 2.3.3).

To favor the formation of reduced symmetry particles, the use of a directing agent is required. A surfactant such as CTAB, known to bind preferentially to the pentatwinned crystallographic faces of a seed, leaves other regions of the particle available as growth sites. This method suggests that the surfactant simply acts as a directing agent, rather than a soft micellar template, although the surfactant does form stabilizing bilayers along the length of the nanorod. Surfactants with longer hydrophobic tails naturally form more robust bilayers, and thus higher aspect ratio materials are achieved. Mulvaney has suggested an alternative mechanism (see Figure 12), where gold ions are encapsulated within micelles and preferentially delivered to the ends of a growing nanorod, since the ends of the rod have the highest electric field gradient compared to the rest of the structure.[65] The authors note that while this mechanism may explain anisotropic growth, it does not provide a clear description of the symmetry-breaking events that initiate anisotropy.

Murphy, Mann, and co-workers explored the crystal structure of nanorods at various stages of growth from smaller seed particles prepared by the $NaBH_4$-enhanced reduction of $HAuCl_4$ in the presence of citrate anions, which serve primarily as a capping agent.[66] Spherical particles were iteratively exposed to fresh growth solutions containing $AuCl_4^-$, ascorbic acid, and CTAB. After a single exposure to the growth medium, the average particle size had evolved to from 4.3 ± 1.2 nm to 9.6 ± 2.1 nm. Using HRTEM selective area electron diffraction, it was found that shape anisotropy arises from the emergence of a penta-tetrahedral twin crystal at the surface of a growing spherical nanoparticle. It is believed that once symmetry breaking occurs within a spherical particle, subsequent growth will occur preferentially along the {110} axis (see diagram in Figure

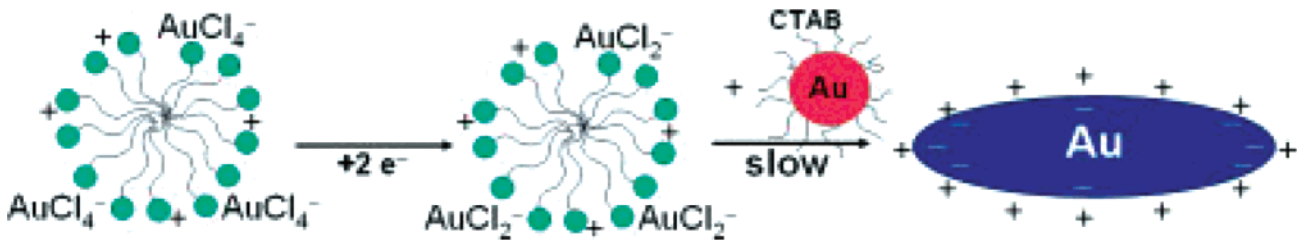


Figure 12. A possible mechanism for gold nanorod formation. $AuCl_4^-$ anions displace bromide at the surface of CTAB micelles, where they are reduced from Au(III) to Au(I) by ascorbic acid. Transport from the micelle to the micelle-coated gold seeds is favored by double layer interactions, leading to deposition at the tips of the seeds. (Reprinted with permission from Perez-Juste, J.; Liz-Marzan, L. M.; Carnie, S.; Chan, D. Y. C.; Mulvaney, P. *Adv. Funct. Mater.* **2004,** *14*, 571, Scheme 1. Copyright 2004 Wiley-VCH.)

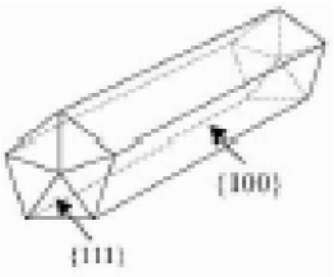


Figure 13. Diagram of a pentatwinned gold nanorod, highlighting the major crystal faces of the structure. Preferential binding of stabilizers to a particular face is believed to play a role in nanorod formation. (Reprinted with permission from Johnson, C. J.; Dujardin, E.; Davis, S. A.; Murphy, C. J.; Mann, S. *J. Mater. Chem.* **2002**, *12*, 1765, Figure 3a. Copyright 2002 Royal Society of Chemistry.)

13). Nanorod structures evolve from such a configuration by elongation of the fivefold {100} axis central to the five (111) faces which will become the capping ends of the nanorod. Subsequent exposures to the growth medium resulted in the formation of larger spherical colloids, in addition to an emerging population of reduced symmetry materials. It is proposed that Au−surfactant complexes are incorporated into the (100) side faces, while noncomplexed clusters and ionic species favor the end faces, leading to an overall elongation of the nanorod.

As the role of surfactants in seeded growth approaches to nanorod synthesis was better understood, delineating the impact of the nature of the seed particles used in such techniques became the focus of later mechanistic studies. Murphy has suggested that the sterics of the ammonium head group of CTAB are most compatible with the lattice arrangement found along the crystal faces making up the length of the nanorod (see Figure 14).[7] Prior to more focused studies of this topic, Nikoobakht and El-Sayed published a follow-up study to Jana's silver ion enhanced studies of seeded growth methods, replacing citrate-capped seed materials with CTAB-stabilized gold nanoparticles, and assessed the use of a cosurfactant (benzyldimethylammonium bromide, BDAB) in addition to small amounts of silver ion.[67] Both modifications of the iterative seeded growth process strongly favored the growth of nanorods over larger spherical colloids to the extent that spherical particles composed only 0−1% of the nanomaterial products.[68,69]

A more exhaustive study describing the impact various types of gold seed particles have on nanorod synthesis was undertaken by Gole and Murphy, comparing particles differing in both their average diameter and surface chemistry.[70] In this work, negatively charged seeds were compared to positively charged seeds (where citrate, mercaptobutylamine, and glucose stabilizers impose a negative charge, and CTAB-stabilized particles bear an overall positive charge, due to partial bilayer formation). Negatively charged seeds produced materials with a wider range of aspect ratios, where positively charged seeds produced nanorods with relatively consistent dimensions. The average core size of the particles within these categories was varied, ranging from 3.5 to 18 nm. It was found that the gold nanorod aspect ratio has an inverse relation to the size of the seed particle, and larger seeds produce bimodal populations of shorter and longer nanorods. Since nanorod synthesis is believed to take place largely through unencumbered epitaxial growth at the ends of the rod coupled with hindered growth along the surfactant-protected longitudinal faces, it is quite likely that facile rearrangement or displacement of the original capping agent is essential to the formation of high-aspect-ratio materials. Thus, particles having covalently bound thiol capping agents

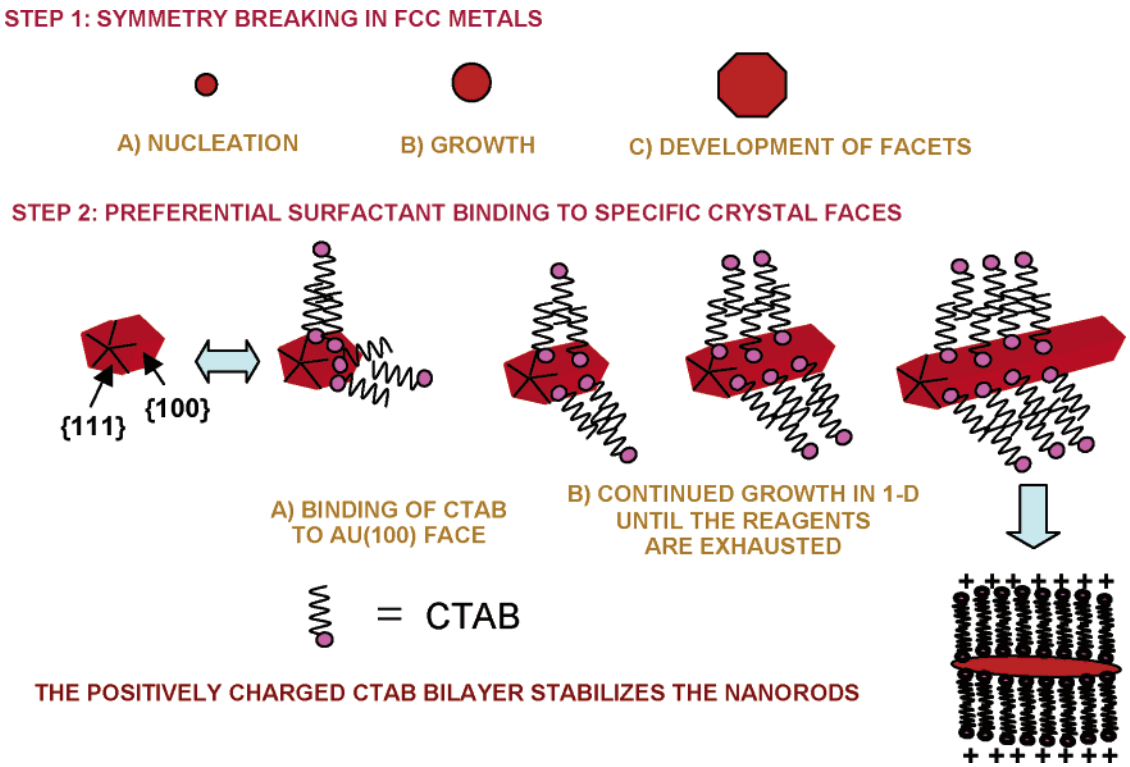


Figure 14. Surfactant-directed growth of gold nanorods. Once seed particles grow large enough to develop facets, surfactants bind preferentially to (100) faces, permitting growth at the exposed ends of the nanorod. (Reprinted with permission from Murphy, C. J.; Sau, T. K.; Gole, A. M.; Orendorff, C. J.; Gao, J.; Gou, L.; Hunyadi, S. E.; Li, T. *J. Phys. Chem. B* **2005**, *109*, 13857, Figure 8. Copyright 2005 American Chemical Society.)

are ill-suited to surfactant-directed growth processes, whereas those stabilized by materials similar to those present in the growth medium readily interact in a manner consistent with the proposed nanorod formation mechanism.

Less obvious factors in the synthesis of anisotropic materials have been explored, focusing on the presence of various ions in solution. Gold seeds were added to growth solutions containing CTAB, $HAuCl_4$, ascorbic acid, and sometimes $AgNO_3$. The morphology of the particles was related to the interdependent factors imposed by the concentrations of the growth solution components, suggesting that the surfactant-induced faceting processes compete with growth kinetics to determine the final shape of the product.[71]

The role of silver ions is still not completely understood. It is proposed that Ag^+ binds to the surface of the particles as AgBr, restricting the growth of the particle in a manner similar to CTAB. Silver ions are not reduced in the presence of ascorbic acid or trisodium citrate at room temperature. Bromide ions were also found to be essential: substitution with iodo or chloro analogues of both the silver salt and the ammonium surfactant does not lead to growth of anisotropic materials.[7] Cyanide dissolution studies of nanorods prepared with either CTAB or Ag^+ as a directing agent have differing degrees of resistance toward decomposition, suggesting that CTAB may be more densely packed on the rods if Ag^+ is present, leaving the tips of the rods vulnerable to cyanide digestion.[4]

Recently, it was determined that pH has a significant role in directing the formation of gold nanoprisms.[72] A simple solution-phase seeded growth method was used, employing standard procedures similar to those described above, with the exception of NaOH as an additive in the growth medium. Increasing the pH of the growth solution deprotonates ascorbic acid, giving the monoanion form in solution. The monoanion is believed to bind more effectively to the ends of the nanorod, facilitating gold reduction at this site. Paradoxically, at pH values exceeding 5.6, a mixture of large spherical particles and crystalline flat triangular nanoprisms is obtained by this method, rather than the nanorod structures typically afforded by seeded growth in the presence of CTAB.

Clearly, tremendous effort has been put forth toward understanding the mechanisms of anisotropic nanocrystal growth, which will hopefully set the stage for redesigning synthetic methods to meet greener standards. Elimination of surfactants is clearly the greatest challenge, followed by the need to improve the yields of nanorods grown from spherical seeds. Aside from these shortcomings, seeded growth approaches allow the researcher to perform nanosynthesis of sophisticated materials under mild conditions, using relatively benign reagents.

2.3.3. Control of Nanoparticle Shape

Modifications of the citrate reduction method for silver and gold ions have led to numerous reports of anisotropic materials synthesis. The following section discusses methods that provide access to nanomaterials with unusual shapes, some of which avoid the use of harsh reducing agents, surfactants, and organic solvents. Many of these reports expand upon established knowledge of common nanosynthesis techniques (such as seeded growth) while exploring the use of new additives as shape modifying agents.

Pei reported a simple method for synthesizing gold nanowires from spherical citrate-stabilized gold particles simply by introducing excess $HAuCl_4$ to a solution of gold nanoparticles.[73,74] Excess chloroaurate ions adsorb to the surface of the nanoparticles, introducing an attractive force that draws the particles together, while additional gold ions fill in the gaps between particles. Schatz and co-workers reported a citrate reduction that was bolstered by the addition of hydrogen peroxide and a capping agent, bis(*p*-sulfonatophenyl)phenylphosphine (BSPP), resulting in the formation of unique, single crystal branched gold nanoparticles exhibiting one, two, or three distinct tips.[75] The particles begin as small triangular nuclei, and subsequent selective binding of the BSPP directing agent results in anisotropic crystal growth in a direction parallel to the nuclei edges. Chu recently reported the citrate reduction of a surfactant−gold complex formed between $HAuCl_4$ and cetyltrimethylammonium bromide (CTAB) yielding flat gold structures. Hexagonal, triangular, and truncated triangular materials (Figure 15) can be obtained by varying the ratio of reagents and the reaction time.[76]

Occasionally, removal of the directing agent can be difficult, hindering the use of these materials in applications such as surface-enhanced Raman spectroscopy and self-assembly processes, where good control over the particles' surface chemistry is essential. Murphy reported the synthesis of crystalline silver nanowires in the absence of surfactants. Silver salt was reduced by citrate anion at 100 °C, in the presence of a small amount of hydroxide ion. A moderate amount of hydroxide (6−8 μL of 1 M NaOH and 40 μL of 0.1 M $AgNO_3$ dissolved in 100 mL of deionized water) yields predominantly nanowires (35 ± 6 nm) when reduced by citrate. If the hydroxide source is omitted, this preparation results in spherical nanoparticles. Citrate performs in multiple capacities in this reaction, as it complexes with silver ions, reduces the ions to metallic silver, and caps the resulting structure, imparting water solubility. The relatively small amounts of NaOH ensure that citrate is completely deprotonated, making it a stronger complexing agent, yet hydroxide competes with citrate for binding sites on the growing nanostructure, thus directing crystal growth.[77] In an alternative shape-controlling procedure, Swami reported the synthesis of nanoribbons at the air−water interface.[78] Alkylated tyrosine is capable of acting as a phase transfer material, a reducing agent, and a capping stabilizer. Due to the limited water miscibility of this organic reagent, gold reduction is restricted to the air−water interface, reducing the possible degrees of freedom for crystal growth.

More unusual nanocrystal shapes have been produced by the polyol reduction method. In 2003, Xia reported the synthesis of nanoprisms having tunable optical properties.[62] Silver nitrate was reduced by citrate and sodium borohydride in the presence of poly(vinyl pyrrolidone) (PVP), initially yielding spherical nanoparticles. Irradiation of the solution with a halogen lamp initiated a photochemical reaction leading to the formation of triangular nanoprisms. Further UV irradiation led to an additional morphological change, transforming the nanoprisms to circular disks. In a later report, the synthesis of nanocubes and truncated cubic structures (shown in the TEM image in Figure 16) by a modified polyol procedure was described, where silver nitrate was thermally reduced in a PVP/ethylene glycol solution.[79] Initially, only twinned crystals were observed by TEM. After stirring under ambient conditions for 2 days, single crystal cubes and tetrahedral structures were obtained in high yield. The addition of sodium chloride to the reaction mixture was

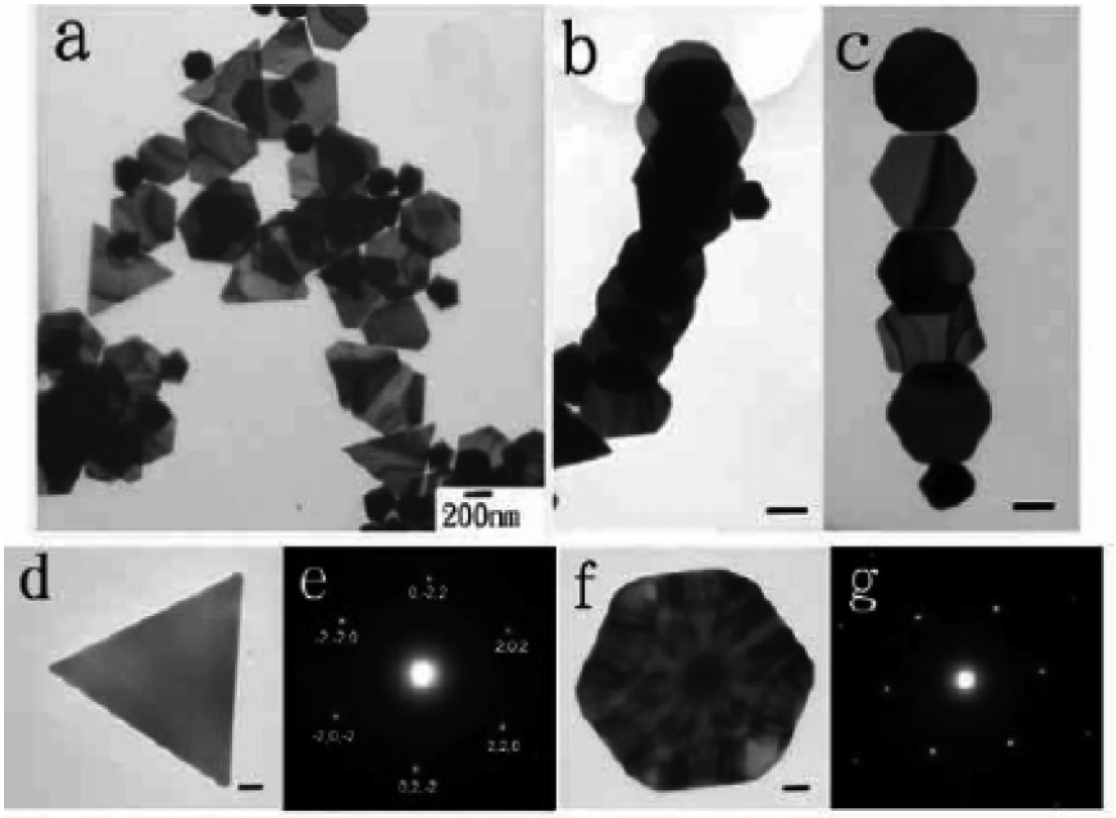


Figure 15. TEM images of gold nanoplates and chainlike arrangements of gold nanoplates (a−c). Triangular and hexagonal plates with their corresponding electron diffraction patterns (d−g). (Reprinted with permisison from Chu, H.-C.; Kuo, C.-H.; Huang, M. H. *Inorg. Chem.* **2006**, *45*, 808, Figure 4. Copyright 2006 American Chemical Society.)

