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Improved Methods for Evaluating the Environmental Impact of Nanoparticle Synthesis

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Abstract: With the market for products containing nanoparticles growing, improvements in the efficiency of nanoparticle synthesis are poised to have significant positive economic and environmental impacts. While many metrics have been designed for measuring the efficiency of small molecule synthesis, the use of these metrics for evaluating nanoparticle preparation has not been optimized. Here a critical evaluation of various green chemistry metrics is provided as they are applied to a common set of nanoparticle synthetic methods. The effect of the nanoparticle polydispersity on the relative greenness of different synthetic methods is also examined. Using metrics modified to account for polydispersity, a case study of gold nanoparticle syntheses is provided and three different methods of preparing monodisperse gold nanoparticles are compared. Interestingly, not all of the metrics provide the same rankings for the synthetic methods. And when polydispersity is ignored, the metrics provide a different rank order of the methods, highlighting the importance of clearly defining the desired nanoparticle size range to avoid underestimating the environmental impact.

Introduction

Inherent to nanoscience is the promise that nanomaterials can achieve more using less. However, the potential environmental benefit of using these efficient materials often comes with an unseen environmental cost. Specifically, the inefficiency in many nanoparticle synthetic methods means that a large amount of collateral waste is produced along with the desired nanoparticle products. While many reports claim to provide green routes to nanoparticles due to the selection of benign reagents, the efficiency of converting starting materials into nanoparticles often remains very poor. It is not uncommon for the synthesis of grams of nanoparticles to result in kilograms of waste. Beyond this synthetic inefficiency, which is analogous to a poor yield in a chemical synthesis, there is a second type of inefficiency that does not have an analog in conventional synthesis. As prepared, nanoparticles are typically disperse in size and shape. Because most nanoparticle properties vary significantly with both size and shape, only a fraction of nanoparticles obtained during a synthesis will have desirable properties. The additional inefficiency that stems from polydispersity has been overlooked in evaluating the greenness of nanoparticle synthetic methods.

One barrier to reducing the waste generated by nanoparticle synthesis is the difficulty in accurately quantifying ~~the~~ efficiency to allow a comparison of available methods. The recognition of poor nanoparticle synthetic efficiency has been slow. In 2007 it was first demonstrated that the twelve principles of green chemistry could be applied effectively to nanomaterials.[1] Since then, there have been a handful of efforts to quantify nanoparticle syntheses using green chemistry metrics (Table 1) such as E-factor.[2] Process mass intensity (PMI), reaction mass efficiency (RME), and molar

efficiency (ME) are additional metrics that have been applied to organic reactions but not to nanomaterials.[3, 4] Atom economy (AE) has been used extensively in organic synthesis but invoked only as a qualitative descriptor of nanoparticle syntheses.[5] Significantly, we are aware of only a single example where six competing single-step routes to nanoparticles have been compared using any of these metrics.[2] In contrast, pathway comparisons in chemical synthesis have facilitated great improvements in efficiency as seen for example in adjustments to ibuprofen synthesis that led to an increase in overall AE from 40% to 80%.[6] One roadblock to making effective comparisons of nanoparticle synthetic routes is the inability of the available green chemistry metrics to quantify the inefficiency associated with the nanoparticle dispersity.

Table 1. Summary of Metrics and Suitability for Nanoparticle Application

Metric	Formula	Description	Value for Most Efficient	Value for Least Efficient	Nanoparticle Suitability
Atom Economy (AE)	$\left(\frac{MW\ of\ desired\ product}{\Sigma\ of\ MW\ of\ stoichiometric\ reactants}\right) \times 100$	Expresses the efficiency of a reaction based on how many atoms of the stoichiometric reactants are incorporated into the product.*	100%	0%	Requires molecular formulas to implement and fails to include non-stoichiometric reagents commonly responsible for NP waste
Molar Efficiency (ME)	$\left(\frac{mole\ yield\ of\ desired\ product}{\Sigma\ of\ moles\ of\ inputs}\right) \times 100$	Expresses the efficiency of a reaction based on the ratio of the number of moles of product created to the sum of the number of moles of inputs.**	100%	0%	Unfairly penalizes NP syntheses for being high molecularity. Becomes metric of nanoparticle size rather than efficiency.
Process Mass Intensity (PMI)	$\frac{\Sigma\ of\ mass\ of\ inputs}{mass\ yield\ of\ desired\ product}$	Expresses the efficiency of a reaction based on the ratio of the total mass of all inputs to product mass.**	1	∞	Suitable for NP analysis when adapted to account for polydispersity.
E-factor	$\frac{\Sigma\ of\ mass\ of\ inputs - mass\ yield\ of\ desired\ product}{mass\ yield\ of\ desired\ product}$	Expresses the efficiency of a reaction based on the ratio of the total mass of all inputs less the product mass (waste), to product mass. **	0	∞	Suitable for NP analysis when adapted to account for polydispersity.

