

# Full Disclosure: The Practical Side of Nanoscale Total Synthesis

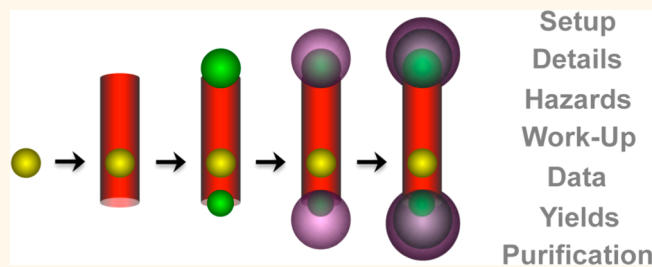
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CdS nanorods that are asymmetrically decorated with Pt and ZnSe tips, producing a linear Pt–CdS–ZnSe arrangement, photocatalytically evolve hydrogen from water.<sup>1</sup> Nanoscale heterostructures with CdS–Au–TiO<sub>2</sub> linkages photocatalytically split water using a Z-scheme architecture that mimics the energetics of natural photosynthetic systems.<sup>2,3</sup> The Au and Fe<sub>3</sub>O<sub>4</sub> domains of hybrid Au–Fe<sub>3</sub>O<sub>4</sub> nanoparticles can be independently functionalized to permit *in vivo* optical imaging of protease expression.<sup>4</sup> These three examples (Figure 1) represent just a few of the many types of multicomponent nanoscale architectures that are at the forefront of emerging advances in energy and medicine, as well as other application areas that include electronics, plasmonics, and catalysis.<sup>5,6</sup> In the simplest cases, such hybrid nanostructures simultaneously exhibit all of the properties of their constituent materials. However, synergistic effects often emerge, and these effects can lead to new or enhanced properties such as directional electron transfer or increased catalytic activity.

The complexity of such heterostructured architectures is rapidly expanding, both in terms of increasingly stringent design criteria and the level of achievable synthetic sophistication. The ability to target and to synthesize asymmetric nanoscale heterostructures with precisely defined material linkages underpins both the expansion of their application portfolio as well as the advancement of our understanding of nanostructure–property relationships and nanoscale interfacial phenomena. Recent trends in the synthesis of multicomponent nanoscale heterostructures have emphasized multistep reaction pathways, where simple nanoscale building blocks serve as precursors that can be predictably modified in a stepwise manner in order to construct larger, higher-order nanostructures. For example, to generate the linear Pt–CdS–ZnSe nanorods that photocatalytically evolve hydrogen from water,<sup>1</sup> a thin CdS shell is first

## ABSTRACT



Colloidal hybrid nanoparticles merge multiple distinct materials into single particles, producing nanostructures that often exhibit synergistic properties and multifunctionality. As the complexity of such nanostructures continues to expand and the design criteria become increasingly stringent, the synthetic pathways required to access such materials are growing in sophistication. Multistep pathways are typically needed to generate complex hybrid nanoparticles, and these synthetic protocols have important conceptual analogies to the total synthesis framework used by chemists to construct complex organic molecules. This issue of *ACS Nano* includes a new nanoscale total synthesis: a five-step route to Co<sub>x</sub>O<sub>y</sub>–Pt–(CdSe@CdS)–Pt–Co<sub>x</sub>O<sub>y</sub> nanorods, a material which consists of CdSe@CdS nanorods that have Pt and cobalt oxide (Co<sub>x</sub>O<sub>y</sub>) at the tips. In addition to the conceptual analogies between molecular and nanoparticle total syntheses, there are practical analogies, as well, which are important for ensuring the reproducible and high-yield production of multicomponent nanostructured products with the highest possible purities. This Perspective highlights some of the practical considerations that are important for all nanoparticle syntheses but that become magnified significantly when multiple sequential reactions are required to generate a target product. These considerations include detailed reporting of reaction setups, experimental and workup procedures, hazards, yields of all intermediates and final products, complete data analysis, and separation techniques for ensuring high purity.