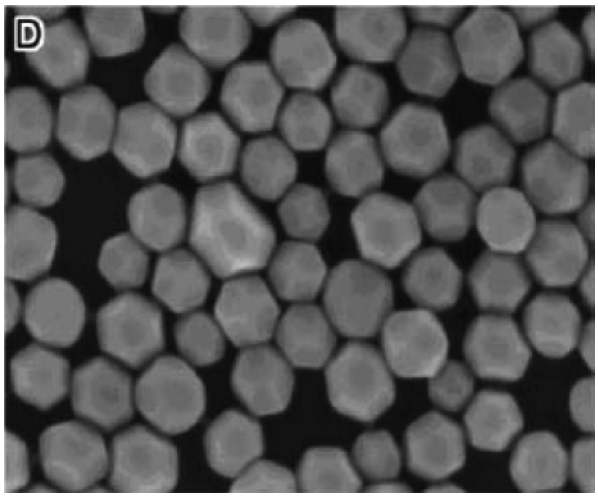


Figure 16. Silver nanoparticles prepared by the polyol route, featuring cubic and truncated cubic structures. (Reprinted with permission from Wiley, B.; Herricks, T.; Sun, Y.; Xia, Y. *Nano Lett.* **2004**, *4*, 1733, Figure 2D. Copyright 2004 American Chemical Society.)

a critical factor in the evolving crystal morphology. It was proposed that exposure to oxygen selectively etched the twinned materials, and chloride stabilized the liberated silver ions, allowing only the remaining single crystal materials to grow. In a somewhat analogous procedure reported by Kan, gold ions were reduced by a polyol route, yielding large gold nanoplates with morphologies that were dependent upon the reaction times.[80] Physisorption of polar groups likely restricted crystal growth on the (111) face, leading to flat structures.

2.3.4. Size Evolution and Nanoparticle Etching

Modification of existing nanostructures such that their size or shape changes with the use of minimal reagents further increases the multitude of uses for materials produced by a single synthetic procedure, opening up the possibility of recycling nanomaterials for secondary uses. For example, smaller nanoparticles having diameters below 2 nm are most often studied for their electronic properties, but if these same particles are transformed (perhaps by a ripening process) to larger single crystal nanoparticles, one could envision launching studies of the optical properties associated with these materials without developing an entirely different synthetic protocol. Such procedures are especially useful if the size evolution process leads to nanomaterials with excellent size monodispersity. One common drawback of some convenient nanomaterial preparations is the tendency to form polydisperse products. This is often the case for many variations of the Brust nanoparticle synthesis.

Several of the nanoparticle-enlarging techniques described below require the use of (quite toxic) TOAB as a stabilizing agent. The green value of these methods could be greatly improved by identifying an alternative stabilizer. In some cases, commendable efforts toward the removal of TOAB from the final product were made. Purity of nanoproducts will continue to be a universal issue for the application of nanoscience, especially since the elimination of surfactants remains one of the greatest challenges in greener nanosynthesis. With this in mind, we have included a section highlighting various purification methods (see section 2.4.2).

The transformation of larger nanomaterials to smaller structures is also attractive from the standpoint of generating high-quality materials, as well as the prospect of studying

size dependent physical properties. To this end, the controlled etching of a crystalline nanorod affords the opportunity to study fundamental properties associated with changing aspect ratios, without the complications that arise from multiple product morphologies produced by growing nanorods from spherical seed particles (including highly faceted materials, nanocubes, prisms, and other truncated structures). In this manner, well-defined nanomaterials may serve as synthons, appropriate for reuse in subsequent reactions to yield products with altered morphologies. This section highlights various procedures that can be used to modify the size of nanomaterials, yielding high-quality products that can be utilized in applications beyond their initial purpose.

In 1999, Hutchison and co-workers found that they were able to transform 1.5 nm triphenylphosphine-stabilized particles to 5 nm amine-stabilized materials in a highly reproducible manner, simply by stirring the smaller particles in a solution containing a primary amine.[81] Visible spectroscopy (Figure 17) shows the development of a narrow

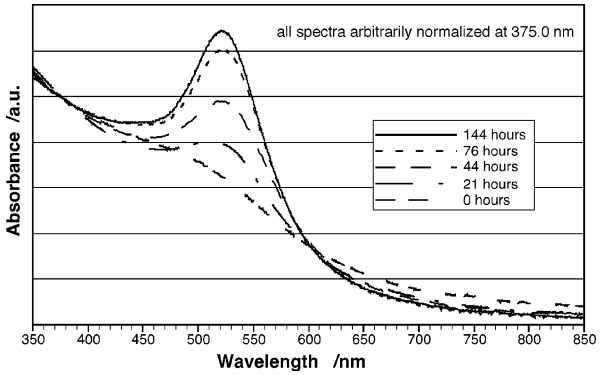


Figure 17. Triphenylphosphine-stabilized nanoparticles evolve to larger amine-stabilized gold nanoparticles with strong optical absorption upon reflux with a solution of alkylamines. (Reprinted with permisison from Brown, L. O.; Hutchison, J. E. *J. Am. Chem. Soc.* **1999**, *121*, 882, Figure 3. Copyright 1999 American Chemical Society.)

plasmon resonance at ~525 nm as the growth process proceeds. Similar conditions are often applied with thiols for the purpose of ligand exchange reactions, but no core size evolution was ever noted in those cases. A bimodal size distribution is maintained throughout the course of the reaction, indicating that smaller particles are consumed as larger particles grow. Analysis of the nanoparticle composition by XPS indicates that displacement of the triphenylphosphine stabilizer is complete, and no small particles remain, yielding products with excellent reproducibility in terms of their size and composition. Besides providing a secondary use for smaller particles, this method also features the green merits of room-temperature operation, nearly quantitative yields, and additive processing.

While Hutchison's report is an excellent example of creating larger monodisperse nanoparticles from smaller precursor materials, an even greater challenge lies within the transformation of relatively polydisperse materials to those having a more uniform size distribution. Miyake and coworkers reported size evolution processes in the solid state.[82−84] Having identified the boiling point of a nanoparticle mixture as a key limitation in thermal size evolution processes, dodecanethiol-stabilized particles prepared by the Brust route were used as a starting material for the thermal reaction. When the crude nanoparticles were stripped of their solvent and heated to temperatures of 150, 190, and 230 °C, the 1.5 nm particles grew to sizes of 3.4 ± 0.3, 5.4 ± 0.7, and 6.8 ± 0.5 nm, respectively,[82] suggesting that the nanoparticles grow until they become thermodynamically stable at the heat treatment temperature. Unfortunately, molten TOAB is essential in this reaction, as particles heat treated in its absence did not experience a similar growth.[83] Additionally, a mechanism for the thermal reaction was elucidated, whereby the small thiol-stabilized particles are believed to melt and coalesce to a thermodynamically stable product, which is once again capped by thiols as the ligands rearrange around the product.

More recently, Miyake and co-workers explored the thermal size evolution of gold nanoparticles stabilized by 11-mercaptoundecanoic acid (MUA).[84] The pH dependent solubility of the MUA-stabilized particles played a critical role in the thermal reaction. Since it has been established that TOAB is critical to uniform size evolution processes, treatment of the particles with HCl leads to reduced solubility in nonpolar solvents, as TOAB readily complexes with the particles in their ionized state. Such pH treatments were essential for comparison of the thermal treatments in the presence and absence of TOAB, since treatment with HCl is required for the complete removal of TOAB. Once again, the particles formed monodisperse products in the presence of TOAB. Upon heating to temperatures of 150, 160, and 170 °C, the 1.8 nm particles grew to average diameters of 2.4 ± 0.4, 4.6 ± 0.8, and 9.8 ± 1.2 nm, respectively. While it is reassuring that excess surfactants may be removed from the products, surfactants must be eliminated from thermal size evolution processes so that the merits of this method (improving monodispersity, materials recycling, and preserved atom economy) overshadow the drawbacks.

In contrast to transforming nanomaterials to larger structures, simple etching processes are helpful for controlling reaction conditions by removing unwanted material from a mixture, as well as the straightforward modification of larger materials to smaller, simpler structures. Etching not only provides a clear route to secondary applications of nanomaterials, but it may also serve as a means of narrowing size dispersity.

Control over nucleation events is critical in the synthesis of many larger and more complex nanostructures. Xia and collaborators reported the use of a selective oxidative etchant capable of reducing the number of seed nuclei in solution, thus allowing larger nanostructures to develop without competitive reactions with emerging nucleation centers.[85] $FeCl_3$ was used in conjunction with the polyol reduction of $PdCl_4^{2-}$, leading to an unprecedented synthesis of larger Pd nanocubes ranging from 25 to 50 nm. When the same reduction was carried out in the absence of Fe(III), the resulting Pd structures had a maximum dimension of only 8 nm. This reaction was performed under ambient conditions, which were later determined to be critical to the suppression of excess nucleation, since oxygen is required to sustain the continuous etching activities by converting Fe(II) back to Fe(III). $FeCl_3$ is a known noble metal etchant whose use in nanosynthesis could certainly be applied to other materials where control over nucleation and growth processes is key toward reaching a synthetic target structure.

Etching techniques are most commonly used to completely decompose noble metal structures, usually for the purpose of analyzing their organic components. Recently, Stucky et al. reported the use of mild oxidation methods to reduce the

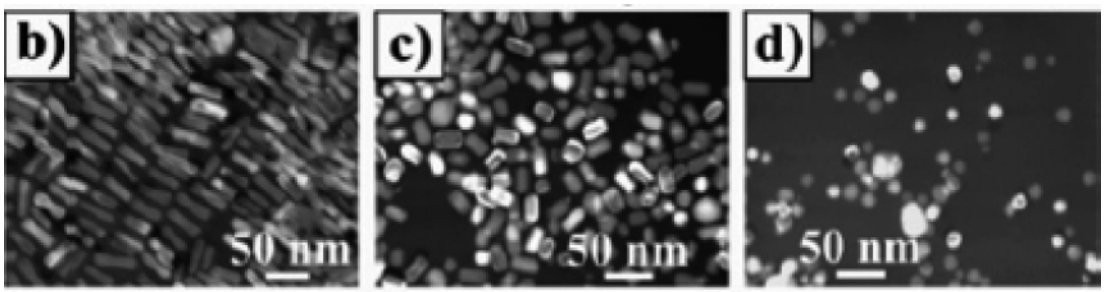


Figure 18. Gold nanorods (b) can be selectively oxidized to yield structures with reduced aspect ratios (c). Continued oxidation results in spherical particles (d). (Reproduced with permission from Tsung, C.-K.; Kou, X.; Shi, Q.; Zhang, J.; Yeung, M. H.; Wang, J.; Stucky, G. D. *J. Am. Chem. Soc.* **2006**, *128*, 5352, Figure 1b,c,d. Copyright 2006 American Chemical Society.)

aspect ratio of gold nanorods by selectively etching the ends of the structures, eventually arriving at spherical nanoparticles as shown in Figure 18. Gold nanorod solutions were acidified with HCl, and oxygen gas was bubbled through the stirring solution. The oxidation rate was proportional to the concentration of hydrochloric acid and temperature. This reaction requires the use of additional CTAB to stabilize the nanomaterials as they are etched, but this controlled method of size evolution allows researchers to decompose nanomaterials in a manner that avoids the use of harsh oxidizers, such as nitric acid or concentrated hydrogen peroxide, and entirely avoids toxic reagents, including cyanide.[86]

2.4. Emerging Approaches in Nanoparticle Synthesis

2.4.1. Preparations Involving Minimal Reagents

While continuous efforts have been made to improve overall reaction yields, atom economy is often overlooked as a potential refinement to nanosynthesis techniques. Atom economy can be improved by choosing solvents and reagents capable of serving multiple roles. For example, one could employ reducing agents which also function as a stabilizing material (such as carboxylates and amines), employ solvents which can act as a reducing agent or stabilizer (such as diglyme), or change solvent systems such that auxiliary materials such as phase transfer reagents may be omitted. From a completely different angle, the use of solid-state techniques provides an opportunity to completely bypass the need for solvents. Another benefit of reducing the number of components of a reaction is that subsequent purification needs are often simplified, or even eliminated. The following section highlights reports of syntheses that have taken advantage of minimal reagent use, while yielding high-quality materials.

The Brust synthesis of gold nanoparticles involves the reduction of a gold(I)−thiol polymeric complex, yielding thiol-protected gold nanoparticles. As part of an investigation intended to better characterize these polymeric precursors, Kim et al. found that irradiation under the electron beam of a transmission electron microscope led to the formation of gold nanoparticles. As shown in Figure 19, by changing the accelerating voltage of the electron beam, particles ranging from 2 to 5 nm in diameter could be obtained. Higher accelerating voltages promote particle nucleation, whereas lower voltages favor growth of larger particles. Additionally, as is the case for many other nanoparticle preparations, it was found that the length of the hydrocarbon chain of the thiol is inversely proportional to the size of the resulting nanoparticles.[87] While this example does not provide an especially practical means of preparing larger particles, it highlights the importance of product purity, as excess unreacted starting materials can induce changes in product morphology.

Recently, it was discovered by Yamamoto and Nakamoto that gold(I) thiolate complexes can form nanostructures via simple pyrolysis reactions. The controlled thermolysis of a gold(I) thiolate complex, $Au(C_{13}H_{27}COO)(PPh_3)$, at 180 °C under an inert atmosphere for 1−10 h leads to particles capped primarily by myristate and a small amount of phosphine, ranging in size from 12 to 28 nm. This reaction does not require the use of solvents, stabilizers, or reducing agents, although higher reaction temperatures are required and purity may be an issue. Thermolysis temperatures can be elevated to access particles with larger diameters. The particles are soluble in acetone and remain in solution for weeks. The reaction occurs by the elimination of the myristate ligand, which reduces the gold and caps the particles. Eliminated PPh_3 reacts with the precursor complex, producing $Au(PPh_3)_2C_{13}H_{27}COO$, which does not participate in thermolysis reactions. Triphenylphosphine is believed to act as a stabilizing agent for the intermediate gold(0) species formed during the thermolysis reaction.[88]

Last, silver nanoparticles (3−14 nm) were prepared at the air−water interface below Langmuir monolayers of Vitamin E. Using an alkaline solution of Ag_2SO_4 is key to promoting reduction by the phenolic groups of vitamin E, since the resulting phenolate ions are capable of transferring electrons to the silver ions during nanoparticle formation.[89] This method bears some analogy to the biphasic Brust procedure, in that Vitamin E monolayers behave as a solventless organic phase. The green merits of this procedure are quite pronounced, since it uses no organic solvents, harsh reducing agents, or phase transfer materials, and it does not require extensive washes or precipitation-based purification techniques. Although the procedure is difficult to scale up in its current form, the use of continuous-flow microchannel reactors may enable greater production.

2.4.2. Advances in Nanoparticle Purification

Although they are not readily detected in the most commonly employed analytical techniques (e.g., TEM and SEM), impurities (including unreacted starting materials, excess reagents, and byproducts resulting from side reactions or degradation pathways) are present in nanoparticle samples and have been shown to have a significant impact on properties such as reactivity,[90] stability,[91] and toxicity. Nearly all end applications of nanomaterials will necessitate the use of highly pure materials, particularly those intended for electronic or medical purposes. The development of structure−

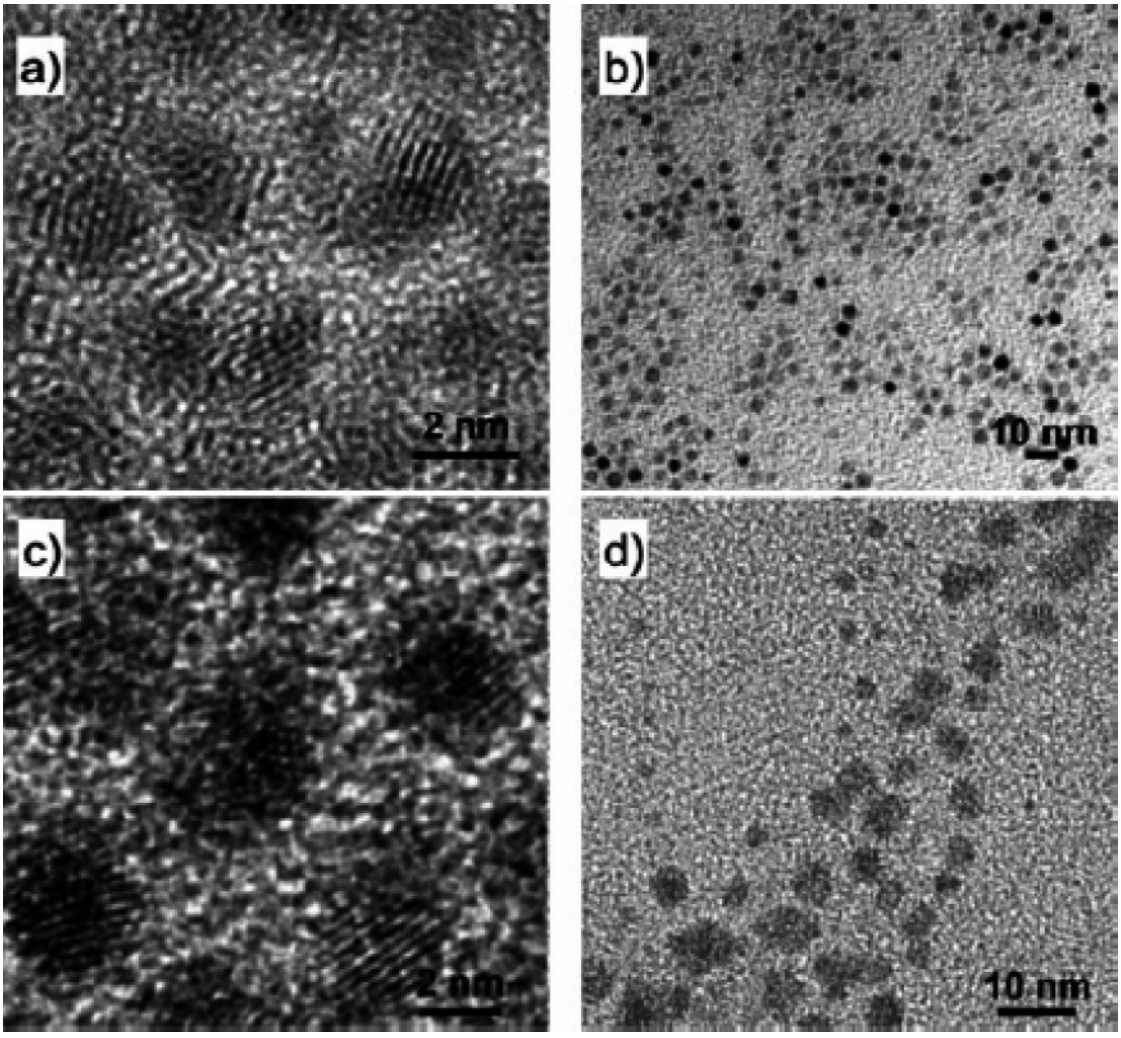


Figure 19. TEM images of nanoparticles formed via electron-beam irradiation of gold(I) salts with various hydrocarbon chain lengths and accelerating voltages: (a) Au(I)-SC_{18} at 300 keV; (b) Au(I)-SC_{18} at 80 keV; (c) Au(I)-SC_6 at 300 keV; (d) Au(I)-SC_2 at 300 keV. (Reprinted with permission from Kim, J.-U.; Cha, S.-H.; Shin, K.; Jho, J. Y.; Lee, J.-C. *J. Am. Chem. Soc.* **2005**, *127*, 9962, Figure 2. Copyright 2005 American Chemical Society.)

activity relationships (SARs) critically depends upon the availability of pure samples. For example, in developing the SARs related to the health impacts of nanomaterials, these studies become more complicated, or impossible, when one must delineate whether or not a nanomaterial is inherently toxic, or if the deleterious effects are due to contaminants and byproducts. Thus, a key to furthering our understanding of SARs for nanoparticles and to designing greener nanoparticles for a wide range of applications is the development of effective purification strategies that can provide samples with fully characterized and reproducible purity profiles. The greenness of the purification methods themselves should be a central focus, since many techniques currently used rely on the use of large amounts of solvents (often liters/gram) for extraction or washing purposes. A brief comparison of purification methods currently in use is offered below, with the intention of illustrating the state of nanoparticle purification methods, guiding the researcher to the most appropriate, efficient techniques, and motivating the development of new purification strategies.