Reaction Mass Efficiency (RME)	$\left(\frac{mass\ yield\ of\ desired\ product}{\Sigma\ of\ mass\ of\ stoichiometric\ reactants}\right) \times 100$	Quantifies the efficiency of a reaction based on the ratio of the product mass to the sum of the masses of the stoichiometric reactants. ***	100%	0%	Fails to include non-stoichiometric reagents commonly responsible for NP waste

*Atoms of solvents and catalysts are not included in the metric value. ** Inputs include reactants, catalysts, acids/bases, and any other additives. Sometimes solvent moles are also included. *** Does not consider the mass of solvents, catalysts, acids/bases, and any other additives.

Here the impact of nanoparticle polydispersity on nanoparticle synthetic efficiency is explored. The efficiency of a common gold nanoparticle synthetic method is evaluated using a range of different metrics and the effect of dispersity on the metric values is also evaluated. This analysis reveals that the greater the mismatch between the dispersity of nanoparticles obtained and the size that is desired, the worse of a value is revealed by the metric. In performing this analysis it also becomes apparent that some green chemistry metrics work well for analyzing nanoparticles while others are less effective. Finally, a case study is provided that compares three different methods of obtaining a sample of gold nanoparticles with defined size. Which method is rated as most efficient depends on whether dispersity is considered in the calculation or not, underlining the importance of this factor.

Results

While many types of nanoparticles are used in a growing number of applications, we selected to analyze the synthesis of thiol-stabilized gold nanoparticles as an example. We anticipate that the lessons learned from this analysis will be generally applicable to other nanoparticles and this analysis could be readily repeated with materials such as silica, carbon, or semiconductor nanoparticles that are also commonly prepared in disperse form. One advantage of selecting thiol-stabilized gold nanoparticles is that

recent advances in structural characterization by X-ray diffraction[7] and scanning transmission electron microscopy[8] have reduced the uncertainty regarding the composition of these nanoparticles.