grown conformally onto the surface of ZnSe nanoparticles. A CdS nanorod is then grown unidirectionally off of the ZnSe<sub>core</sub>–CdS<sub>shell</sub> particle seeds, followed by deposition of a Pt nanoparticle at the tip of the CdS nanorod. Likewise, Fe<sub>3</sub>O<sub>4</sub>–Pt–Au–PbS heterotetramers are constructed by nucleating a single Fe<sub>3</sub>O<sub>4</sub> domain on each Pt nanoparticle, selectively depositing a Au nanoparticle on each Pt domain, then depositing a PbS nanoparticle on each Au domain.<sup>7</sup>

These multistep synthetic pathways that lead to hybrid nanoparticle architectures

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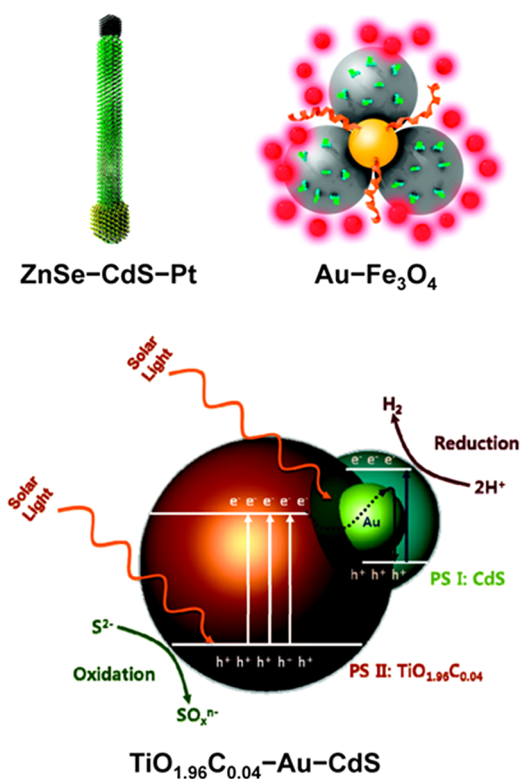


Figure 1. Schematics representing functional hybrid nanostructures: ZnSe–CdS–Pt nanorod photocatalysts, surface-functionalized Au–Fe<sub>3</sub>O<sub>4</sub> nanoflowers for *in vivo* protease imaging, and TiO<sub>1.96</sub>C<sub>0.04</sub>–Au–CdS photocatalytic nanocomposites. Adapted from refs 1, 3, and 4. Copyright 2011 American Chemical Society.

are conceptually analogous to the total synthesis framework that chemists use to construct large molecules.<sup>8</sup> For example, chemists begin with small and simple molecules that can be modified or linked together using a large library of available chemical reactions. Similarly, nanoparticles can be modified using nanoscale chemical transformation reactions,<sup>9</sup> and one type of nanoparticle can be grown off of another nanoparticle's surface to construct higher-order hybrid nanoparticles.<sup>5,6</sup> Indeed, there have already been several reports of three- and four-component hybrid nanoparticles that have been synthesized using rational, multistep total synthesis pathways.<sup>1–3,7,10,11</sup>

In this issue of *ACS Nano*, Pyun and co-workers report a new nanoscale total synthesis: a five-step route to CdSe@CdS nanorods capped with Co<sub>x</sub>O<sub>y</sub>-coated Pt nanoparticles (Figure 2).<sup>12</sup> The authors begin by synthesizing CdSe colloidal

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quantum dots, then using them as seeds to grow CdS nanorods. Pt nanoparticles are then deposited at either one or both ends to produce Pt–(CdSe@CdS) matchsticks or Pt–(CdSe@CdS)–Pt dumbbells, respectively. The Pt nanoparticle tips promote the deposition of Co to form Co–Pt–(CdSe@CdS) and Co–Pt–(CdSe@CdS)–Pt–Co, and selective oxidation of the Co domains yields