Centrifugation and precipitation techniques are among the most established means of isolating nanomaterials from the bulk reaction mixture. Centrifugation isolates materials based on mass and relative solubility, while precipitation is effected by a loss of solubility in the reaction media due to the introduction of an antisolvent. Both methods have been used for the separation of noble metal nanoparticles and carbon-based nanomaterials. Each can be time-consuming and solvent intensive. Although the volumes of solvent consumed in these purifications are hard to quantify based upon the reported procedures, one analysis of a typical purification method has recently been reported. In a traditional purification strategy, purification of a thiol-stabilized gold nanoparticle requires a combination of precipitation, extraction, and ultracentrifugation. This sequence of steps generates considerable organic solvent waste (>15 L of solvent/gram of nanoparticle) and is not effective in removing all the small molecule impurities.[92] A more rigorous purification required a combination of extraction, ultracentrifugation, and chromatography steps. Recently, extractive methods have been developed to include more sophisticated means of separation, using surface-selective reagents to promote cross-linking or phase separation exclusively among the products, ensuring that other contaminants remain in the bulk of the reaction mixture.[93−97]

Chromatography provides a means of purification and size fractionation, provided the products are sufficiently stable and not excessively retained by the column support. In the authors' experience working with dozens of ligand-stabilized gold nanoparticles, chromatography (particularly size exclu-

sion chromatography)[98] has proven effective for removal of small molecule impurities from the nanoparticle products. However, in nearly all cases, recoveries are quite low (a few percent) due to sample degradation and/or irreversible binding to the support. Despite these limitations, size-exclusion chromatography is still a viable method for producing milligram quantities of relatively pure material. Others have reported recent advances in this technique that include the separation of carbon nanorods[99] and recycling of size exclusion materials.[100] Electrophoresis has also been used to separate metal nanoparticles based on the relative core size, and recently, it has been proven to be a useful method of separating particles based on the relative number of functional groups.[101] Most chromatographic methods reported to date are also solvent-intensive methods (with the exception of those carried out in water) and have proven difficult to scale to produce larger amounts of pure nanoparticles.

In an attempt to find new methods of purification that reduce solvent consumption while enhancing separation performance, a number of researchers have turned their attention to nanofiltration methods and have made significant strides toward purifying noble metal and magnetic nanomaterials in a greener, more efficient process.[92,102,103] Such methods typically employ solvents such as water and simple alcohols, as other organic solvents are often incompatible with filter membrane materials. In particular, diafiltration affords a simple, rapid method of isolating nanomaterials with superior purity and yield compared to the more traditional techniques described above. Sweeney et al. demonstrated the efficiency of diafiltration for the purification of ligand-stabilized gold nanoparticles by comparing the proton NMR spectra of products from different purification methods. The spectra in Figure 20 show that the sharp signals due to free ligand, top trace, are absent in the diafiltered sample but exist to varying degrees in the samples purified by the other methods. In this case, diafiltration produces higher purity material while eliminating the use of organic solvent in the purification process. As noted above, the traditional purification of these materials requires liters of solvent per gram of nanoparticle and does not effectively remove the contaminants. Diafiltration, on the other hand, is more effective and eliminates the use of organic solvent in this purification. Membrane-based methods such as diafiltration are scalable to large volumes.

Given the importance of purity for fundamental studies and practical applications of nanoparticles and the convenience and effectiveness of nanofiltration for purification, further research is warranted to develop membranes with finer control over pore size and size dispersity and to develop membranes that are compatible with organic solvents (for use with nanoparticles that are soluble in those solvents).

2.4.3. Electrochemical Methods

Electrochemical synthesis routes provide an attractive alternative to the standard methods of synthesizing nanomaterials. By simply applying a potential between two active electrodes, current flow can drive oxidation and reduction processes of materials suspended in solution, often improving atom economy by avoiding the use of reagents that are not a component of the final product. Electrochemistry can utilize many of the twelve principles of green chemistry; for example, waste prevention, energy conservation, maximize atom economy, use of safer solvents, and use of catalyst.[104]

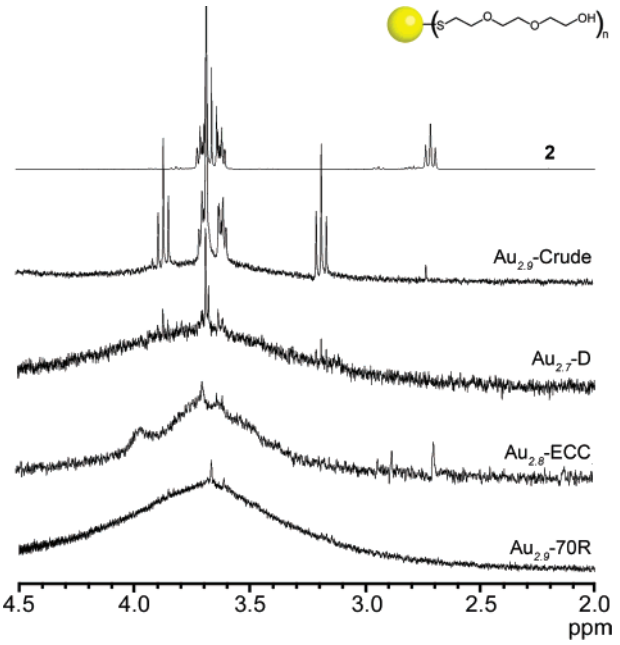


Figure 20. ^{1}H NMR comparison of nanoparticles purified by various methods. From the top: NMR signals arising from the ligand alone, crude nanoparticles, and nanoparticles purified via dialysis ($Au_{2.7}$-D), extraction, chromatography, and centrifugation ($Au_{2.8}$-ECC), and diafiltration ($Au_{2.9}$-R) The sample purified via dialysis has an undetectable amount of free ligand, whereas the presence of free ligand is readily detected by NMR for the other samples. (Reprinted with permission from Sweeney, S. F.; Woehrle, G. H.; Hutchison, J. E. *J. Am. Chem. Soc.* **2006**, *128*, 3190, Figure 2. Copyright 2006 American Chemical Society.)

Reactions may occur at low temperature, often under aqueous conditions, and the flow of electrons can be considered a reagent.[105,106] The green merits are numerous: such procedures typically consume little energy beyond the operation of the electrodes, very little waste is generated, and the supporting media have low volatility, thus reducing inhalation hazards. Pure products are easily recovered, since the electrodes may be considered easily separable catalysts, and one can even use solid-supported electrolytes to further simplify product recovery.[107,108] A significant drawback remains in the area of scale up, but electrochemical techniques remain useful for research in the discovery phase.

Stucky reported an electrochemical synthesis of ZnO nanostructures using very small amounts of surfactant, avoiding the formation of liquid crystalline phases in solution that may impact structure morphology.[109] Liu offered several reports of stabilizer-free electrochemical syntheses of stable gold complexes. Particles having an average diameter of 2 nm were generated in a dilute KCl solution by first roughening the gold electrodes by oxidative−reductive cycling (ORC), followed by the application of an overpotential bias to form the particles. It was also discovered that pyrrole autopolymerizes on the surface of the particles to form core−shell structures.[110,111] Liu later reported that larger structures can be achieved by increasing the number of oxidative−reductive electrode cycles prior to nanoparticle synthesis[112] and that such methods may be applied to the deposition of gold on titania nanoparticles to form stable core−shell structures.[113] Further sonication separates the nanoparticle from the polymer. The long-term stability of these gold-containing nanocomposites is unknown. Choi et al. prepared ZnO thin films using electrodeposition from aqueous $Zn(NO_3)\cdot 6H_2O$ and dilute surfactant (0.1% sodium

dodecyl sulfate, SDS).[109] They showed that formation of thin films was independent of surfactant concentration but dependent on the type of surfactant. CTAB was insufficient to form ZnO films, but dilute SDS was able to coordinate deposition. Furthermore, the surfactant could be washed from the surface with ethanol and water, suggesting that it is only weakly physisorbed to the surface, resulting in pure ZnO thin films.

2.4.4. Microcapillary and Integrated Microchannel Reactors

A key to using nanoparticles in commercial products or in devices will be the development of methods for producing them in larger volumes. In addition to the development of new synthetic methods that are more readily scaled, a parallel approach involves gaining control of process conditions that are known to influence product dispersity even in small batch reactions, particularly the rates of mixing and timing of reagent addition. In larger scale batch reactions, these mixing problems will be exacerbated. One avenue researchers are exploring to address this issue is the use of microfluidic reactors to develop and then scale up production. The approach involves optimizing nanosynthesis in a microchannel format and then "numbering up" the process, using many parallel channels to produce larger volumes of material. Kilogram scale production of organic compounds has been demonstrated with benchtop microreactors.[114] The primary benefit of the microreactor approach for green nanosynthesis is the opportunity to gain greater control of process conditions (speed of mixing reagents and adding reagents at later stages of the reaction, residence time within the reaction zone, and speed of reaction quenching) and perhaps to monitor the reaction process in real time with integrated sensors. A recent review describes the merits of this approach for the production of compound semiconductor nanoparticles.[30]

These types of reactors have been used in the synthesis of a plethora of materials, from biological materials[115] to synthetic materials such as semiconductor nanoparticles (e.g., CdSe and TiO_2).[116] Microchannel reactors are unique mixers because their interior volumes are small and under moderate velocities the fluid flow is laminar. Working within the boundaries of laminar flow is important because it facilitates spatial delivery of fluids within a capillary; thus, mixing of a multisolvent system is controlled at precise locations in the capillary. Lin et al. created narrow-dispersity silver nanoparticles by thermal reduction of silver pentafluoropropionate dissolved in isoamyl ether and a surfactant (trioctylamine) using a single phase precursor system in a continuous flow microchannel reactor.[116] By varying the temperature, flow rate, and reaction times, they demonstrated control of the size of the silver nanoparticles, yielding 7−8 nm products. Increasing the flow rate led to polydisperse particles ranging from 3 to 12 nm. Reaction temperature was also critical. Silver nanoparticles formed at temperatures ∼100 °C, while 120 °C yielded the best results, whereas 140 °C provided smaller, but more polydisperse, nanoparticles. These results suggest that microchannel reactors may be versatile systems for synthesizing nanoparticles with controlled size and shape in scalable quantities.

3. Toward Greener Preparations of Semiconductor and Inorganic Oxide Nanoparticles

Studies related to greener methods of synthesizing semiconductor nanomaterials are still relatively scarce, and this area thus presents one largely unexplored frontier in nanoscience. Synthetic challenges are numerous, providing significant opportunities to incorporate green nanoscience principles in the design of new methods. One specific challenge involves the synthesis of true nanoalloys, free of significant phase separation between individual components. Another area of exploration includes controlling the unique surface chemistry of such materials at the nanoscale. Despite the fact that many of these materials are inherently toxic, green nanoscience principles developed through metal synthesis could be applied to semiconductor and oxide materials to enable greener process development to minimize overall impacts on human safety and the environment.

Several particular materials have been the focus of intense research, and a great deal of progress has been made toward greener processing. The discussion below highlights advances in the synthesis of cadmium, zinc, and iron compounds, with special emphasis on processes that reduce hazards in preparation and enable materials applications.

3.1. Cadmium Selenide and Cadmium Sulfide

Although these materials contain toxic elements, they remain the focus of intense study. Fortunately, numerous modifications have been made to standard procedures, leading to safer and greener methods. Ultimately, the inherent safety of these materials is contingent upon identifying an appropriate substitute for Cd^{2+}, without compromising the optical properties that make these materials so useful.

Typically, CdSe nanocrystal synthesis involves the use of dimethyl cadmium with trioctylphosphine oxide (TOPO). The raw materials (organometallics, usually) are especially toxic, pyrophoric, unstable, and expensive, and the reactions often lack control and reproducibility.[117] The reaction solvent TOPO is prohibitively expensive and hinders the possibility of industrial scale up procedures,[118] and the surface chemistry of such materials is limited, reducing the options for further manipulation of the particles. However, although the established synthetic procedures suffer these apparent shortcomings, this approach has been useful for the formation of high-quality CdSe nanoparticles. Nevertheless, it is clear that greener, more efficient synthetic procedures are needed, although the development of a completely green technique has remained a daunting task. If we accept that the nanoscale products of CdSe/CdS syntheses are likely to retain their inherent toxicity regardless of the synthetic methods used, multiple opportunities to develop greener methods remain. The modification of a single step in these procedures may eventually build the foundation for the use of safer techniques in nano-semiconductor syntheses, leading to a benign methodology resulting from a composite of incremental improvements.

To this end, early progress was made by O'Brien and coworkers, replacing a pyrophoric cadmium source, dimethyl cadmium, with air-stable precursor complexes, specifically, bis(methyl(*n*-hexyl)dithio or -seleno)carbamato complexes of zinc or cadmium. Nearly monodisperse ($d = 5.0 \pm 0.3$ nm) quantum dots of CdSe, CdS, ZnSe, or ZnS can be prepared by this route. The use of these air-stable complexes has greatly simplified the preparation of such QDs, requiring only the preparation of a solution with trioctylphosphine, followed by stirring with TOPO at 200 °C, yielding air-stable TOPO-capped materials.[119]

Peng reported a significant reduction of the hazard associated with the use of highly reactive dimethyl cadmium,

achieved by conversion to a stable, isolable cadmium complex via the reaction of cadmium oxide with hexylphosphonic acid (HPA). Alternatively, this complex can be formed in situ by the reaction of CdO with HPA at elevated temperatures. The use of this precursor in TOPO-mediated reactions with selenium yields CdSe nanocrystals having a diameter > 2 nm, which is difficult to obtain by the traditional route. The full scope of this breakthrough is being explored, as other precursors have been formed by reaction of CdO with fatty acids, amines, phosphonates, and phosphine oxides. Thus, hundreds of greener combinations are possible. Larger, monodisperse particles ($d = 1.5-25$ nm) have been accessed via syntheses utilizing these precursors, which have a range of reactivity based on the complexing ligand, resulting in a variety of average core diameters.[117]

The use of dimethyl cadmium alternatives was further simplified in a one pot synthesis of core−shell CdSe/CdS quantum dots.[120] Beginning with air-stable, readily available cadmium acetate, quantum dots with excellent photoluminescent quantum efficiencies were prepared in a mixture of TOPO, hexadecylamine, and tetradecylphosphonic acid, which serves as a capping agent. Selenium was introduced in a typical manner as a trioctylphosphine complex. Besides acting as a capping agent, the phosphonic acid slows the growth of the dots, offering more control over the core size. Additionally, the relatively lower reactivity of cadmium acetate (vs dimethyl cadmium) hinders the formation of excess nuclei and consumption of cadmium monomers, permitting the growth of somewhat larger materials. To develop a CdS passivation shell, H_2S was introduced in the gas phase to the crude reaction mixture via injection through a rubber septum into the headspace of the reaction vessel, permitting slow delivery of the reagent to the quantum dot mixture, thus allowing the slow epitaxial growth at the surface of the CdSe particles.

Cadmium chloride has also proven to be a useful alternative to pyrophoric cadmiun sources. Another step was made toward realizing a useful synthetic procedure by eliminating the need for TOPO as a reaction medium.[121] Bao reported the synthesis of CdS nanorods in toluene, utilizing a new class of ligands, alkylisothionium salts, to stabilize the growing nanorods in analogy to the use of alkylammonium salts in the synthesis of reduced symmetry gold and silver materials. A variety of alkyl chain lengths were considered (C12, C14, and C18), and it was found that *S*-dodecylisothionium (C12) salts yield nanorods with the highest aspect ratios. Thiourea and ethylenediamine play key roles in the mechanism of nanorod formation. The authors propose that ethylenediamine forms a complex with Cd^{2+}, which then reacts with thiourea to form CdS nuclei. The surfactants bind preferentially to certain crystal faces, thus directing subsequent growth into a nanorod. More recently, Querner et al. reported the use of another class of bidentate ligand, carbodithioic acids, as an alternative shell material for the passivation of CdSe cores.[122] Besides offering passivation comparable to that of CdS, ZnS, or ZnSe, such ligands permit control over the surface chemistry of the nanomaterials. Specifically, the ligands feature a pendant aldehyde that can participate in subsequent coupling reactions, allowing the introduction of various functional groups without disturbing the photoluminescent properties of the core materials.