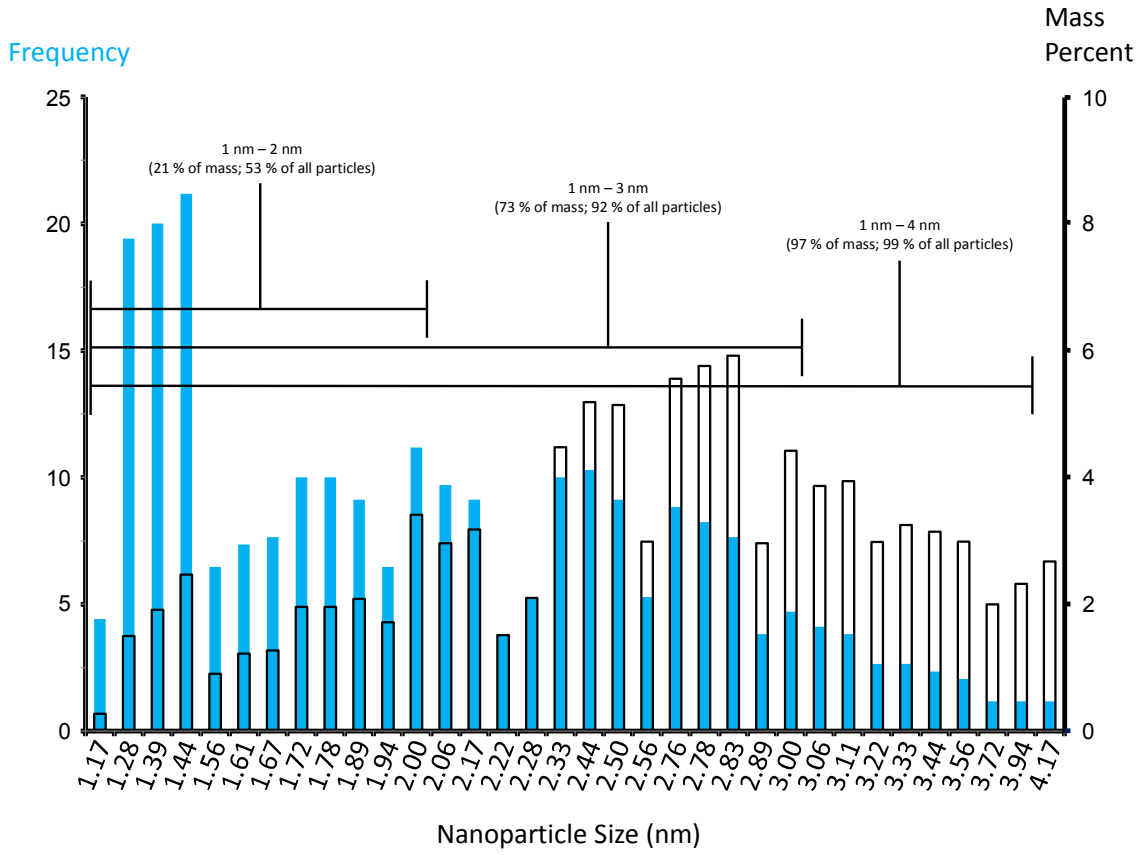

Figure 1. Histogram of nanoparticle diameters (blue bars, left axis) and calculated mass percent (white bars, right axis) of thiol stabilized gold nanoparticles prepared by Brust method[9] as reported by Murray.[9]

The synthesis of thiol-stabilized gold nanoparticles was first reported in 1994 in a landmark paper by Brust et al.[10] Many other routes have been derived from these original routes.[11-14] The simplicity and flexibility of this synthesis helped establish thiol coated gold nanoparticles as one of the most studied categories of nanomaterials. Later work by Murray fully characterized the size of the nanoparticles that result from the Brust synthesis with a suite of techniques.[15] The original size histogram obtained by Murray's

TEM analysis is recreated in Figure 1. Overlaid with that is a second histogram that was calculated from the first. In this second histogram, rather than reporting nanoparticle count, the fraction of the total mass that can be accounted for by particles of that given size is shown. To generate this, a calculation was used to estimate the molecular weight of the nanoparticles and then the fraction that each band of sizes contributes to the total mass was determined (details in supporting information). This shows the same pattern as the size histogram but the distribution is skewed toward the larger diameters as one expects for a mass-based distribution.

Prior to evaluating efficiency metrics for the reaction, a definition of the desired product was established. The mass-based histogram was then used for calculating a correction for mass-based metrics such as E-factor, PMI, and RME. Arbitrary windows were selected and the mass fraction within the window was multiplied by the metric value in each case.