Co<sub>x</sub>O<sub>y</sub>–Pt–(CdSe@CdS) and Co<sub>x</sub>O<sub>y</sub>–Pt–(CdSe@CdS)–Pt–Co<sub>x</sub>O<sub>y</sub>. The terminal Co<sub>x</sub>O<sub>y</sub> domains are hollow because of a nanoscale Kirkendall effect that occurs upon oxidation of Co.<sup>13</sup> Other groups have previously reported several of the intermediate nanostructures, along with the deposition reactions that were used to construct them.<sup>14–16</sup> However, linking these reactions together in a five-step synthesis to yield a target product is a significant synthetic advance, especially due to the high morphological yield, which is on a scale that produces several hundred milligrams of isolatable product.<sup>12</sup>

The morphological and chemical complexity of the Co<sub>x</sub>O<sub>y</sub>–Pt–(CdSe@CdS)–Pt–Co<sub>x</sub>O<sub>y</sub> nanostructures are impressive (Figure 3), as is the sophisticated multistep synthesis used to construct them. However, this report by Pyun and co-workers emphasizes other aspects of nanoscale total synthesis protocols that are important for practical implementation, but that often go unrecognized and unreported. This recent work also emphasizes some of the differences that exist between the synthesis of molecules *versus* nanoparticles.<sup>17</sup> Specifically, this report highlights the impact that subtle synthetic details can have on reproducibility, yield, chemistry, and product formation, as well as the importance of fully disclosing all pertinent experimental details and routinely reporting information about product yields. Indeed, for a multistep total synthesis to be viable, each step much be carried out with the highest possible yield since low yields at any step of a reaction propagate and can produce extremely low isolatable yields of the final products. Reporting the yields highlights the realization that almost all chemical reactions result in product recoveries that are less than theoretically predicted. In addition, the products often contain unreacted intermediates or undesired byproducts, when one considers that not all reactions go fully to completion,

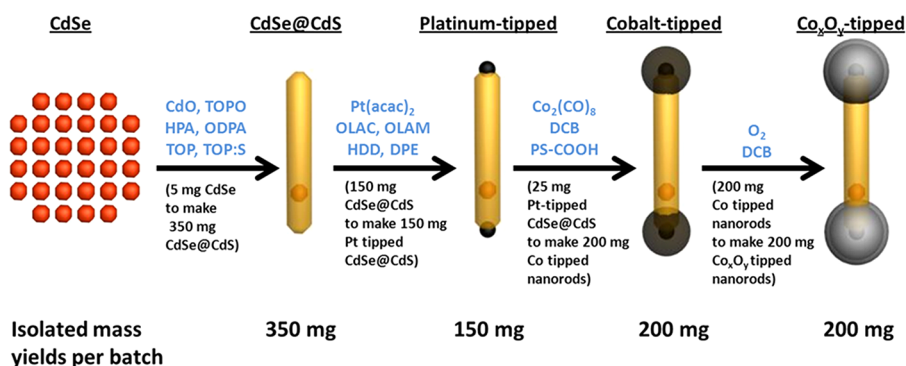


Figure 2. Schematic representing the five-step total synthesis of Co<sub>x</sub>O<sub>y</sub>-Pt-(CdSe@CdS)-Pt-Co<sub>x</sub>O<sub>y</sub> nanorods, indicating the chemical reactions and the isolated yields for each intermediate and the final product. Adapted from ref 12. Copyright 2012 American Chemical Society.

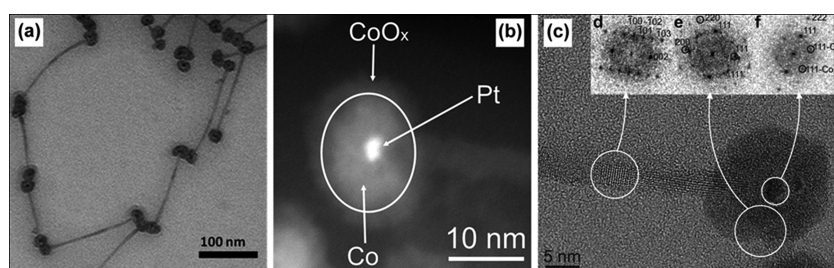


Figure 3. (a) Transmission electron microscopy image of representative Co<sub>x</sub>O<sub>y</sub>-Pt-(CdSe@CdS)-Pt-Co<sub>x</sub>O<sub>y</sub> nanorods. (b) High-angle annular dark-field scanning transmission electron microscopy (HAADF-STEM) image of Co-tipped Pt-(CdSe@CdS) nanorods, and (c) high-resolution transmission electron microscopy image and power spectrum analysis of one tip of a Co<sub>x</sub>O<sub>y</sub>-Pt-(CdSe@CdS)-Pt-Co<sub>x</sub>O<sub>y</sub> nanorod. Adapted from ref 12. Copyright 2012 American Chemical Society.