Commercially available heat transfer solvents have proven to be useful as a direct substitute for TOPO, if one wishes to preserve all other aspects of the traditional preparation of CdSe quantum dots. Wong and co-workers explored the use of two commercially available solvents, Dowtherm A (a mixture of biphenyl and diphenyl ether) and Therminol 66 (a terphenyl-based blend), which are able to sustain the high temperatures which warrant the use of TOPO.[123] Cadmium oxide was reacted with a trioctylphosphine selenium complex in the presence of oleic acid, yielding 2.7 nm particles, somewhat smaller than those obtained by analogous reaction conditions in TOPO. Other alternative solvents having high boiling points, such as octadecene and octadecene/tetracosane blends, have also been used to achieve the temperature control required for the greener synthesis of ZnSe and ZnS nanomaterials from the alkylamine-catalyzed reaction of Zn−fatty acid complexes with selenium−phosphine compounds.[124]

As suggested earlier in this section, incremental improvements to the traditional preparation of cadmium-based nanomaterials have the potential to add up to an all-around greener synthesis. An excellent example was offered by Deng and co-workers, using paraffin as the reaction medium for the synthesis of high-quality (demonstrated by the characterization methods shown in Figure 21) cubic CdSe quantum dots.[125] In this greener procedure, CdO and oleic acid were dissolved in heated paraffin. Selenium was dissolved in a separate aliquot of paraffin, and the two mixtures were combined, yielding particles with diameters of 2−5 nm,

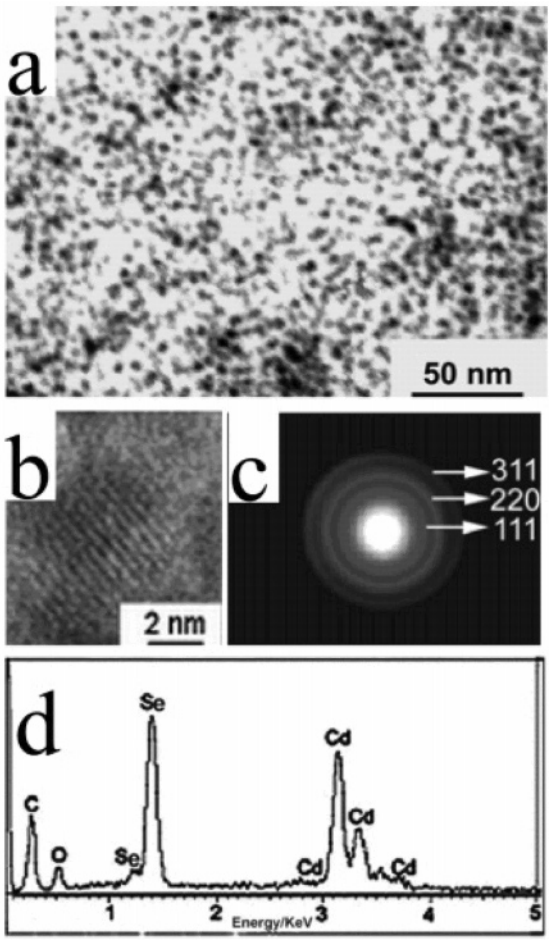


Figure 21. Oleic acid-capped CdSe nanocrystals: (a) TEM image; (b) HRTEM image; (c) electron diffraction pattern; (d) EDX pattern of corresponding particles. (Reprinted with permission from Deng, Z.; Cao, L.; Tang, F.; Zou, B. *J. Phys. Chem. B* **2005**, *109*, 16671, Figure 5. Copyright 2005 American Chemical Society.)

depending upon the reagent concentration. This low-cost procedure not only eliminates the use of TOPO but also dispels the need to prepare a selenium−trioctylphosphine complex, greatly reducing the majority of hazardous reagents and reaction conditions associated with the preparation of these materials.

Although CdSe and CdS quantum dots are inherently toxic regardless of the method of preparation, careful manipulation of the surface chemistry of such materials can facilitate more "hands-off" approaches to the handling of these materials. We have already described the clever use of a chelating ligand that promotes modification of the pendant functionality of quantum dots, and such approaches are likely to gain further prominence if self-assembly techniques are used in the fabrication of quantum dot arrays. Templating approaches offer an alternative means of dictating the relative positioning of quantum dots. Broadly speaking, templates can serve multiple roles, acting as nucleation centers during synthesis,[126] stabilizing agents for synthesized materials, and assembly directing matrices. While there is a trend toward minimizing risks by reducing the direct handling of quantum dots, it should be noted that this solution is only as robust as the stability of the particles within a given application; that is, accidental release of tethered particles remains a possibility, so long-term greener solutions rely on the identification of alternative materials, rather than the containment of toxic nanoparticles.

3.2. Zinc Nanomaterials

The formation of spherical zinc oxide nanoparticles is a very straightforward process, commonly achieved through a simple base-catalyzed reaction of zinc acetate with hydroxide ions, hydrothermal reactions of various Zn(II) sources in the presence of base, and gas-phase reactions of organozinc compounds, involving either thermolysis or controlled oxidation. Although the reports are too numerous to completely review, they have provided a foundation of knowledge over the years, contributing to the discovery of a number of methods for the synthesis of anisotropic ZnO nanostructures, several of which are especially noteworthy for their greener merits.

The use of ionic precursor compounds is common in the synthesis of anisotropic materials, since their general preparation closely matches the classic techniques of spherical particle synthesis. Chang created 2-D arrays of nanorods through a solution process using aqueous preparations of zinc nitrate and hexamethylenetetramine (HMTA).[127] The amine generates ammonium hydroxide in the presence of water, which reacts with Zn^{2+} to form ZnO. The arrays were formed on various substrates featuring a ZnO overlay formed by atomic layer deposition. It is proposed that such substrates are critical to nucleation events, since their lattice-matched surface templates seed layer formation that leads to the growth of single crystal materials. Electron energy loss spectroscopy revealed the presence of nitrogen at the core of the nanorods, confirming that larger nanorods are the product of smaller, thinner individual rods that fuse together as the reaction proceeds. A somewhat similar process was reported by Sun and Yan et al., whereby ZnO nanowires form via the stacking and fusion of rectangular nanoplates.[128] Briefly, $Zn(OH)_4^{2-}$ is prepared from zinc acetate and sodium hydroxide and reacted in SDS reverse micelles, resulting in the formation of small uniform nanoparticles. The particles fuse together in a hexagonal crystal arrangement (wurzite structure), creating plates that stack together to form nanorods, retaining their rectangular cross section.

Elemental zinc has also proven useful in greener nanosynthesis. Zhao and Kwon synthesized aligned single crystal ZnO nanorods by a hydrothermal reaction between zinc powder and hydrogen peroxide.[129] This preparation has the added advantage of being completely templateless, avoiding issues of persistent organic contamination. As a solid state alternative, Chaudhuri's oxygen-assisted thermal evaporation of elemental zinc on quartz substrates yields nanorods of various morphologies, depending upon the vapor pressure of zinc.[130] This reaction demonstrates excellent atom economy, since no reagents are used save zinc and oxygen. A self-catalyzed vapor−liquid−solid equilibrium between zinc vapor, liquid zinc, and the substrate is responsible for the formation of nuclei, followed by a simple vapor−solid equilibrium that facilitates longitudinal growth. Again, the products are free of contaminants that may compromise their utility in a given application.

3.3. Iron Oxides

The synthesis of magnetic nanoparticles has received increased attention as the possibility of creating functional materials became more apparent, generating interest as isolable sequestering agents for removal of solution-phase contaminants (magnetically assisted chemical separation), heat transfer reagents, and medical imaging enhancers. Typically, colloidal magnetite is synthesized through the reaction of a solution of combined Fe(II) and Fe(III) salts with an alkali.[131] Magnetite (Fe_3O_4) precipitates from this solution as particles ranging in size from 5 to 100 nm, depending upon the solution concentrations, the identity of the alkali, and the general reaction conditions. In the synthesis of such materials, care must be taken to prevent agglomeration driven by the inherent magnetic properties of the particles. The inclusion of excess salts or surfactants provides a general means of passivation. More recently, a simple solid state "ball-milling" technique was reported.[132] Anhydrous Fe(II)/Fe(III) salts are mixed with NaOH and excess NaCl and milled in the solid state, yielding particles ranging from 12.5 to 46 nm, depending upon the final annealing temperature. Excess NaCl (rather than excess surfactants and dispersion agents) prevents agglomeration of the magnetic particles, which can be purified through simple washes. While ball-milling is energy intensive, it remains a valuable industrial-scale production method whose green merits can be improved by avoiding the use of dispersion agents, which in turn require extensive washing to ensure complete removal.

Micellar surfactants have been used as microreactors in the synthesis of maghemite (Fe_2O_3).[133] Ions (as $FeCl_2$) have been sequestered within mixed anionic/cationic micellar vesicles composed of CTAB and dodecylbenzenesulfonic acid. Excess extravesicular ions are removed through ion exchange chromatography. Isotonic sodium hydroxide is capable of diffusing to the interior of the micelle, reacting with iron ions to form maghemite nanoparticles. The superparamagnetic particles range from 2.1 to 2.7 nm in diameter, depending upon the size of the micelles and the concentration of NaOH. The magnetic diameter of the particles is somewhat smaller, indicating that the particles possess a deactivated surface layer. Micellar synthesis of such materials presents the advantage of preventing further growth and possible aggregation of the particles.

Ordered arrays of magnetic nanoparticles can be accessed through templating methods. Li et al. reported the synthesis

of ordered two-dimensional nanoparticle arrays formed within a porous film. Maghemite structures were obtained by depositing $Fe(NO_3)_3$ in between the pores formed by a network of polystyrene beads.[134] Subsequent drying and annealing steps lead to the formation of Fe_2O_3, and the polystyrene template can be removed via solvent washes. Further control over the size of the nanostructures is made possible by partially dissolving the polystyrene template prior to depositing the iron-based reagents.

As with other nanomaterials, functionalization chemistry provides an opportunity to alter solubility and impart stability to as-synthesized materials. Surfactants have been used to impart temporary stability to magnetic particles, allowing for subsequent functionalization.[135] Aqueous maghemite (Fe_2O_3) particles with average diameters of 8 ± 2 nm were synthesized by reacting a mixture of Fe(II)/Fe(III) ions with NaOH in the presence of sodium dodecylsulfate (SDS). Methylmethacrylate was introduced to the solution, displacing SDS. The addition of a polymer initiator led to the growth of poly(methylmethacrylate) around the particles, with no apparent cross-linking. The functionalized particles are stable against oxidation and present pendant carboxylate groups which allow for further functionalization through grafting techniques, taking advantage of many possible coupling reactions. Core−shell nanoparticles having an iron oxide core and a gold shell have been obtained through seeded growth techniques.[136] Magnetic nanoparticles ($d = 9$ nm) were synthesized using standard precipitation methods. Citrate ions were exchanged for hydroxyls on the surface of the particles, in preparation for gold deposition. Gold shells were deposited through a series of treatments (monitored by visible spectroscopy, shown in Figure 22) with a growth solution of

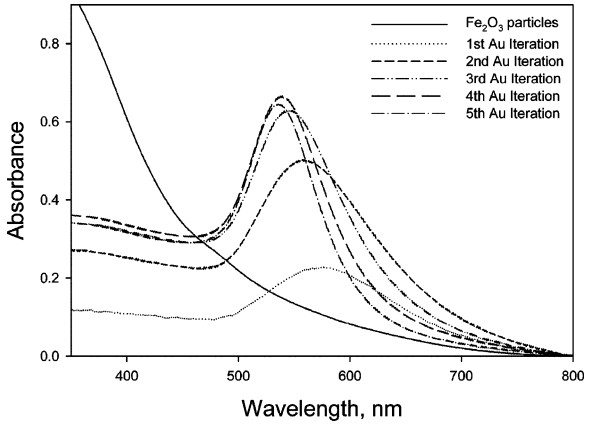


Figure 22. Iterative formation of gold nanoshells around iron oxide cores, as followed by changes in the UV−vis spectrum. (Reprinted with permission from Lyon, J. L.; Fleming, D. A.; Stone, M. B.; Schiffer, P.; Williams, M. E. *Nano Lett.* **2004**, *4*, 719, Figure 3. Copyright 2004 American Chemical Society.)

$HAuCl_4$ and hydroxylamine, leading to particles having a final average diameter of 60 nm. The magnetic properties of the core were unaffected by the presence of the gold shell.

Since some of the most promising applications of magnetic nanomaterials lie within the medical imaging field, functionalization designed with biological environments in mind has been an area of increasing focus. Rotello reported the use of a cubic silsesquioxane ligand to functionalize magnetic materials, resulting in excellent stability in a variety of aqueous solutions, resisting aggregation upon encountering environmental variations such as changes in pH and salt concentration.[137] Wang and co-workers reported the functionalization of magnetite nanoparticles by ligands featuring a surface-binding catechol moiety and a bisphosphonate pendant group, designed to remove uranyl ions from blood.[138] Neither group reports complete functionalization of the particles' surface, but the coverage is adequate to impart new surface properties, thus broadening the range of applications for these materials.

4. Alternative Solvents and Energy Sources for Nanoparticle Synthesis

In the pursuit of particular nanosynthetic targets, the choice of starting materials may be somewhat non-negotiable, especially if a particular surface functionality is essential to a given application. Reaction conditions, on the other hand, can often be tuned such that one arrives at the same product in a more efficient, benign manner. Variations in reaction media can involve fairly simple modifications such as substitution of the solvent, reduced temperature and pressure, or more advanced techniques that provide a supporting environment for the reaction while continuing to produce high-quality products. In this section we highlight recent progress in the use of alternative solvents, including supercritical fluids and ionic liquids, and energy sources, namely photochemical and microwave-assisted reactions.

4.1. Supercritical Fluids

Supercritical fluids (SCFs), at temperatures and pressures beyond the critical point of liquid−vapor equilibrium possess density, viscosity, and solvation properties that are intermediate between those of the vapor and liquid phases. As such, they have recently gained attention as benign solvents for the synthesis of inorganic nanoparticles. SCFs such as H_2O and CO_2 are nonflammable, nontoxic, easily accessed materials. The relative strength of the solvent may be continuously tuned by adjusting temperature and/or pressure in the supercritical state, while maintaining unique wetting properties arising from the lack of surface tension, as there is no liquid−vapor interface. Supercritical CO_2 is readily accessed at relatively low temperatures and pressures, although it should be noted that, as a solvent, SC-CO_2 acts as a rather nonpolar material; thus, the use of fluorinated metal precursors and capping ligands is often required to impart solubility to inorganic materials. Esumi reported the preparation of particles from a fluorinated organometallic precursor, triphenylphosphine gold(I) perfluorooctanoate, reduced by dimethylamine borane in SC-CO_2.[139] The products had an average diameter of 1.0 ± 0.3 nm and could be redispersed in ethanol, although aggregation tends to occur upon standing. On the other hand, SC-H_2O allows the researcher to employ highly elevated temperatures that cannot be sustained by most conventional solvents, which can be a useful property for the synthesis of many metal and semiconductor materials.[139−143] Korgel used supercritical water to create hexanethiol-capped copper nanoparticles.[142]

The use of CO_2 emulsions can sometimes mitigate these extreme cases, generating solvent environments with intermediate properties. Silver and copper crystals were prepared in a surfactant-containing water-in-CO_2 microemulsion, where the structure of the emulsion acted as a shape-directing template.[144] Supercritical CO_2 has been used for both the synthesis and deposition of gold nanoparticles into low-defect films. The use of CO_2-expanded liquids (i.e., organic solvent/SC-CO_2 mixtures) as an alternative to pure SC-CO_2 systems

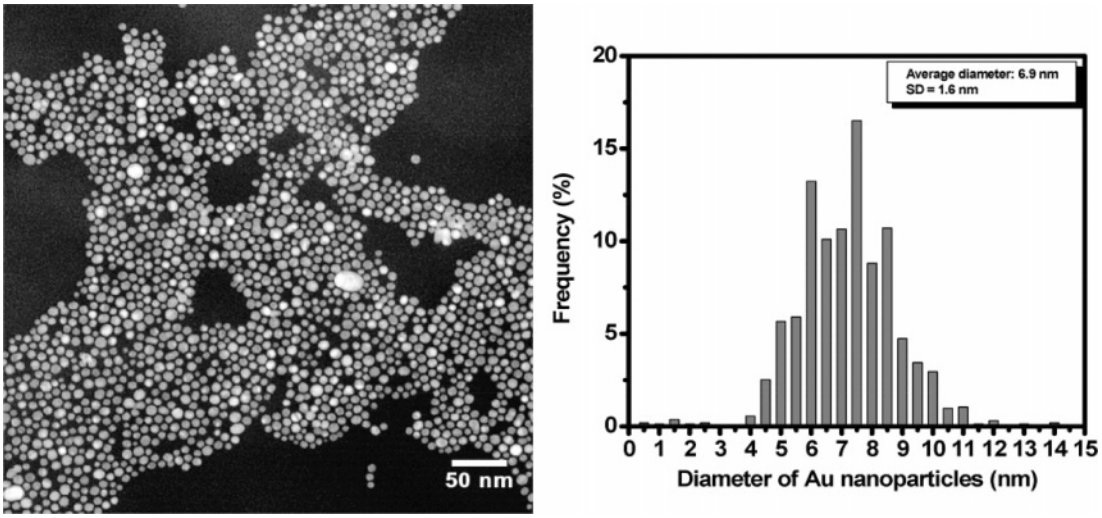


Figure 23. TEM image of β-D-glucose-capped gold nanoparticles, and a histogram showing the corresponding size distribution. (Reprinted with permission from Liu, J.; Anand, M.; Roberts, C. B. *Langmuir* **2006**, *22*, 3964, Figure 2. Copyright 2006 American Chemical Society.)

holds the advantage of eliminating the need for perfluorinated compounds by increasing the range of solvent properties, allowing inorganic−hydrocarbon composites to remain stable under SC conditions. This concept was demonstrated recently by Roberts, creating wide-area, low-defect films of alkanethiol-capped gold nanoparticles (see Figure 23) from CO_2-expanded hexane solutions.[145] Previously, supercritical CO_2/ethanol mixtures have proven useful for the preparation of copper nanocrystals prepared by thermal decomposition of a perfluorinated organometallics precursor.[146] A unique method described as "precipitation by compressed antisolvents" was used to drive the preparation of nickel and cobalt nanoparticles, where SC-CO_2 is fed into a solution of the metal compound. Taking advantage of the limited solubility of inorganic materials in SC-CO_2, supersaturation conditions are reached, leading the precipitation of nanoparticulate materials.[147] If these reports are taken together, one may conclude that supercritical fluids hold great promise in the development of more benign synthetic routes, with demonstrated utility in nanosynthesis, assembly, and purification. The development of new (benign) surfactants and supercritical solvent systems is likely to increase the range of materials that are soluble under such conditions, potentially eliminating the need for perfluorinated materials in this area of research.