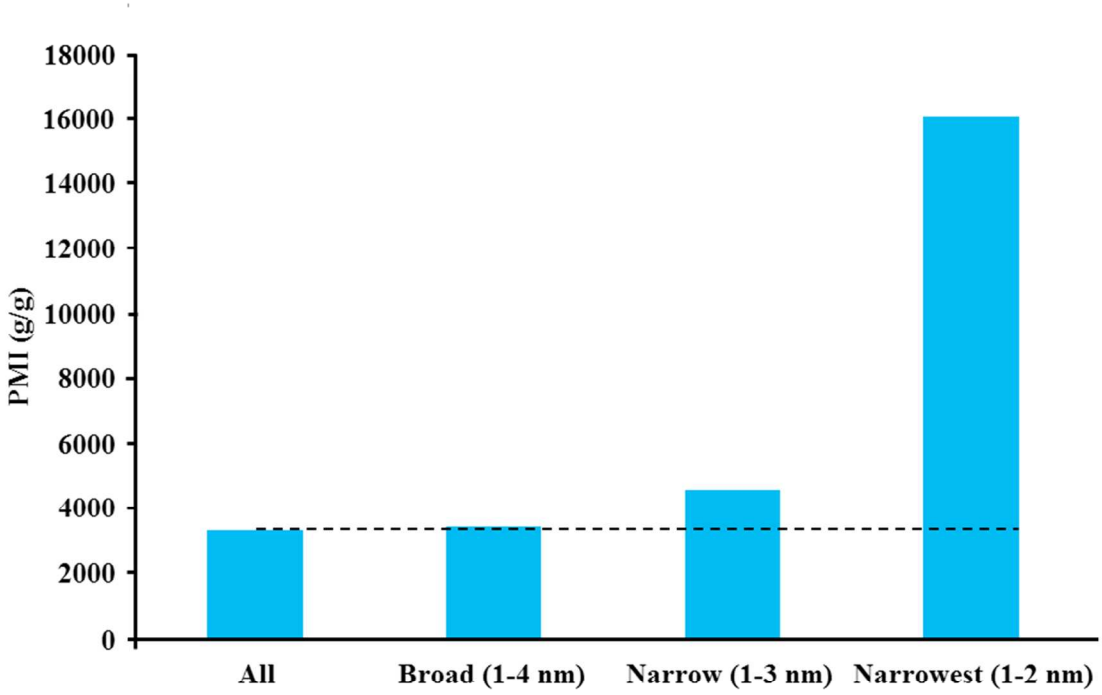

Figure 2. Process mass intensity of Brust[10] nanoparticles when all nanoparticles are considered product (no correction), or a subset of particle sizes (range listed on bar) is defined as product and other nanoparticles treated as waste in calculating the PMI value.

When the PMI value for the Brust method of nanoparticle preparation was calculated (shown as no correction in Figure 2) a value of 3328 was obtained. This means that producing one kilogram of raw, polydisperse nanoparticles would result in 3327 kg of waste. This value treats all of the nanoparticles obtained in the synthesis as desired product and only excess solvents and unused reagents as waste. The metrics obtained without the inclusion of solvent are included in the supporting information.

Taking into consideration that only a subset of nanoparticles would be considered valuable for many applications, a series of corrections were next applied to the PMI. First, by arbitrarily defining nanoparticles between 1 and 4 nm in diameter as being the

desired product, a new PMI value was calculated. Because 99% of the particles (by number) are within this size range, the PMI increases by less than 1% to a value of 3420. In part this is because the handful of particles now being considered as waste have the highest molecular weight. As a result only 97% of the nanoparticle mass is now considered desired product. This analysis was then repeated with a narrower range (1 to 3 nm) being treated as desired product and a PMI value of 4569 was obtained. Finally, when the narrowest range was applied (1 to 2 nm) the PMI increased to 16,095. Looking at this another way, the product is a 62 ppm "impurity" amongst a sea of waste. The value of PMI increases as the size of the window of nanoparticles defined as desired products narrows.