that competing side reactions often occur, and that some product loss is inevitable during workup. This suggests that separation and purification techniques, which are included among standard workup procedures for molecular syntheses, may also be necessary for achieving nanoparticle samples with the highest purities.<sup>17</sup>

Browsing the report by Pyun and co-workers,<sup>12</sup> it is easy to see the emphasis on synthetic details. The abstract mentions the reporting of isolated yields for intermediates and products, as well as considerations for scaling up reactions. The last paragraph of the introduction highlights the rationale for including extremely detailed synthetic protocols, which centers around the need for larger amounts of isolatable intermediates and products, given the five-step synthesis that has the potential for material loss at each step. Synthetic details, yields, and product distributions are prominently

featured in the text, figures, and figure captions. A summary paragraph on “Synthetic Considerations” further emphasizes the need for detailed synthetic protocols in order to scale up reactions and to carry them out reproducibly.

The authors are right on the mark with this emphasis: details *are* important, and the ability for one scientist to reproduce the experiments of another lies at the heart of scientific research and publishing. However, most striking is the level of experimental detail that Pyun and co-workers provide, included in the 47 page Supporting Information file. The authors provide the requisite Supporting Information that is typical for such papers, including experimental details that were not integrated in the manuscript, additional transmission electron microscopy (TEM) images, and ancillary data such as thermogravimetric analysis, UV–visible absorption spectroscopy, fluorimetry,

X-ray diffraction (XRD), and magnetic characterization. The authors then go far beyond this ancillary information, providing a level of synthetic detail that will hopefully allow other trained researchers to reproduce their work fully and as efficiently as possible. Such details sometimes appear in manuscripts, but rarely are they all collected into a single document and presented in such depth. Some of the primary types of details disclosed by Pyun and co-workers are highlighted below. This list is not exhaustive, nor is everything listed below necessarily relevant to every synthesis. The key point is identifying what needs to be included and ensuring that it is.

*Detailed description of reaction setup.* Important for reproducibility are details such as the size and shape of the reaction vessel, the size of the magnetic stir bar (if used), and the stirring rate in rpm, all of which impact issues such as the degree of mixing and the rate of

heat transfer. Also important is whether or not the reaction vessel is insulated and, if so, the material used to do so. Many other parameters can be important as well, such as (but not limited to) the type of thermometer or temperature probe, the heat source, the procedures for pretreatment or drying of glassware, etc.

**Complete synthetic details.** Providing both the masses (or volumes) of reagents, along with the corresponding numbers of moles, helps with calculations and also with verifying accuracy. Disclosure of any unique aspects associated with a synthetic protocol, such as sensitivity to sonication, provides important insights into how the reaction proceeds and how sample integrity can be maintained. Cooling rates, including how such cooling rates are achieved, can impact nanoparticle size and morphology. Reporting precise concentrations of nanoparticles in stock solutions is important for optimizing multistep reactions, and while this can be nontrivial, finding an appropriate way of doing so (and describing how such concentrations were determined) is helpful.

**Hazards.** Many colloidal nanoparticle synthesis protocols combine toxic, air-sensitive, and pyrophoric reagents with highly corrosive and flammable solvents and then heat the reaction mixtures to temperatures at or near their boiling points, which are typically several hundred degrees Celsius. Scientists have an obligation to disclose unusual hazards associated with such reactions, especially as the community of researchers carrying out such reactions continues to expand to include those that do not have a background in air-sensitive chemical manipulations. For example, Pyun and co-workers fully disclose that the cotton they use to insulate their reaction vessels can ignite if left in contact with high-temperature surfaces for too long. This may seem like a minor detail, but it is important and with potentially serious consequences if others try to reproduce or

to modify the protocol. As another example, the commonly used solvent/stabilizer oleylamine, despite its ubiquity in nanoparticle synthesis protocols, can cause severe burns if it comes into contact with skin. Many other hazards can exist, and they should be fully disclosed.