4.2. Ionic Liquids

Ionic liquids (ILs) have received attention as alternative solvents and stabilizers for nanomaterials synthesis, due to their general ease of synthesis, stability (nonflammable, thermally stable), and low vapor pressures. Ionic liquids feature low interfacial tension that allows them to adapt to the surrounding reaction media, and their relative solubility may be tuned by varying their anionic and cationic components. Careful choice of the anion is critical to their use within a green chemistry context, since BF_4^- and SF_6^- are believed to evolve hydrofluoric acid over time,[148] and variations in vapor pressure arise from individual cation/anion combinations.[148] Their limited miscibility with water and organic solvents often simplifies product purification and promotes recovery and recycling, although drying ionic liquids prior to use can be difficult. Nanomaterials composed of noble metals, oxides, and semiconductors have been prepared in such solutions.

The vast majority of IL syntheses are carried out using imidazolium derivatives having various counterions. Kim reported the synthesis of gold and platinum nanoparticles by $NaBH_4$ reduction of $HAuCl_4$ in the presence of a thiolated IL, yielding nanoparticles with diameters of 2.0−3.5 nm. The monodispersity was dictated by the number of thiol groups present in the reaction mixture.[149] Tatumi used a zwitterionic material as an IL, based on the imidazolium functionality derivatized with a thiol headgroup and a pendant sulfonate, to synthesize 2.5 nm gold particles.[150] Others have used ionic liquids as capping agents despite the absence of thiol functionality. Itoh and co-workers described such a use of ILs in the synthesis of gold nanoparticles, finding that the product solubility could be tuned by exchanging the anion.[151] Large gold nanosheets were prepared by Kim et al. in a neat, microwave-assisted reaction between $HAuCl_4$ and an imidazolium-based IL.[152] More recently, the synthesis of an alcohol-derivatized IL was reported, where the IL may act as both a reducing agent and a capping material to create nearly monodisperse 4.3 nm gold particles.[153] To further ease isolation and purification of nanomaterials synthesized in ionic liquids, Wang described how the addition of oleic acid as a primary capping agent facilitates the precipitation of gold nanoparticles from an IL-based reaction mixture.[154]

Platinum nanoparticles may be synthesized by similar routes. Scheeren et al. reported the reaction of $Pt_2(dba)_3$ with an imidazolium-type IL to yield nanoparticles with average diameters ranging from 2.0 to 2.5 nm. Larger particles could be accessed by varying the counteranion.[155,156] Zhao and colleagues recently described the ionic liquid-mediated synthesis of platinum nanoparticle-studded carbon nanotubes.[157]

Ionic liquids may also be used for the general synthesis of inorganic nanostructures.[158] Kimizuka reported the synthesis of hollow titania microspheres in a toluene/ionic liquid medium. The nanospheres form at the interface of a microdroplet of toluene and the surrounding ionic liquid.[159] A modified sol−gel technique employing ionic liquids and an immiscible titanium tetraisopropoxide/alcohol solution was used to create 5 nm titania crystals.[160] Ionic liquids have been used to drive the synthesis of ZnO nanostructures with unusual morphologies, as in the case of ZnO pyramids where all exposed surfaces are the very polar (0001) and {1011} planes.[161] The strongly polar environment imposed by ionic liquids helped to form PbO nanocrystals featuring the PbS

crystal structure.[162] Manganese oxide molecular sieves were synthesized from ionic liquids, where the ionic liquid acts as a reducing agent, cosolvent, and shape-directing material.[163] The thermal stability of ILs assisted the synthesis of CoPt nanorods from a mixture of $Co(acac)_3$, $Pt(acac)_2$, and CTAB (present as a shape-directing agent).[164] Unusual Bi_2S_3 "flowers" were synthesized in ILs, and it was discovered that prolonged aging of these materials ultimately led to the structural breakdown, followed by nanowire growth.[165] Finally, rounding out the range of synthetic applications afforded by this class of reagents, nanoscale metal fluorides were synthesized in ionic liquids, demonstrating predictable rodlike morphologies, regardless of the metal precursor employed.[166]

4.3. Sonochemical

Sonochemical synthesis provides an additional approach that can be used to control particle size and morphology. Although it has not been extensively studied, the results reviewed in this section suggest that sonochemistry could represent a green alternative to synthesis of nanomaterials. The chemical effects of a sonochemical reaction result from acoustic cavitation, defined as the formation, expansion, and rapid implosion of bubbles. The bubbles create transient localized hot spots upon implosion with extremely high temperature and pressure, which have been measured to be ~500 K and ~1800 atm.[167] Metallic nanoparticles result from decomposition of volatile precursors within these rapidly collapsing bubbles. The nanoparticles created from these reactions have been shown to have significantly higher catalytic activity compared to similar nanoparticles produced by different methods.[167,168] For example, hollow MoS_2 nanospheres were made using sonochemical deposition on silica powder followed by hydrofluoric acid etching.[168] The hollow MoS_2 nanospheres were used as a catalyst in hydrodesulfurization of thiophene and found to be superior to commercially available MoS_2. The authors speculate that the superior catalytic activity of these hollow MoS_2 nanospheres rests in access to the inner surface and edge defects along the outer surface.

Sonochemistry has been studied in relation to gold nanoparticle synthesis with a fair measure of success. Several factors are important in using sonochemistry to create gold nanoparticles using green chemical principles. In particular, the size of gold nanoparticle produced depends on the frequency used and the rate of Au(III) reduction.[169] Su et al. used sonochemistry to prepare ~20 nm gold nanoparticles in an aqueous environment without the addition of alcoholic or surfactant stabilizers.[170] The gold nanoparticles formed in aqueous solution at 4 °C contained trisodium citrate at concentrations greater than 1.9 mM. They observed that the citrate concentration was important in controlling nanoparticle production using this method. Liu et al. used a combination electrochemical oxidation/reduction and sonochemical reduction to create 2−15 nm gold nanoparticles in an aqueous solution without addition of stabilizers.[171] They were able to control the ratio of nanoparticles to nanocomplexes by altering the sonoelectrochemical reduction time.

4.4. Laser Ablation

Laser ablation is a physical technique used to generate nanoparticles or nanostructured films within a wide range of conditions. Using this physical method to fabricate nanoparticles in a contamination free environment, such as pure water, produces high-purity nanoparticles.[172] Ablation in liquids results in nanoparticles that have different surface contaminants depending on the solvent or surfactants used. Laser ablation in vacuum, gases, or solids has been examined extensively, yet only recently have researchers begun studying ablation at the solid−liquid interface. Once more fully developed, this approach could provide alternative greener approaches to the preparation of nanoparticle samples with tunable size and shape.

Studying laser ablation at the solid−liquid interface yields mixed results, suggesting complex interactions between the metal and the liquid environment. Gold and silver metals ablated in water, ethanol, or *n*-hexane produced sols containing around 12−20 nm nanoparticles, but ablation in chloroform resulted in metal compounds.[173] X-ray photoelectron spectroscopy (XPS) of the chloroform sample revealed the formation of a gold−chlorine compound, which the authors confirmed to be $[H_3O]^+[AuCl_4]^-$. Silver produced similar results in chloroform. Laser ablation of gold dipped in liquid alkanes from *n*-pentane to *n*-decane produced Au sols with varying results.[174] The length of the hydrocarbon chain controlled the shape and rate of formation of the nanoparticles. Figure 24 shows that the relative particle aspect ratio

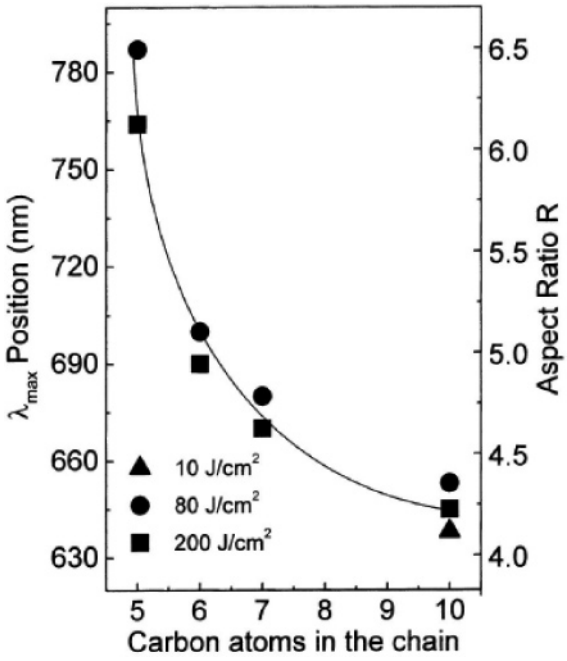


Figure 24. Hydrocarbon chain length is inversely proportional to nanoparticle aspect ratio. (Reused with permission from G. Compagnini, *Journal of Applied Physics*, *94*, 7874 (2003). Copyright 2003, American Institute of Physics.)

decreases from 6 to ~4.5 nm as the number of carbon atoms in the chain increases. At low fluence (less than 5 J/cm^2), spherical nanoparticles form, but as the fluence increases, more elongated nanoparticles appear (as evidenced by TEM and a second extinction peak in the UV−vis region). The aspect ratio is controlled by the molecular mass of the alkane (see Figure 25), showing that the carbon chain length determines the nanoparticle shape.

Simakin et al. observed similar results using pure water.[175] In their case, using low fluence (1−40 J/cm^2), they observed disk-shaped Au and Ag nanoparticles with diameters of 20−60 nm that were only a few nanometers thick. Another study produced monodisperse, small colloidal gold nanoparticles

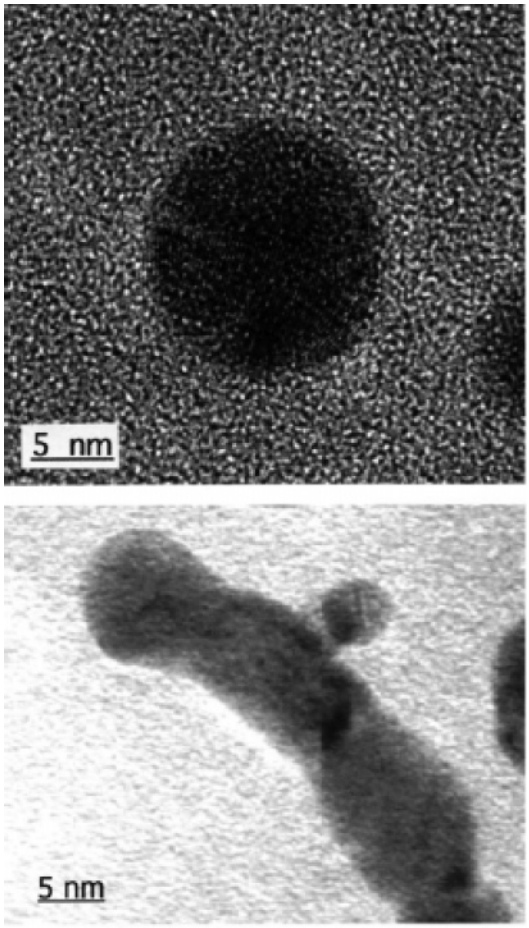


Figure 25. Relationship between fluence and nanoparticle shape. TEM images of products obtained by Au laser ablation in *n*-decane at 1 J/cm^2 (top) and 80 J/cm^2 (bottom). (Reused with permission from G. Compagnini, *Journal of Applied Physics, 94*, 7874 (2003). Copyright 2003, American Institute of Physics.)

using pure water as a solvent and a femtosecond laser.[172] These results suggest that the type of liquid, ablation time, energy density, and wavelength affect nanoparticle size.[176] The sol-based gold and silver nanoparticles discussed above were subsequently used to prepare thin films by spin-coating the sols, showing that it is possible to use these nanoparticles in nanocomposite films if the right solvent is chosen.[173] Clearly, producing nanoparticles from bulk noble metals with tunable properties by laser ablation represents a green alternative in the laboratory. However, the ability to scale up to production level, the cost of laser maintenance, the energy requirements needed to produce the final product, and the choice of media (e.g., liquid, gas, vacuum) are other important factors that must be considered when determining whether the use of laser ablation is practical for generating nanoparticles with tunable properties.

4.5. Microwave

Microwave synthesis is a relatively new chemical method to facilitate reactions and could be another avenue for green synthesis of nanomaterials. Several attributes of microwave heating contribute to greener nanosyntheses, including shorter reaction times, reduced energy consumption, and better product yields. It is possible to scale up the production of nanoparticles using this methodology for industrial applications.[177,178] High-quality semiconductor nanowires and nanorods made from metal sulfides or selenides can be made in large batches in under 3 min using microwave irradiation.[179] Complex semiconductor materials such as InGaP, InP, and CdSe can be rapidly made in scalable, industrial batch quantities using microwave heating.[177] A very simple method was developed to produce high-quality, high-purity nanoparticles for use as catalysts, showing that nanoparticles formed by microwave irradiation have industrial applications.[178] Microwave heating occurs through the interaction of electromagnetic radiation with the dipole moment of molecules; thus, polar solvents with a high dipole moment, such as water[180] and ionic liquids,[181] are among the best solvents to use in microwave synthesis.[181] Room-temperature ionic liquids (RTILs) have recently received attention as a replacement to noxious volatile organic solvents because of their many useful properties, such as high fluidity, low melting temperature, stability in air and water, high ionic conductivity, and ability to dissolve a variety of materials.[181−185] RTILs have been used in the synthesis of a variety of metallic nanoparticles, including Pt, Pd, Ir, Ag, Au, ZnS, ZnO, CdSe, Te, and metal sulfides such as Bi_2S_3 and Sb_2S_3.[181−184,186] In many cases, the microwave temperature is ∼100 °C and the total reaction time is ∼10 min. Many of these studies report producing nanospheres of varying sizes using RTILs. Nanorods and nanowires were made out of Co_3O_4,[55] Te,[184] and metal sulfides[165] using RTILs and microwave heating, whereas ZnO formed flower-like nanosheets.[182] Other solvents were employed in an attempt to produce Te nanorods and nanowires. Of the solvents tested, ILs were the most successful for formation of Te nanorods and nanowires.[184] Jiang and Zhu found that an ionic liquid was necessary for the formation of metal sulfide nanorods as well.[183] In the absence of an ionic liquid, Bi_2S_3 formed branched "urchin-like" structures, whereas Sb_2S_3 formed irregular crystalline sheets. Cao et al. also reported the importance of using ionic liquids in combination with microwave heating to produce ZnO nanosheets, suggesting that this combination of method and solvent plays a critical role in formation of these structures.[182] Wang and Zhu showed that both ionic liquid and reaction temperature were important in controlling the morphology of Co_3O_4 nanorods.[186] It is unclear why this combination is so effective, but its speed, the use of benign reactants, the ability to scale up product quantities, and the ultimate purity of the final product make this technique a potentially useful green application.

Many studies have explored the effects of temperature, solvent, reductant, and reaction times on nanoparticle formation.[180,181,184,187−190] The reaction temperature, the ramp time (rate at which the temperature reaches the reaction temperature, usually in °C/min), and the reaction time are all critical factors in controlling the size and shape of gold nanoparticles.[180] Using microwave radiation, monodisperse gold nanoparticles around 15−20 nm in diameter could be produced from a narrow range of citrate concentrations (2−6 mM), using higher synthesis temperature (∼125 °C), faster ramp rates (>20 °C/min), and reaction times of at least 15 min.[180] Silver nanospheres or nanorods can be produced from the same reaction conditions by simply altering the reaction temperature; intermediate temperatures produced both nanorods and nanospheres.[187]

Microwave heating has also been used in the preparation of TiO_2. The three primary polymorphic phases of TiO_2 are anatase, rutile, and brookite. Anatase and rutile are commonly used in commercial products from paints to solar cells or

for remediation. Anatase is used for a variety of applications, such as photocatalysts, solar cells, production of hydrogen and electric energy, and optical coatings. Rutile is typically used in cosmetics and paints. Mixtures of anatase and rutile exhibit higher photoactivity and greater ability as a catalyst, yet pure phases are often needed for specific applications,[191] although obtaining industrial quantities of pure phases of TiO_2 is caustic and cumbersome. Recently, a few studies have explored microwave heating to produce TiO_2 nanostructures.[189,192] A microwave hydrothermal method using urea and $TiOCl_2$ resulted specifically in ~10 nm nanoparticles of anatase.[192] Omitting urea resulted in a mixture of rutile and anatase, showing the importance of urea in directing the formation of a single phase. Using a similar microwave−hydrothermal process, Baldassari et al. produced pure rutile, pure anatase, or a mixture, depending on reaction temperature and time, demonstrating specific impacts on crystal formation.[189]

5. Bio-Based approaches

Harnessing nature's synthetic machinery is an exciting approach to nanosynthesis that embodies most of the twelve principles of green chemistry. It creates intricate nanostructures with tunable properties using materials found in local surroundings and carefully crafts devices, protective armor, lighting, and energy vessels with highly efficient materials use. Materials scientists, engineers, physicists, and chemists have turned to nature in an effort to understand its mechanisms and develop clean, green nanomaterials through biomimetic and biosynthetic approaches. One of the key tenets of biology is the ability of biomolecules to self-assemble into supramolecular structures. This intrinsic ability has piqued the interest of scientists and engineers to develop a bottom-up approach to nanofabrication. Biological self-assembly occurs at the molecular scale and is often reversible, self-correcting, and self-healing. The shape and size of self-assembled structures are intricately controlled on the nanoscale. Thus, understanding these mechanisms can open doors for development of a wide variety of new materials from self-healing fibers for wound repair to faster, smaller computer devices. Understanding how biology self-assembles structures can also lead to synthetic methods for creating supramolecular structures, using nature's blueprints to create synthetic nanomaterials.