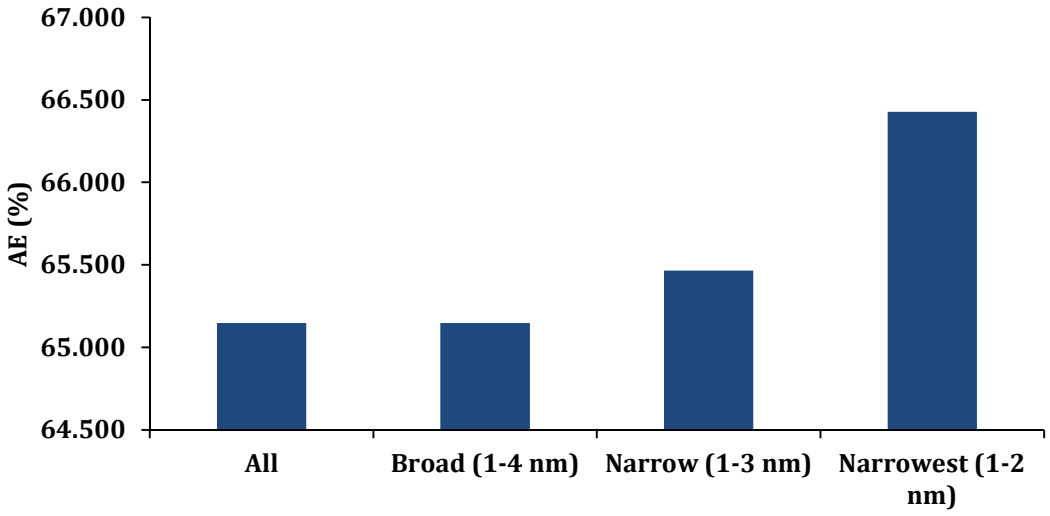

Figure 3. Atom economy calculated for a Brust[10] type nanoparticle preparation. The entire batch was considered as desirable product (All) and then the product is limited to a desired size range as defined in Figure 1.

In contrast to PMI, the value calculated for AE is relatively insensitive to the range of nanoparticle sizes considered to be product as it is a metric based on molecular formula rather than mass. AE is unique to the other metrics in that it only expresses a

theoretical efficiency, including no information about how the procedure is performed such as reactant equivalents, product yield, and solvent use. AE can be thought of as an aspirational goal for those designing syntheses as it sets a maximum possible efficiency. However, AE correlates poorly with the actual waste for specific reaction conditions.[16] In order to calculate the AE of a nanoparticle, a single, discrete structure of the product was first defined. A weighted average formula was calculated for particles within the given size range to calculate AE. For the full set of particles, the average molecular formula is $Au_{286}(C_{12}H_{25}S)_{95}$ and the AE is 65.15. For the broadest window this remains unchanged but for the next narrower window the molecular formula changes slightly to $Au_{247}(C_{12}H_{25}S)_{86}$, and the AE increases to 65.47. For the narrowest window, the formula is $Au_{127}(C_{12}H_{25}S)_{56}$, and the AE increases to 66.43. As the range of sizes changes, the average formula changes slightly. This is because the quantity of gold atoms scales with the volume of the nanoparticles while thiols in the product scale with the surface area. Because gold is incorporated less efficiently (loss of four chlorines) than thiol (loss of a proton), the fraction of atoms that are incorporated changes with size.

The value of AE for a given size range depends on the weighted average molecular formula of the nanoparticles in that range, therefore depending on the composition of that given range, the AE value may increase with decreasing window or it may decrease. Changing the size of the desirable window has different effects on the value of AE depending on the shape of the histogram.

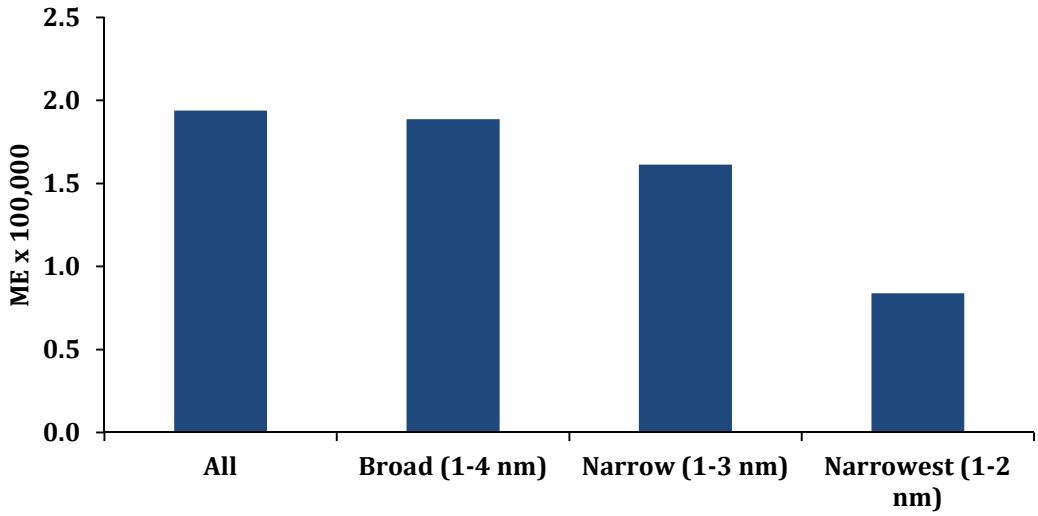

Figure 4. Molar efficiency calculated for a Brust[10] type nanoparticle preparation. The entire batch is considered as desirable product (All) and then the product is limited to a desired size range as defined in Figure 1.