**Workup procedures.** Workup procedures are important because they result in the isolation of the target product from the crude reaction mixture, and they also impact, and give insights into, colloidal and chemical stability. Details of how, or if, powders are separated, isolated, and dried are therefore important, as are their storage conditions and how long they are stable under such conditions. Also important, and rarely reported, are complete centrifugation details, despite the prevalence of this technique in colloidal nanoparticle workup procedures. Simply stating the rpm setting is insufficient. To be fully useful, one also needs to report the radius of the rotor, the length of time of each centrifugation step, and the volumes of the centrifuge tubes and their liquid contents.

**Yields.** Organic chemists routinely report yields, providing important insights into the chemistry that is occurring in the reactions, the viability of using a particular reaction as part of a multistep synthesis, and the practicality of using the products for a desired function or application. While the same is true for nanoparticle syntheses, yields are rarely reported, perhaps due to ambiguities in defining what “yield” means for systems that do not benefit from molecular precision. Pyun and co-workers emphasize the reporting of isolated yields for all intermediates and products, and the rationale is the same as for organic molecules. Accurate disclosure of yields requires one to report the recovered mass of product as well as the percent organics because colloidal inorganic nanoparticles inherently contain both organic surface stabilizers and the inorganic material that is often the target.

**Data acquisition, workup, analysis, and reporting.** Details of how each instrumental technique was carried out and how data workup and analysis were performed, including background subtraction, modeling procedures, fitting parameters, error bars, etc., are important for understanding the data and their implications. This includes statistical analyses of morphological distributions (including an indication of how many particles were measured) and other relevant characteristics garnered from microscopy techniques (such as TEM), in order to verify that the images shown are indeed representative. Also helpful are large-area TEM images and bulk-scale measurements that validate the homogeneity of the sample and the reported yields. These measurements include XRD data showing that the peak widths correspond to grain sizes matching what was observed by TEM or the identification of preferred orientations in the bulk samples that are consistent with microscopically observed nonisotropic morphologies. Such data can also include a number of appropriate property measurements (magnetic, optical, etc.), which in some cases can rule out the presence of significant impurities and can provide correlations between the intensities of characteristic signals and those expected if the microscopically observed features indeed comprise the bulk of the samples.

Many of these considerations help to ensure reproducibility, as well as to facilitate the synthesis of samples with the highest possible purity. However, as is also the case for molecular systems, as-synthesized products are often inherently impure, with the target phases being present alongside unreacted reagents and undesired byproducts. Target molecules are almost always separated from these mixtures and purified, and, likewise, colloidal nanoparticles are usually separated from the solvent and soluble impurities, although nanoparticles that differ only subtly from one another—in size,



shape, or composition—are difficult to fractionate.

A crude method that is typically used for isolating colloidal nanoparticles involves repeated cycles of centrifugation, redissolution, and precipitation. Magnetic particles that are superparamagnetic can also be separated from solution and from other nonmagnetic particles using permanent magnets. Both of these methods are sufficient at removing soluble impurities but are unable to fractionate polydisperse mixtures, and there can be user-dependent variability in the efficacy of the separations. Neither method is sufficient for ensuring the purity of a particle sample nor for providing a quantitative means to validate purity.