Some organisms have the capability to take up minerals from their surrounding environment and create intricate inorganic−organic hybrid structures that possess remarkable nanoscale properties. Bone, teeth, and seashells are just a few examples that utilize calcium carbonate to make hard composites. Some unicellular organisms make exoskeletons: coccolithophores create exoskeletons using calcium carbonate much like seashells, and diatoms produce shells from amorphous silica. Calcium carbonate producing animals are under intense investigation in the hopes of producing artificial bone or dental composites.

In the remainder of this section, we discuss two active areas of research at the bio−nano interface that relate to the synthesis of inorganic nanomaterials. The first section describes the use of biomolecules to control the shapes of inorganic structures under growth conditions. The second reviews the use of whole organisms to produce nanoscale particles.

5.1. Shape Control with Biomolecules

Size, shape, and functionality are key attributes to the tunability of nanoparticles. Controlling these parameters using green chemistry methods will be integral in developing new nanostructures. Several methods exist for controlling the size and shape of nanoparticles. For example, nature creates nanoparticles of very defined shapes and sizes using genetic control. We can exploit similar biomechanisms to create nanoparticles using biological molecules or organisms as precursors or seeds for growth.

To date, whole organism systems have been used to produce metallic nanoparticles, although some limited studies have begun to explore fabrication of Ge[193] in bioreactors or Ti from purified organic cellular components.[194] Nevertheless, attempts have been made to ascertain which organic components of microorganisms are responsible for directing crystal growth. Proteins, polysaccharides, lipids, peptides, and amino acids are among the most studied organic biomolecules responsible for directing crystal growth and can be considered capping agents in production of nanocrystals. Proteins and polysaccharides have been partially purified from the marine organisms that direct calcium carbonate crystallization in the production of exoskeletons.[195,196] Proteins responsible for silica deposition in diatoms[197] and sponge spicules[198] have been well characterized, and in many cases recombinant proteins have been produced. These organic components are under genetic control and can potentially be used to fabricate novel nanostructures. For example, Shimizu et al. cloned and sequenced silicatein, the protein responsible for silica deposition in sponge spicules.[198] Curnow et al. then used this silicatein by fusing it onto the outer coat of a bacterial cell to fabricate layered amorphous titanium phosphate at low temperature and neutral pH (see Figure 26).[194]

Others have fused proteins that direct silica deposition in diatoms with a spider dragline silk protein, which is known for self-assembly properties and mechanical strength.[199] Fusion proteins have been used in drug delivery applications, formation of quantum dots, gels, and sensor applications. This novel fusion protein could be used to make self-assembled nanofilms and mineralized silica-based nanocomposites by altering the solution conditions. Nanofibers were also produced from the fusion proteins by electrospin methods. The authors speculate that the silica deposition protein could be replaced by moieties that direct titanium, hydroxyapatite, or germanium. However, given that diatoms can fabricate Si−Ge nanoparticles in vivo,[193] it is conceivable that this chimeric protein can be used to produce Ge nanoparticles or nanofibers.

Many naturally occurring proteins have been shown to control the shape and size of materials. Proteins isolated from seashells or unicellular organisms with inorganic exoskeletons can be purified and used to direct the growth of crystals.[195] Proteins isolated from silica producing organisms have been used to create TiO_2 nanoparticles and other nanostructures.[194,198] Creating artificial proteins a priori has not been wholly successful, although proteins have been redesigned through genetic engineering to be more robust for use in creating novel nanostructures with specific shapes and sizes.[200]

5.2. Whole Organism Approaches

Biological organisms have been used in environmentally friendly methods to create nanoparticles. Organisms from

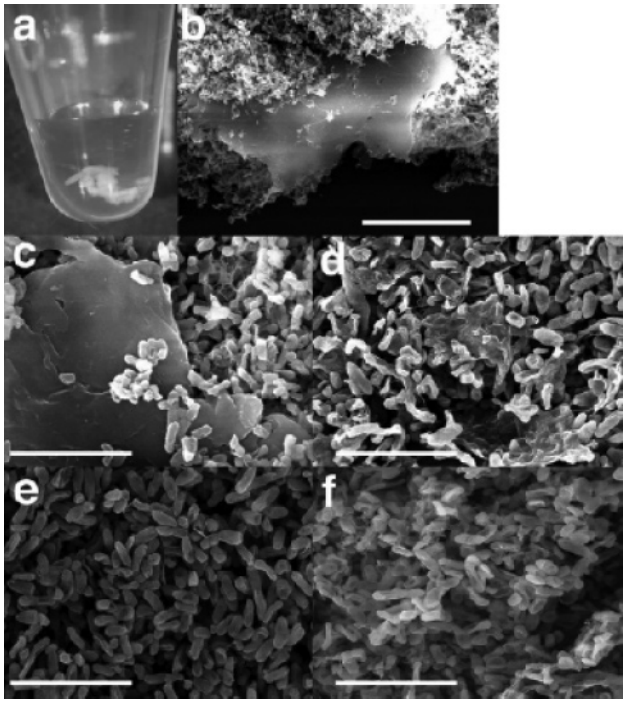


Figure 26. Microscopic analysis of the cell surface after interaction with titanium. Aggregation is apparent in the cells expressing silicatein on the surface. Higher magnification by SEM reveals "sheets" of titanium not apparent in control cells (e and f). (Reprinted with permission from Curnow, P.; Bessette, P. H.; Kisalius, D.; Murr, M. M.; Daugherty, P. S.; Morse, D. E. *J. Am. Chem. Soc.* **2005**, *127*, 15749, Figure 3. Copyright 2005 American Chemical Society.)

microbes to complex multicellular systems are able to synthesize nanoparticles with precisely controlled size, shape, and functionality. Just a few examples include magnetobacteria, diatoms, and coccolithophores. Multicellular organisms produce nanoscale composites, tough organic−inorganic hybrid structures such as shell and bone. These organic−inorganic hybrid structures are composed of an inorganic component (e.g., calcium or silica) and an organic matrix (e.g., polysaccharides, proteins). The composite materials are orders of magnitude stronger than the crystalline inorganic component, since the organic matrix lends strength to these composite materials.[201] All of these organisms extract materials from their surrounding media to fabricate these intricate nanostructures under ambient, environmentally safe conditions. Bacteria are used directly in many applications from bioremediation, as described above, to catalysis of mineral precipitation. For example, magnetobacteria synthesize nanosized Fe_3O_4 and Fe_2S_4.[202] These bacteria produce single magnetic crystals that are folded into ordered chain or ring structures, which can be used as nanomagnets.[203] Noble metal nanoparticles, such as Au or Ag, will precipitate in certain bacteria, with the nanoparticle size and shape being dependent on growth conditions.[202] These bacteria become resistant to these metals, allowing particular strains to be used to produce and accumulate nanoparticles of gold or silver. Silver can accumulate up to 25% of the dry weight biomass within a cell wall, suggesting potential for industrial quantity production using these types of whole organisms.[203] Sulfate-reducing bacteria produce ZnS biofilms naturally under anaerobic conditions. Some bacteria such as *Clostridium, E. coli*, and *Klebsiella* have been shown to produce CdS quantum dots either on the cell surface or intracellularly.[203,204] Sweeney et al. found that when certain strains of *E. coli* were incubated with cadmium chloride and sodium sulfide, CdS nanocrystals spontaneously formed during the stationary phase of growth.[204] Since transcription increases during this stage, it is possible that one or more transcriptional products serve as capping agents to control nanocrystal formation.

Eukaryotic organisms have the ability to produce nanomaterials. For example, fungi have been used to produce Au,[68] Ag,[67] ZnS,[202,203,205,206] CdS,[202,203,205,206] and Au−Ag alloy nanoparticles.[71] In the formation of gold nanoparticles, the reduction of $AuCl_4^-$ most likely occurs through the NADH reductase system. Ahmad et al. recently showed that fungi can produce silver[205] or gold nanoparticles[206] either intracellularly or extracellularly. The authors speculated that extracellular production of gold or silver nanoparticles occurs through fungal release of reductases into solution. Extracellular nanoparticle production could provide highly pure nanoparticles, thus eliminating the need to extract nanoparticles from intracellular biomass. This would expand the capability of nanoparticles for use in such systems as nonlinear optics, optoelectronic devices, or thin films. Most of these biogenic nanoparticles have not been tested in device applications. One potential problem with using whole organisms to produce nanoparticles might reside in the methods needed to purify the nanoparticles after synthesis. Extraction and purification methods might be caustic, involve organic solvents, or cause destabilization of the nanoparticle. Though biological contaminants may not be toxic or environmentally harmful, they could interfere with device applications. Nevertheless, using whole organisms as putative bioreactors could be a poignant environmentally friendly method to produce nanoparticles, particularly semiconductor nanoparticles that are often made under harsh conditions. One study showed that CdS quantum dots produced in yeast function as diodes, suggesting that these biologically produced nanomaterials can be used in nanodevices.[207] Biologically produced nanoparticles tend to be stable in solution, perhaps due to protein interactions, further suggesting that purification may not be an issue in some cases. Diatoms, a type of microalgae that produce intricate nanostructured silica cell walls, have been used recently as bioreactors to fabricate Si−Ge oxide nanocomposites.[193] These Si−Ge nanocomposites were ordered into microstructures within the diatom cell wall, suggesting this route could be used to directly assemble nanodevices with optical or electronic applications.

Gaskin et al. reported the first "proof of concept" using viral phage display libraries to direct crystal growth through directed evolution of viral coat proteins.[208] Since proteins have been shown to control crystallization of biological structures (e.g., exoskeletons, bone, and seashells), Gaskin postulated that combinatorial phage libraries could be used to genetically modify the coat proteins to bind to specific crystal faces. Bound viruses were allowed to replicate, selecting for those viruses that produce proteins that can direct the crystallization of specific metals.[209] Applying directed evolution, proteins or peptides can be genetically selected to bind specific crystal faces. The advantage of this approach is that knowledge of secondary protein structure is not necessary for designing templates. Using this method, unique peptide sequences on the outer surface of a viral phage display can specifically bind silver and cobalt nanoparticles.[210] Viral phage display libraries were also used to direct crystallization of FePt metal alloys under ambient conditions.[211] Peptides specific for FePt nanocrystals were

identified and used to synthesize nanoparticles and nanowires, which were further tested for ferromagnetic capabilities, suggesting that these nanomaterials could be used in storage device applications. Nucleic acid-based in vitro display techniques and PCR-based approaches, for example RNA display libraries, have been developed that increase the library size several orders of magnitude (10^{15}, compared to that for phage displays: 10^{7}).[209,212]

6. Functionalization

While our primary focus has been on the topic of nanomaterials synthesis, efforts to control the surface chemistry of products are key to defining how the material interacts with its surroundings, whether in a solution or in the solid phase. Nanoparticle syntheses of the Brust-type can provide a direct route toward a product that features the desired surface chemistry as synthesized, assuming reagent compatibility (i.e., the thiol-based capping agent must not react with sodium borohydride). However, there are a few caveats to this approach if multiple products are desired. The preparation of similar nanomaterials differing only in their surface chemistry often requires that individualized optimization efforts are applied to a general synthetic route, since the choice of capping ligand can greatly impact the average size and morphology of the products. Because unique products must be generated in a single batch, larger amounts of solvent are required to support numerous parallel reactions. In order to circumvent these issues, the preparation of versatile core materials amenable to surface modifications may be a more strategic approach if one wishes to create a diverse library of materials with uniform core sizes, differing only in the composition of the ligand shell. Surface modification methods can be categorized into two major classes (see Figure 27): postsynthetic modification of the existing

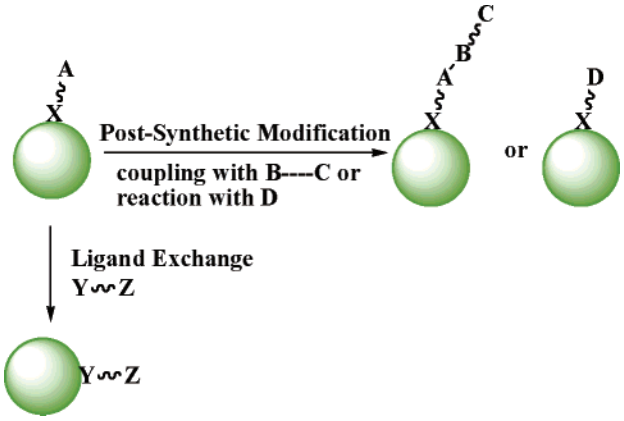


Figure 27. Strategies for nanoparticle functionalization. Postsynthetic modifications take advantage of the existing stabilizing shell, using either coupling reactions or simple organic transformations to impart the desired functionality. Ligand exchange reactions displace the existing stabilizing shell with a ligand featuring either the same headgroup or one that demonstrates greater binding affinity than the original.

ligand shell, involving simple transformations of pendant functionalities or grafting, and ligand exchange, where an existing ligand shell is displaced by a different incoming ligand.

6.1. Postsynthetic Modification of the Ligand Shell

Postsynthetic modification methods involve the direct synthesis of a stable nanoparticle that can sustain secondary reactions intended to introduce a new chemical functionality to the surface of the particle. Candidates for postsynthetic modifications are generally produced by direct synthesis (ω-functionalized particles created by Brust preparations) or sometimes ligand exchange methods (usually involving the introduction of a ligand bearing a reactive pendant functional group). Modification reactions include polymerizations,[213−216] coupling reactions,[40,48,217−221] or transformation of an existing chemical moiety.[48,222−224] In all cases, the success of such modifications relies not only on the nanoparticles' tolerance for various reaction conditions but also on the overall reactivity and steric environment presented by functional groups that are constrained through binding to a nanoparticle. Factors that impact the efficacy of postsynthetic modifications may include the following: the length of the ligand composing the stabilizing shell, since this impacts the steric mobility of ω-functional groups, the spatial density of such groups, and the bulk of the incoming nucleophile (for S_N2 type reactions). Nanoparticles featuring amino, carboxylate, and bromo or iodo terminal groups are commonly used to generate libraries of functional materials through postsynthetic modifications. Although this method affords greater versatility to a single precursor material, it should be noted that characterization of the modified materials might be exceedingly difficult, due to difficulties encountered when assessing the extent of modification.

6.2. Ligand Exchange

Ligand exchange methods are somewhat of a hybrid technique, as they require the direct synthesis of a versatile precursor nanoparticle stabilized by a labile ligand shell, followed by a ligand exchange step where the original ligand shell is partially or fully displaced by another ligand that bears pendant functional groups, thus introducing the desired chemical functionality to the surface of the particle. This strategy offers multiple green advantages, since a single batch of nanoparticles can be divided and exchanged with multiple ligands, yielding numerous products while consuming minimal resources. Solvent use is reduced, compared to one-off direct synthesis routes, and no coupling reagents are necessary, as is often the case for postsynthetic modifications. The products are easily characterized via NMR and XPS, particularly if a different headgroup is introduced (e.g., thiol vs phosphine). Triphenylphosphine-stabilized nanoparticles, having a relatively labile ligand shell, readily undergo ligand exchange reactions with other phosphines, amines, and thiols. The nanoparticles obtained by Hutchison's procedure have been functionalized by a wide range of ligands through exchange reactions, yielding a diverse library of functional nano "building blocks" ideal for use in the bottom-up assembly of new nanostructures.[225,226] Ligand exchange reactions that displace phosphines in favor of incoming thiols (Figure 28) are among the most versatile and well studied examples of ligand exchange reactions;[227−230] however, in the past decade, ligand exchanges have been performed on a wide variety of materials having other stabilizing ligands. Several different classes of ligand exchange reactions have emerged, with one commonality: the incoming ligand used in the exchange reaction has equal or greater affinity for gold than the ligands composing the original stabilization shell for the nanoparticle. Thus, one may start from a product that is stabilized by weakly coordinating materials, such as organic acids (citrate, ascorbate, tannic acid) and surfactants, or more robust materials (such as phosphines, amines, or

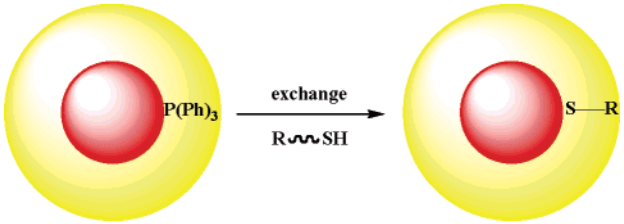


Figure 28. The labile triphenylphosphine ligand shell is easily displaced by an incoming thiol without significantly altering core size, allowing for complete ligand exchange and rapid generation of a library of functionalized nanoparticles.

thiols), bearing in mind that the options for incoming ligands become more limited as the strength of the initial stabilizing ligand is increased; that is, a phosphine is unlikely to displace a thiol. Ligand exchange reactions can be carried out under a range of solution conditions that can be tailored to achieve the desired product, including aqueous, organic, and biphasic conditions, if a change in solubility is likely to occur as the ligand exchange proceeds. The following discussion will illustrate the versatility of ligand exchange by providing examples of ligand exchanges performed on precursor particles with a variety of stabilizing ligand shells.

6.2.1. Place Exchanges Involving Ligands of the Same Class

Phosphine-to-Phosphine Exchange. This place exchange technique may be used to introduce functionality to phosphine-stabilized precursor particles, although complete exchange of the original ligand shell is difficult to achieve.[231] Early examples include (1) the functionalization of triphenylphosphine-stabilized undecagold clusters by introduction of ω-functionalized aminophosphine ligands (2) and the production of water soluble clusters via exchange with $Ph_2PC_6H_4SO_3$.[56,232] Although the exchange kinetics are quite rapid,[233] the use of such exchanges is limited by the general instability of phosphine-stabilized clusters and the inability to perform complete ligand exchanges.