A third comparison was made using ME, which is the ratio of the moles of product to moles of reactants.[3] This metric has recently been applied to a series of reactions from the medicinal chemistry literature.[3] Given the additive nature of nanoparticle syntheses, the values for ME are very low. The ME value for nanoparticle preparations decreases with decreasing window, starting at 1.94×10^{-5} with no filtering, decreasing to 1.89×10^{-5} for the broadest window, then to 1.61×10^{-5} for the narrow window, and finally to 8.40×10^{-6} for the narrowest window. This decrease occurs because there are fewer moles of product in a smaller window compared to a larger window.

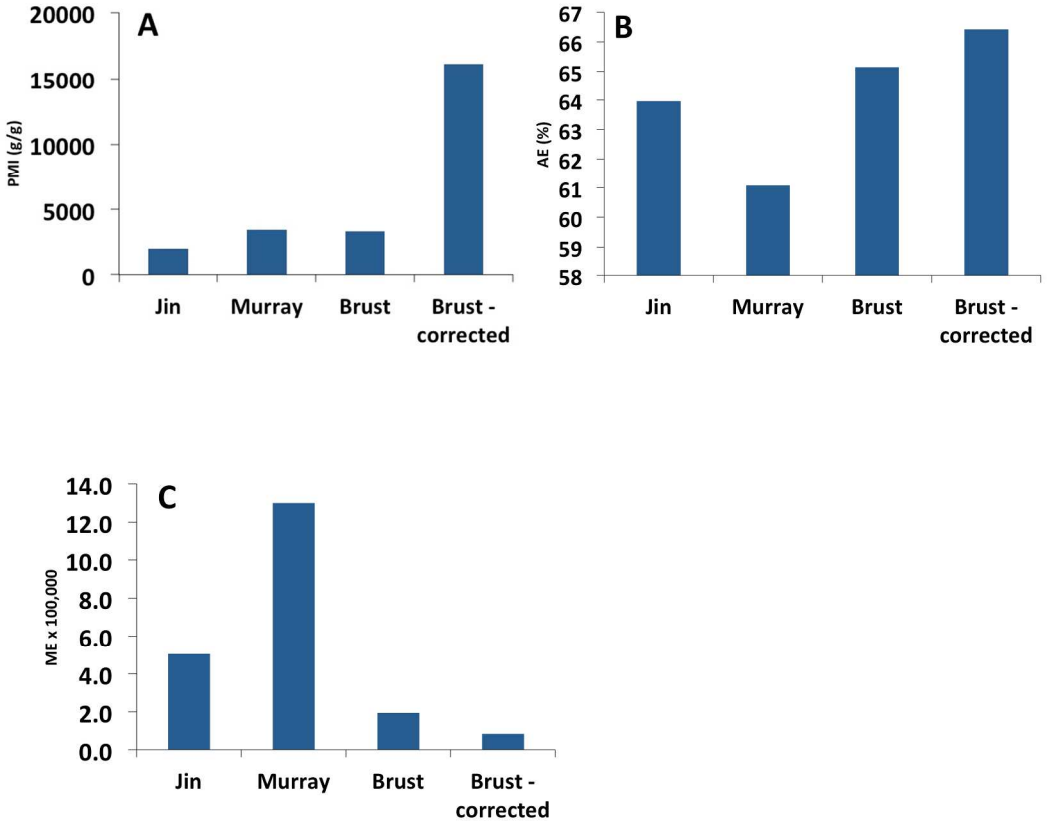

Figure 5. Comparison of synthetic routes to monodisperse nanoparticles reported by Jin[14] and Murray[9] to a polydisperse synthesis[10] (Brust) and to the same Brust preparation after applying a correction to the PMI (Brust corrected) using three metrics; A) process mass intensity B) atom economy, and C) molar efficiency.