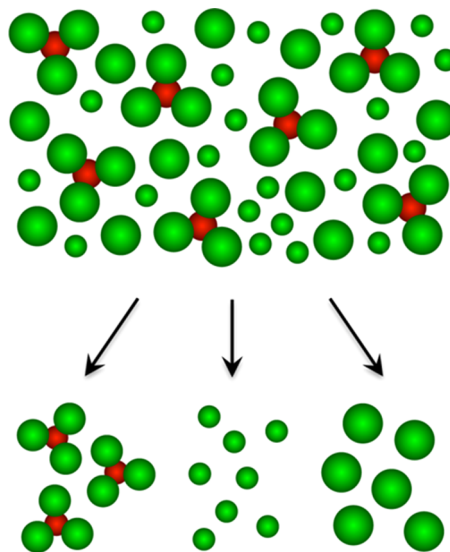
Analogous to the routine use of chromatographic separation techniques in the multistep synthesis of organic molecules, broadly applicable tools for the separation and analysis of nanoparticles, which are capable of fractionating polydisperse mixtures into distinct isolatable populations, are needed and have begun to emerge on the research scene.<sup>18</sup> Microcapillary hydrodynamic chromatography (HDC) has been used to separate colloidal particles with sizes ranging from 0.07 to 40  $\mu\text{m}$ .<sup>19</sup> Field flow fractionation (FFF) uses open channels to perform separations of a variety of samples with nanoscale dimensions including particles, polymers, and macromolecules.<sup>20,21</sup> For example, quadrupole magnetic field flow fractionation has been used to separate and to characterize magnetite ( $\text{Fe}_3\text{O}_4$ ) nanoparticles.<sup>22</sup> Centrifugation techniques have also been used to separate Au nanoparticle dimers and trimers and to assist in the characterization of nanoparticles.<sup>23,24</sup> These methods rely on differences in the mass (density) or diameter of the particles and, therefore, cannot distinguish other types of polydispersity, such as crystallinity or chemical composition.

For magnetic nanoparticles, magnetic fields can facilitate separations

using techniques such as high-gradient magnetic separation (HGMS).<sup>25</sup> In some cases, higher-resolution magnetic separation techniques have begun to distinguish among populations of nanoparticles that are morphologically similar but differ in other characteristics. For example, differential magnetic catch and release (DMCR) can be used to separate polydisperse magnetic nanoparticles into monodisperse fractions and to analyze the magnetic moments of individual populations of particles, in contrast to the ensemble measurements that are typically reported.<sup>26,27</sup> Differential magnetic catch and release has proven to be particularly attractive for separating the types of hybrid particles that result from multistep nanoscale total synthesis protocols, yielding samples that are significantly enriched in the target hybrid particles relative to the undesired nonhybrid nanoparticles that form as byproducts (Figure 4).<sup>28</sup> Differential magnetic catch and release has also succeeded in identifying differences in the magnetic properties of hybrid nanoparticle fractions that appeared morphologically identical by TEM.<sup>28</sup> For nanoparticle separations the potential power of DMCR, or other new techniques that may provide similar resolution and discrimination capabilities, is analogous to chiral high

performance liquid chromatography for the fractionation of L and D isomers in natural product syntheses.

The five-step synthesis of a  $\text{Co}_x\text{O}_y\text{-Pt-(CdSe@CdS)-Pt-Co}_x\text{O}_y$  colloidal hybrid nanostructure emphasizes the practical aspects that are important for successfully implementing a complete nanoscale total synthesis, including efficient and optimized reactions, high isolated yields at each step, and very pure samples.<sup>12</sup> Detailed experimental protocols ensure that other researchers will have a high likelihood of success when trying to reproduce the results; however, the exact same protocol can still produce different results when carried out by different scientists in different laboratories, especially given the large impact that subtle procedural and chemical differences can have on key characteristics of the products.<sup>29</sup> Still, detailed protocols and full reporting of results can help researchers converge on the factors that are most important in a particular synthesis, and this can lead to important mechanistic insights. Some may argue that the inclusion of such exhaustive detail is not needed, and it may be the case that not every detail is important or necessary to rehash in every publication. However, as the community of researchers who



**Figure 4.** Schematic representing the separation of an impure as-synthesized hybrid nanoparticle sample into its constituent fractions.

routinely synthesize and utilize such nanostructures continues to expand, even the smaller details become increasingly important, for reasons of convenience, scientific proliferation, and chemical safety. Similarly, as the complexity of multicomponent nanostructures continues to expand, nanoscale total synthesis protocols will increase in frequency and sophistication, and the practical issues outlined in this Perspective—which are aligned with those of conceptually analogous molecular syntheses—will become increasingly important for ensuring reproducible, high-yield syntheses of high-quality hybrid nanoparticle samples.

**Conflict of Interest:** The authors declare no competing financial interest.

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