Thiol-to-Thiol Exchange. The earliest studies of thiol-for-thiol place exchange reactions were performed on alkanethiol-stabilized nanoparticles prepared by the Brust route. Alkanethiols featuring a range of ω-functionalities were introduced to stirring nanoparticles, with attention to the molar ratio of incoming ligands, offering control over the extent of the ligand exchange reaction to yield products with mixed ligand shells.[234,235] These polyfunctional nanoparticles featured pendant groups capable of participating in secondary chemical and redox reactions, providing proof-of-principle for a range of new applications as nanoreactors. Later reports by Foos and Twigg demonstrated phase transfer during ligand exchange, transferring hexanethiol-capped particles to the aqueous phase upon exchange with water soluble ligands.[236,237]

A great deal of attention has gone toward elucidating the mechanism of thiol-to-thiol exchanges. It is generally accepted that the chain length and steric bulk of an incoming ligand impact exchange rates, with smaller, simpler ligands exchanging most rapidly. The overall mechanism is associative, occurring in two distinct steps, where exchange is initiated at the gold atoms that form the vertices and edges of a nanoparticle surface. The exchanged species then diffuse toward the terraced regions of the surface, eventually leading to an equilibrium state.[234,238,239] Murray explored several other factors affecting exchange rate, including the charge on the particle and the acid/base environment, finding that the ligand exchange reaction proceed faster on particles whose gold cores bear positive charges, as do exchanges that take place in moderately basic environments.[240] In a follow-up study, the impact of core size with respect to ligand exchange rates revealed that two distinct rates corresponding to individual steps of the exchange persist for particles regardless of size regime. However, the rate of the second step (involving diffusion and rearrangement of thiolate species on gold terraces) varies, with the rate being slower for larger particles.[241] Recently, Rotello reported a new method of studying exchange kinetics using dye-functionalized nanoparticles as substrates for exchange.[239] Since gold nanoparticles effectively quench the fluorescence of bound probes, the progress of the ligand exchange could be monitored by the relative fluorescence of the particle solution, since incoming ligands will displace the dyes as the reaction proceeds. While these studies have provided great insight toward a better understanding of ligand exchange, the fact remains that precise control over the extent of exchange is a challenge. Worden has offered a solution that allows for exchange of a single ligand, using a "catch and release" strategy (see Figure 29).[242] Polymeric supports served as an anchor for 6-mercaptohexanoic acid (6-MHA), leaving the thiol group free to bind to a gold particle. The 6-MHA dosing was sufficiently low in order to maintain distance between the tethered molecules. A single butanethiol-capped nanoparticle could then bind to the free thiol, and liberation of the newly monosubstituted particle was achieved using trifluoroacetic acid. To demonstrate that the particles contained only a single 6-MHA molecule, peptide-coupling reactions were performed using the particles and a diamine, resulting in the formation of nanoparticle dimers.

6.2.2. Introduction of a New Surface Binding Functionality

Phosphine-to-Thiol Exchange. As already discussed above, this is the most versatile type of exchange reaction, since it is capable of producing monosubstituted clusters bearing a wide variety of terminal functional groups. Hutchison et al. demonstrated the utility of this exchange with triphenylphosphine-stabilized 1.4 nm gold particles by carrying out exchanges in a single organic phase to introduce organic soluble thiols[227,243−246] or in a biphasic manner, using water soluble thiols to convert the organic soluble precursor particles to water soluble materials without disrupting the original size of the gold core.[226,227,230,246] The extent of exchange in the biphasic case is governed by the degree of mutual thiol solubility in both phases: that is, a water soluble thiol that has a partial organic solubility is capable of more extensive ligand exchange than a thiol that is completely insoluble in organic solvents. Phosphine-to-thiol ligand exchange reactions have also been used to functionalize smaller (0.8 nm) nanoparticles having undecagold cores.[98,247] Murray has reported that the core size of phosphine-stabilized nanoparticles increases during ligand exchange processes,[228] but it should be noted that Murray employed much longer reaction times than Hutchison,[246] making Ostwald ripening processes more likely.

Phosphine-to-Amine Exchange. Amines can displace phosphine ligands in a single phase reaction. One unique aspect of this reaction is that the size of the gold cores may evolve as the reaction progresses, transforming 1.4 nm triphenylphosphine-stabilized particles to larger monodisperse amine-stabilized particles, ranging in size from the original 1.4 nm up to 8 nm, depending on the exchange condi-

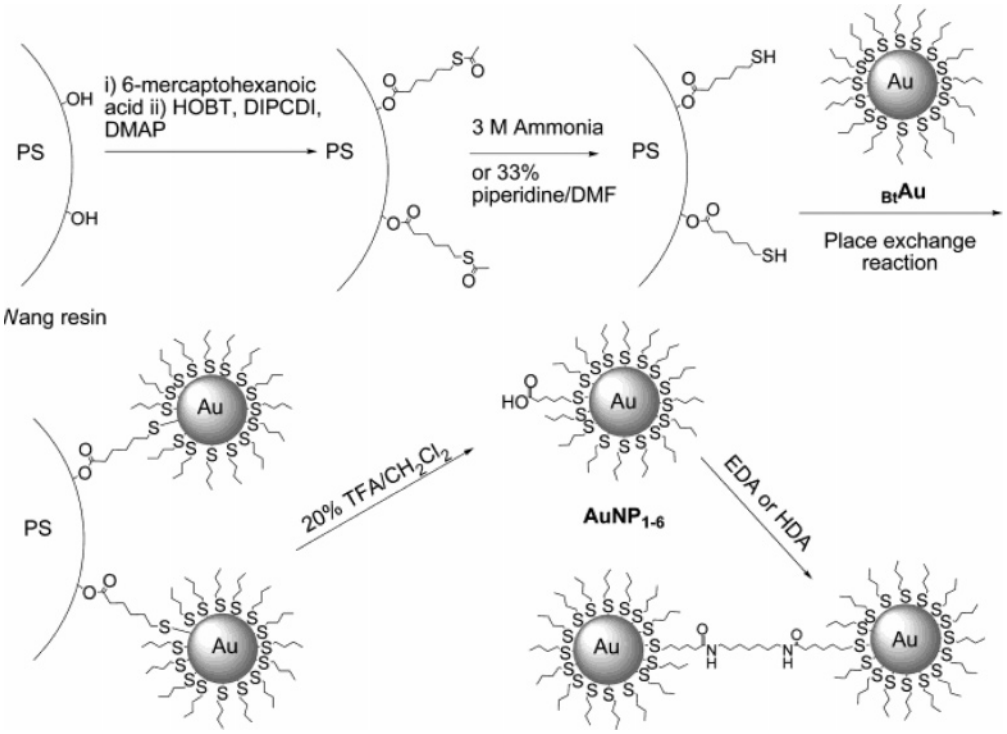


Figure 29. The "catch and release" strategy for controlling the extent of ligand exchange, in this case, adding a single incoming ligand to each particle. (Reprinted with permission from Worden, J. G.; Dai, Q.; Shaffer, A. W.; Huo, Q. *Chem. Mater.* **2004**, *16*, 3746, Scheme 1. Copyright 2004 American Chemical Society.)

tions.[81,243] As mentioned, the amine-stabilized products are nearly monodisperse, and while the exact mechanism of the exchange remains unknown, it is worth noting that a bimodal size distribution is maintained throughout the course of the reaction. These particles are not as robust as those stabilized by thiols, but the relatively labile amine ligands can be exchanged with thiols, potentially providing access to larger functionalized gold nanoparticles by first growing the particles to the desired size through reactions with amines, followed by introduction of surface functionality by an exchange with thiols.

Citrate-to-Thiol Exchange. Citrate-to-thiol exchanges are among the most commonly employed yet least understood methods of creating larger functionalized gold nanoparticles. The reduction of $HAuCl_4$ by citrate anions was pioneered by Turkevich half a century ago, yielding monodisperse, water soluble gold clusters with diameters ranging from 7 to 100 nm. The clusters are stabilized by a complex multilayered assembly of citrate anions in various oxidation states, lending an overall negative charge to the particles.[248,249] This highly charged ligand shell makes solutions of the particles very sensitive to changes in pH, the ionic strength of the medium,[250] and the presence of other organic materials. Incomplete functionalizations involving a few thiolated biomolecular ligands are easily achieved,[251,252] but full functionalization of these particles by a complete thiol ligand shell remains elusive. Levy and co-workers recognized the functionalization challenge presented by citrate-stabilized gold nanoparticles, and they designed a ligand featuring not only a gold binding thiol moiety but also several amino acids capable of stabilizing the citrate surface.[253] For many years, the most successful ligand exchange methods employed a thiol bearing an anionic ω-functionality.[254−256] One example of this type of exchange, involving thioctic acid as a ligand, is shown in Figure 30.

Recently, investigations of this type of exchange by Hutchison et al. have opened up the possibility of extensive thiol functionalization of citrate-stabilized particles by other water soluble thiols, including those having anionic, neutral, and positively charged pendant functional groups. Hutchison found that complete removal of the citrate stabilizing shell by extensive diafiltration is required for maximum surface coverage by thiols (Figure 31). The stripped gold cores remain soluble in water, permitting the introduction of thiol ligands without the usual problems of low surface coverage, aggregation, or cross-linking. The use of a thiol bearing pendant trimethylammonium functionality is unprecedented in the case of citrate-stabilized gold nanoparticles, as excess citrate anions promote cross-linking and aggregation as functionalization proceeds. This method of creating a versatile stripped gold precursor particle amenable to functionalization by a wide range of thiols is promising as a route to nanoscale building blocks capable of self-assembly, much in the way that phosphine-to-thiol exchanges have increased the scope of utility for 1.4 nm triphenylphosphine-stabilized nanoparticles.

Surfactant-to-Thiol Exchange. This class of exchange has been discussed elsewhere throughout the review, as it is a key route to high-aspect-ratio nanorods and prisms. Briefly, gold clusters may be synthesized within micellar templates through reduction of gold salts by $NaBH_4$. Excess surfactant molecules, usually in a tetraalkylammonium form, impart stability to the clusters while providing a ligand shell that is readily displaced by ligands capable of bonding covalently to gold, such as thiols. Although the use of surfactant in this capacity is common, subsequent displacement by thiols or other ligands has not been reported frequently, likely due to the difficulty in obtaining products free of surfactant contaminants. Surfactants have also been displaced by amines, as in the case of Gandubert and Lennox's assessment

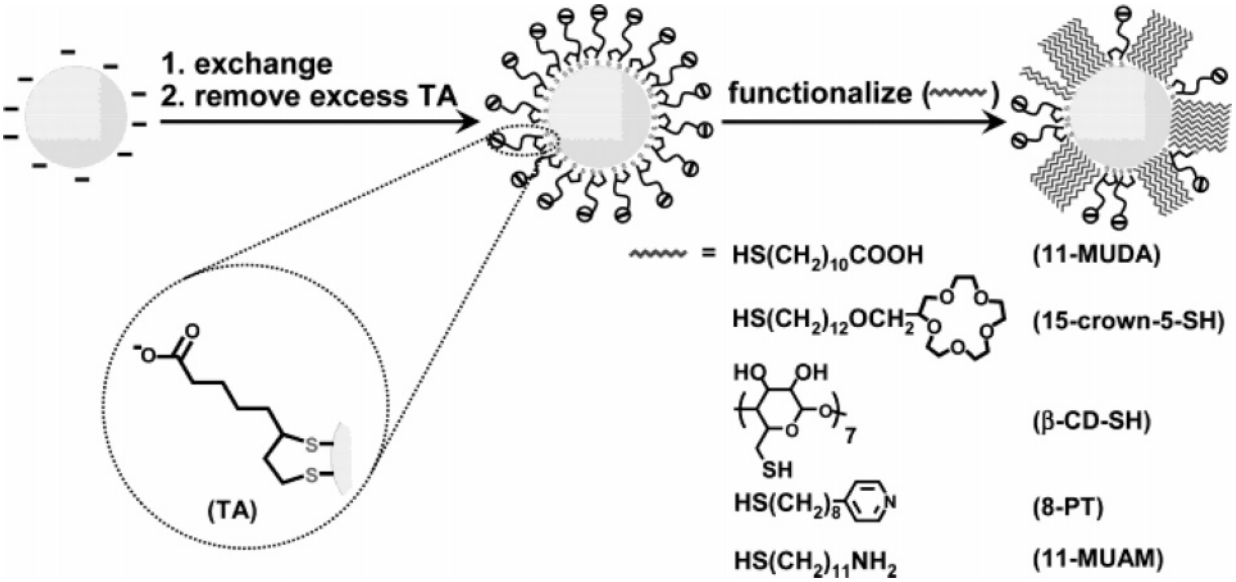


Figure 30. A two-step approach to functionalizing nanoparticles. Thioctic acid binds to citrate-stabilized gold nanoparticles with minimal disruption of the electrostatic environment, stabilizing the particles for a subsequent exchange with another thiol. (Reprinted with permission from Lin, S.-Y.; Tsai, Y.-T.; Chen, C.-C.; Lin, C.-M.; Chen, C.-h. *J. Phys. Chem. B* **2004**, *108*, 2134, Scheme 1. Copyright 2004 American Chemical Society.)

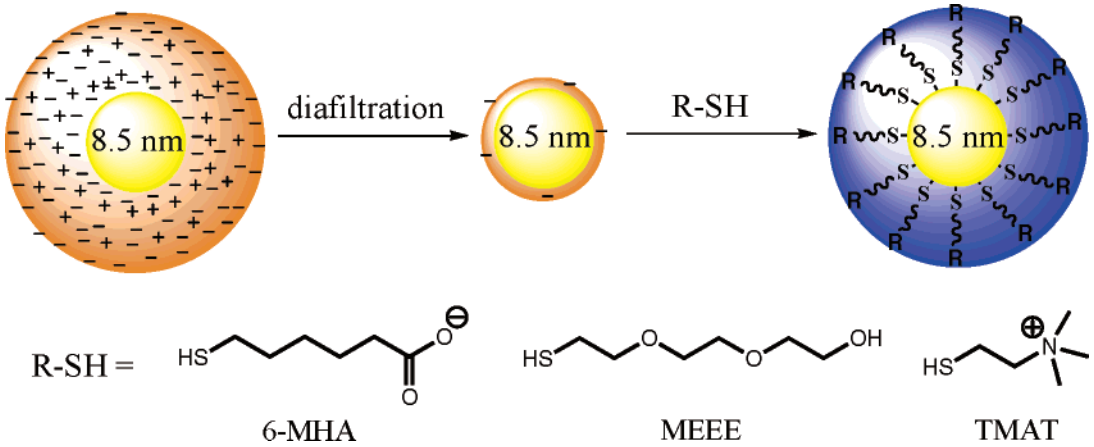


Figure 31. New strategy for functionalization of citrate-stabilized nanoparticles that utilizes extensive diafiltration to remove most ions from the surface of the gold particle, thus allowing facile binding of an incoming thiol ligand.

of dimethylaminopyridine's (DMAP) capability as a stabilizing agent for nanoparticles. Gold nanoparticles were synthesized in a biphasic Brust reaction, yielding TOAB-stabilized clusters suspended in toluene. The clusters were exchanged with DMAP, which is intended to serve as a temporary stabilizer for subsequent ligand exchanges meant to yield functionalized nanomaterials.[257]

7. Nanoparticle Assembly

In order to take full advantage of the unique physical properties of nanomaterials, it must be possible to assemble particles into higher ordered structures, with 1-, 2-, and 3-dimensional architectures. Most applications in the fields of optics, electronics, and sensing require controlled interaction between individual components of an ordered structure. For example, nanoparticle-based electronic devices that operate by tunneling and Coulomb blockade characteristics must be ordered such that the nanoparticle "building blocks" are within relatively uniform, close proximity, separated only by tens of angstroms. Likewise, the optical properties of nanoparticle arrays arise from distance-dependent plasmon interactions, and nanoparticle-based sensing devices, regardless of whether they provide an optical or electronic response, require controlled spatial interactions in order to function reliably. Clearly, the ability to manipulate functional materials at the nanoscale is critical toward realizing the promise of green nanoscience.

Assemblies of nanostructures can be achieved through three main routes, including the binding of nanoparticles to other nanoparticles or nanomaterials, binding to a functionalized surface, or binding to a template. A key design aspect for construction of a nanoassembly is consideration of the nature of the "building blocks", especially the size of the materials and their overall stability, functionality, and solubility. The primary interactions responsible for the construction of robust nanoarchitectures can be classified as either electrostatic attractions or covalent bonding, and thus good control over the surface chemistry is critical when designing building blocks with the right pendant functional groups and solubility properties. These processes can drive the formation of higher ordered structures through several avenues, including directed self-assembly on patterned planar

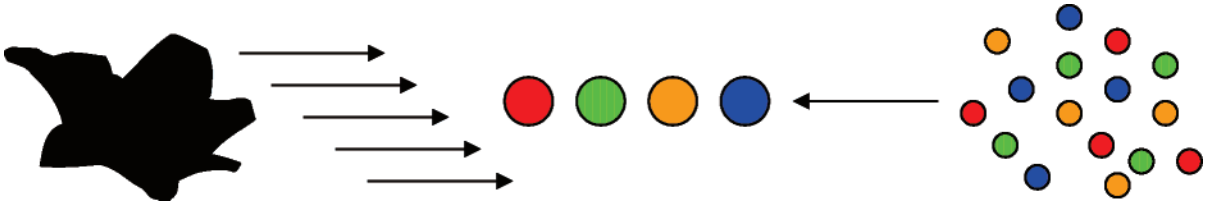


Figure 32. Top-down (left side) vs bottom-up (right side) approaches to materials assembly. Top-down approaches begin with relatively amorphous materials and employ a series of additive and subtractive processing steps to arrive at an ordered structure, generating various amounts of waste with each step. Bottom-up strategies take advantage of functionalized precursor materials which may be assembled through additive processes into a higher order structure, requiring little processing support while sacrificing minimal amounts of starting materials.

and scaffold templates and crystallization within a variety of media, both in the solid state as well as at solvent interfaces. Efficient self-organizational processes enable bottom-up approaches toward novel device fabrication, an inherently greener approach than the top-down techniques (Figure 32) currently employed in commercial micro- and nanodevice production. Although nanomaterial organization relies on only a couple of key interactions, a staggering number of possibilities for assembly have been realized through careful control of surface chemistry and creative selection of substrates for assembly. The following section highlights solution phase assemblies, assembly at interfaces, arrays on surfaces, and materials assembled on scaffold-type substrates.

7.1. Assembly of Extended Nanoparticle-Based Arrays in Solution

Solution phase assembly occurs primarily through cross-linking of soluble materials, which may be driven by hydrophobic or electrostatic interactions[258−265] or via covalent bond formation,[74,266−270] and crystallization processes resulting from a controlled loss of solubility.[271,272] Typical cross-linking strategies include the use of bifunctional linker molecules capable of binding to the surface of a nanoparticle, coupling reactions that take advantage of existing pendant functional groups to bring particles together, electrostatic (ionic) interactions that create dynamic assemblies, and the exploitation of nonspecific (van der Waals, hydrophobic) interactions.

Controlled assemblies of interlinked nanoparticles can be created in the solution phase by the addition of a multifunctional ligand capable of linking two particles, postsynthetic modifications intended to link ω-functionalities, and promotion of ligand−ligand interactions to drive assembly via controlled electrostatic environments. Linked nanoparticles may result in assemblies as simple as dimers, trimers, and tetrapods, or they may be present as extended networks of particles. Early examples of linker ligands include the development of a rigid bifunctional dithiol capable of forming nanoparticle dimers and extended arrays of cross-linked assemblies via place exchange reactions on dodecanethiol-stabilized nanoparticles.[273] The use of a rigid linker molecule offers the advantage of controlled interparticle spacing, corresponding to the length of the dithiol linker. Brust reported dithiol-linked assemblies in solution created by the addition of dithiol linkers to a solution of thiol-stabilized gold nanoparticles.[274] Huo reported the formation of such an extended structure resulting from peptide coupling reactions between gold nanoparticles with several pendant carboxylate groups and the primary amines of polylysine.[222] Leibowitz brought 2 and 5 nm gold particles together by introducing various disulfides in solution.[275] Biomolecules such as DNA and thiolated oligonucleotides have been used as nanoparticle linkers, taking advantage of complementary binding between single stranded derivatives[251,276−278] or by using DNA as a spacer molecule to control the distance between linked particles.[279,280] Electrostatically driven interactions are useful for creating extended networks of particles. Multifunctional fullerenes featuring positively charged piperazinyl groups drive the assembly of citrate-stabilized gold nanoparticles, with the fullerenes serving as a molecular spacer between particles.[264] Similar strategies have been employed with other linking molecules, including the use of a polymeric diamine,[263] and a block copolypeptide to link maghemite particles.[262] Nonspecific interactions, induced by the addition of lower polarity thiols (such as mercaptoethanol and thiolated fullerenes) to highly polar citrate-stabilized nanoparticles, lead to solution phase assemblies via hydrophobic interaction, as seen in Figure 33.[258−261]

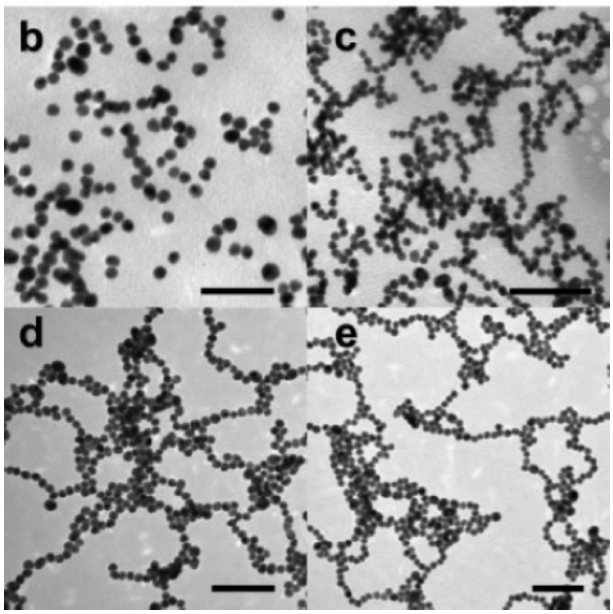


Figure 33. TEM images of gold nanoparticles after exposure to mercaptoethanol for a specific amount of time: (b) 0 h, (c) 3 h, (d) 24 h, and (e) 14 days. Interparticle interactions increase as the neutral ligand adds to the surface, minimizing repulsion. (Reprinted with permission from Lin, S.; Li, M.; Dujardin, E.; Girard, C.; Mann, S. *Adv. Mater.* **2005**, *17*, 2553, Figure 3b−e.)

Crystallization of nanomaterials into higher ordered structures may be achieved by changing solution conditions to cause precipitation, often by adding an antisolvent or altering the ionic environment, by adding a complexing agent that interacts with pendant functionalities, or by performing a

partial ligand exchange in order to alter the solubility of the products. The addition of copper ions has been shown to promote the formation of multilayer films of carboxylate-terminated nanoparticles,[270] while changes in solubility create more complex structures, as in the cases of (1) the esterification of excess citrate ions over prolonged periods to provide a scaffold for the assembly of nanoparticles into tubules[269] and (2) the formation of hexagonal arrays of mercaptosuccinic acid-capped nanoparticles in acidic environments.[272] Layer-by-layer approaches have yielded arrays of gold nanorods,[265] gold nanoparticles,[281] and silicates[282,283] drawn together by surfactant multilayers. Even weaker hydrophobic interactions are capable of driving the formation of highly ordered superlattices of amine-[243] and thiol-stabilized[284] gold nanoparticles.

Polymerization reactions comprise a unique class of solution phase assembly, where linked particles may form discrete structures, extended networks, and stable solid state arrays, either by acting as a complexing matrix or by polymerization reactions initiated at the surface of a nanomaterial. Polymers are capable of directing the assembly of nanoparticles into three-dimensional structures,[285−287] driving the formation of nanoparticle domains on two-dimensional arrays,[288,289] and controlling the optical activity of nanoparticles by governing interparticle spacing.[290−292]

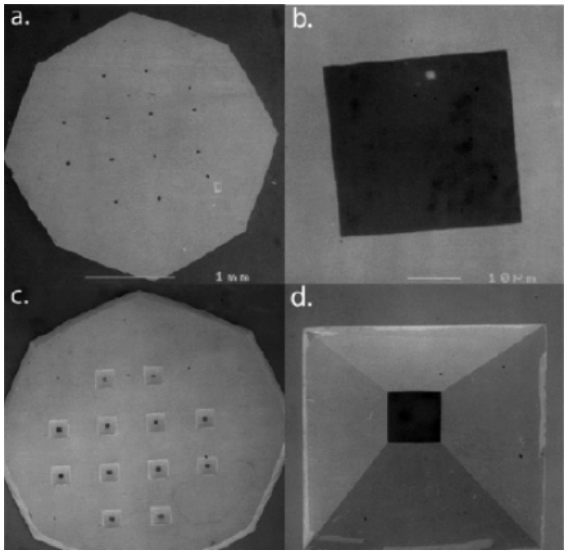


Figure 34. SEM images of Si/SiO_2 TEM grids: (a) top view of windows; (b) a single window with a dust particle; (c) back view showing converging Si(111) etch planes; (d) closer back view of an individual window. (Reprinted with permission from Kearns, G. J.; Foster, E. W.; Hutchison, J. E. *Anal. Chem.* **2006**, *78*, 298, Figure 1. Copyright 2006 American Chemical Society.)

7.2. Directed Assembly on Surfaces and Scaffolds

Assembly on surfaces can be driven by electrostatic interactions or covalent bonding between the chemical functionality of a functionalized nanoparticle and a surface, yielding higher dimension (2- and 3-D) assemblies.[293−296] Ordered structures arise primarily through self-assembly processes, although other techniques such as atomic layer deposition and lithographic methods are finding their place within nanoscience as they become more refined and less resource intensive. Self-assembly stands as the greenest method of creating ordered structures, as it uses minimal materials, consumes negligible amounts of energy, and is often self-passivating, with a tremendous ability to correct defects as the most thermodynamically stable configuration is achieved.

Chemical modification of the substrate may be needed to drive interactions with nanomaterials and can be achieved through common methods of monolayer formation, reviewed elsewhere. A common example of a modified substrate is a dithiol-functionalized gold surface, capable of capturing gold nanoparticles featuring various types of stabilizing ligand shells. The extent of assembly can be controlled based on the type of ligand shell, where nanoparticles containing an extremely labile ligand shell (such as phosphine) will assemble more readily than those having a more stable ligand shell (thiol). Amine-functionalized surfaces have been exploited to drive electrostatic assemblies of nanoparticles having carboxylate and sulfonate groups at their periphery. On a similar note, surfaces featuring stable ionic groups, such as phosphates, are especially useful for attracting functionalized nanomaterials having the opposite charge.

A wide range of substrates may be used as supports for assembled nanoparticles, ranging from simple planar substrates such as glass (including the SiO_2 windows of novel TEM grids, see Figure 34), silicon wafers, and gold,[90,243,281,284,293,294,297] to interfacial substrates found at the liquid−liquid and liquid−gas boundaries,[298−306] to more exotic supports such as biomolecules.

In the past, DNA was the most common biomolecular substrate employed for assembling nanoparticle linkages[251,276,279,280,283,307] and arrays.[225,308−311] An example of this type of assembly from our own laboratory produced by biomolecular nanolithography is shown in Figure 35. A wide range of biologically derived substrates have proven useful, including RNA,[312−314] viruses,[277,278,315−320] and proteins/peptides.[321−329] Proper substrate selection affords an additional opportunity to control the morphology of the assembled array, as the final structure typically mimics that of the substrate; that is, planar substrates may support two-dimensional arrays, whereas substrates having a relatively linear structure are best suited to one-dimensional structures. Advanced surface treatments including lithographic patterning[330−334] and patterning/stamping techniques[335−340] can be used to generate patterned arrays with specifically constrained dimensions, thus improving the versatility of planar substrates, although some techniques (electron and ion beam lithography) lack the efficient, parallel processing methods offered by simple self-assembly on molecular scaffolds.

The application of efficient particle assembly methods will remain an area of focus in the pursuit of nanoproducts produced primarily by green chemistry-inspired routes. Continued challenges in this area are likely to include refinement of assembly methods such that the placement of nanomaterials approaches the level of precision demonstrated by the state-of-the-art lithographic techniques that currently define the industrial standards of the microelectronics industry. Ultimately, the advent of molecularly defined substrates will enable this level of sophistication in self-assembly, allowing the total application of green nanoscience throughout product fabrication, beginning with greener syntheses of nanoparticle building blocks and finishing with processing steps that yield completely green, innovative nanoproducts.

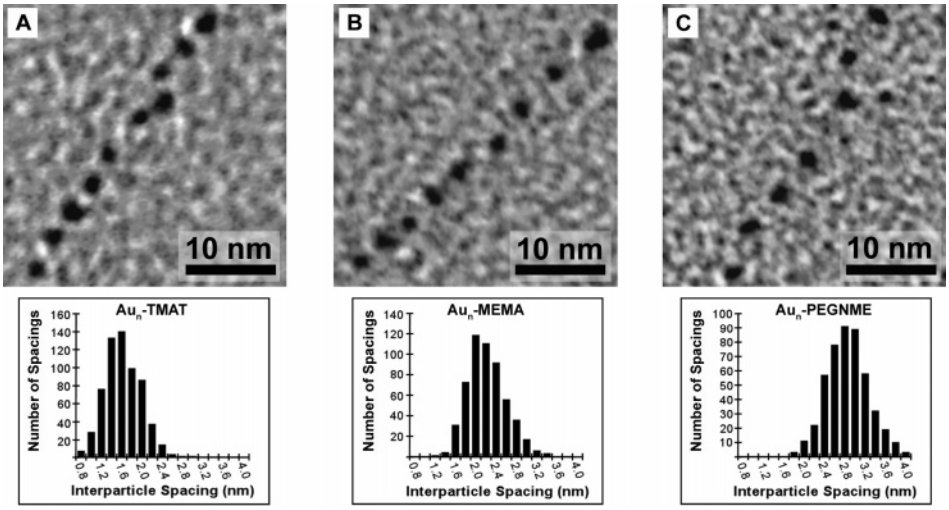


Figure 35. Linear arrays of gold nanoparticles assembled on a DNA scaffold, accompanied by size distributions of the particles composing each assembly. As ligands with progressively longer chain lengths are used to functionalize the particles prior to assembly, the interparticle spacing increases, corresponding to twice the length of the ligand predicted by modeling. (Reprinted with permission from Woehrle, G. H.; Warner, M. G.; Hutchison, J. E. *Langmuir* **2004**, *20*, 5982, Figure 2. Copyright 2004 American Chemical Society.)

8. Concluding Remarks/Research Challenges for Greener Nanosynthesis

The emerging field of green nanoscience faces considerable research challenges to achieve the maximum performance and benefit from nanotechnology while minimizing the impact on human health and the environment. The principles of green chemistry, applied to nanoscience, provide a framework for designing greener nanomaterials and developing greener nanosynthesis methods. As nanoscience emerges from the "discovery phase" to the production level, the need for larger quantities of highly purified, structurally well defined and precisely functionalized materials will require significant improvements in nanoparticle synthesis. This review highlights the growing body of research that addresses the development of these greener processes for nanomaterial synthesis. We focused primarily on the preparation of functionalized metal particles, describing advances in core synthesis, surface functionalization, and shape control that illustrate the current status and future challenges to developing greener approaches. The literature in this area illustrates a few of the many approaches that are being explored in the pursuit of greener nanosynthesis and provides some examples of how these steps can yield high-performance materials with higher efficiency and enhanced safety. However, careful analysis of the examples we describe in this review suggests that there is still much to learn in developing greener nanosynthesis methods and, furthermore, points to a number of important research challenges that would accelerate a transition toward greener nanosyntheses.

Among the key findings thus far have been the discovery of methods to produce nanoparticles and assemblies with desired properties, that (i) eliminate the use of toxic reagents and solvents, (ii) afford higher yields and fewer byproducts, (iii) provide better control of particle size dispersity, (iv) reduce the need for purification or the amount of solvent needed to carry out purification, and (v) enhance material utilization (e.g., in assembly reactions). Finally, initial steps have been taken toward development of metrics by which competing production methods will be compared.

Despite the progress described within this review, there are still considerable research challenges within this field that remain to be addressed. Each of those listed below would have a significant impact toward providing the research base needed to pursue greener approaches, while advancing nanoscience generally. To achieve this end it is necessary to:

1. Develop structure−activity relationships (SARs) needed to predict biological impacts, ecological impacts, and degradation at end-of-life. Each of these SARs is needed to design nanoparticles that will have the desired human health and environmental performance to complement their physical properties. The materials challenge in developing these SARs is accessing diverse populations of nanostructures for investigation that have well-defined structures and purity profiles. This challenge will be met by a combination of developing new synthetic approaches, improved nanoscale analytical techniques, and efficient purification approaches, as described above.

2. Develop new transformations and reagents that are more efficient, safer, and useful in a wider range of reaction media/solvents that will ultimately provide access to greener media. These methods should also produce materials of high quality and purity and allow one to access the composition, size, shape, and functionality desired in a compact synthetic approach. This is a significant challenge that will require enhanced understanding of the mechanisms of nanoparticle formation and the ability to adjust reagent reactivity to address these multiple criteria. These transformations and reagents should be amenable to scale up for production level processing. The use of continuous-flow microreactors should be further examined because they have shown advantages for nanoparticle production and may be useful for large-scale production.

3. Gain improved understanding of product distributions, nanoparticle formation mechanisms, and reaction stoichiometries. Currently, little is known about the mechanistic details of these transformations. Without knowledge of stoichiometry and mechanism, it is impossible to assess atom economy or rationally develop new synthetic methods. Without an understanding of the impurity profiles, one cannot develop new purification strategies. In terms of impact, this is one of the most important challenges, but one that is difficult, in part, because of the limitations of analytical

techniques to assess nanoparticle structure, composition, and purity (vide infra).

4. Optimize analytical techniques that permit the routine analysis of nanoparticles for composition, structure, and purity. In the discovery phase of nanoscience, greater emphasis has been placed on the analysis of structure (e.g., core diameter of a particle by TEM) with little attention paid to the chemical composition of the stabilizing shell or the presence of small molecule impurities in the nanoparticle samples. The availability of routine analytical methods that address these issues is a key to gaining a better understanding of the mechanisms of nanoparticle formation and reactivity. In addition, given the influence of purity on a wide range nanoparticle properties (e.g., self-assembly, ligand exchange, and toxicity), analytical techniques that can detect and quantify impurities will be important to pursuing greener approaches. Importantly, analytical techniques are needed that permit real-time, in situ monitoring to optimize production processes, thus minimizing waste and energy costs as well as providing mechanistic information.

5. Find alternatives to the use of surfactants, templates, or other auxiliary substances to stabilize and control nanoparticle shape during synthesis. A number of the examples provided in this review make use of surfactants for these purposes. Surfactants are often toxic, tend to persist as residual contaminants in the product, and must usually be replaced in order to incorporate new functionality on the particle surface. New approaches wherein the molecule used to control shape during synthesis instills permanent function (beyond initial stabilization) to the material are particularly needed. Some studies have utilized biological molecules to control the size and shape of nanoparticles, often in the absence of surfactants. These biomimetic approaches are in their infancy, but they show great promise in biologically derived nanoparticle production. For these bio-based nanoparticles to be successful, it will be necessary to develop methods that are amenable to scale up, such as those used in microreactor design.

6. Further develop and assess alternative solvents and reaction media. If alternative reaction media (e.g., ionic liquids, supercritical fluids, or other new solvents) are to be exploited, the efficacy, safety, and broader implications need to be assessed to guide selection of the most appropriate medium, whether it be a new material or a traditional solvent. These implications include chemical and energy utilization associated with production and use of the new reaction media.

7. Develop convenient purification methods that provide access to pure nanomaterials without generating large amounts of solvent waste. As nanoscience transitions from the discovery phase to commercialization, the availability of pure nanoparticle samples or those with well-defined impurity profiles will be needed for applications. In addition, pure materials are essential for studies aimed at developing structure−activity relationships needed to predict physical properties, reactivity, toxicity, and ecotoxicity. Current purification methods are wasteful and inadequate, as described in section 2.4.2. Methods that utilize filtration technology can greatly improve purification without generating large amounts of solvent waste and should be investigated to develop greener purification methods.

8. Identify metrics or other approaches for comparing the greenness of competing approaches[341] that consider the relative hazards and efficiencies of the immediately relevant transformation and the relative impacts of each method within a broader life cycle. These metrics are only beginning to be developed, but they will be increasingly important in guiding method selection, particularly during reaction scale up, and the development of new, greener approaches to nanoparticle synthesis.

As the above listing of research challenges suggests, green nanosynthesis is in its early stages and further research is warranted to develop the approach and examine the breadth of its application. There are encouraging results that suggest that the green nanoscience framework can guide design, production, and application of greener nanomaterials across the range of compositions, sizes, shapes, and functionality. Further development and application of this framework to the design and production of a growing number of classes of nanoparticle materials will provide research opportunities and challenges for this community for the foreseeable future.

9. Acknowledgments

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