A Case Study: Here, three different preparations are compared as potential routes to monodisperse gold nanoparticles. For many applications, low dispersity is essential and often there are competing multi-step methods available to achieve low dispersity. Prior to performing a large-scale nanoparticle synthesis we see a benefit to calculating the most efficient method from the available routes to achieve monodispersity. Unlike simple organic reactions, it is not as easy to map the fate of atoms or to quickly gauge the mass of waste that is produced from the experimental details typically reported in nanoparticle synthesis papers.

The three preparations were selected to have a common type of nanoparticle product (approximately 2 nm thiolate-protected gold nanoparticles). The first method,

reported by Jin,[14] uses 2-phenylethanethiol to coat the gold nanoparticle core and reports a single composition of nanoparticles with the molecular formula $Au_{144}(C_6H_5CH_2CH_2S)_{60}$ that are 1.6 nm in diameter.[14] Low dispersity is achieved in a size focusing step that uses a large excess of 2-phenylethanethiol. The second method, reported by Murray,[9] begins by preparing a sample of triphenylphosphine-stabilized gold nanoparticles using diborane reduction[17] and is also followed by a size focusing step that occurs during ligand exchange with an excess of hexanethiol. It is demonstrated that the majority of the nanoparticles (55%) resulting from this have the molecular formula $Au_{75}(CH_3(CH_2)_5S)_{40}$ and a diameter of 1.4 nm.[9] This yield was used to attenuate the metric values calculated for the Murray preparation.

The third option evaluated is simply to use as-prepared Brust nanoparticles[10] without a size-focusing step. For some applications, when the presence of incorrectly sized nanoparticles is not detrimental, it is possible to take this approach. But if only a certain fraction of nanoparticle have the desired properties, only those should be counted as product. In the fourth method described in this case study, we use the value for the Brust preparation from the narrowest acceptable window of 1 to 2 nm (Shown as Brust-corrected). In this way the fact that only a subset of particles have the desired properties is accounted for.

The PMI values (Figure 5A) vary significantly across the three methods. For the two-step Jin method, the PMI value is 2061 while the PMI value for the Murray method is 3448. The PMI value for the Brust method is 3328 even without a correction for the dispersity. When the preparation has been adjusted to reflect using only nanoparticles

that are from 1-2 nm in diameter the PMI value of the Brust preparation is 16,094. This analysis suggest that the Jin method is most efficient.

In addition the AE values were also compared across the three different preparations (Figure 5B). The AE value calculated for the two-step Jin method was 63.96. The AE value for the Murray method was 61.08. The AE value obtained for the Brust method without correction was 65.15 and after applying a correction for the narrowest window of desirable nanoparticles, the AE was 66.43. The Brust method in which most of the sample is discarded is ranked as most efficient using AE.

Finally ME values were compared across the three different preparations (Figure 5C). The ME value calculated for the Jin method was 5.04×10^{-5}. The ME value obtained for the Murray method was 1.30×10^{-4}. The ME value for the Brust method without correction was 1.94×10^{-5} and after applying a correction for the 1-2 nm window of nanoparticles, the ME was 8.40×10^{-6}. Murray ranks as the most efficient method here.

Discussion: Gold nanoparticle synthesis is typical of other nanoparticle synthetic methods in that there are many routes available to choose from. The selection of a specific route for a given application is often determined by a combination of factors about the nanoparticle core, such as size and shape, and the nanoparticle coating. A researcher preparing nanoparticles will typically pick the method that gives them the closest match to the size, shape, and surface functionalization they desire. Synthetic efficiency is often not considered as this information is not readily available and most often the small scale of the synthesis masks the environmental and economic costs.

It is worthwhile to compare the efficiency of nanoparticle syntheses to pharmaceutical syntheses. Our perceptions of nanomaterial associated risks are likely

anchored by our opinions and understanding of the relative risks associated with pharmaceuticals. Risks such as accidental overdose, poor drug design causing side effects, or accidental release of a drug into the environment may seem more significant to people than the risks associated with the synthetic inefficiency of pharmaceutical preparation. The effects of excess waste generation and inefficient utilization of resources are not immediately obvious to a consumer. Similarly, concerns about nanosafety have centered on accidental exposure rather than methods of production.[18] However it is worth noting that in the aforementioned case of ibuprofen, it is estimated that a PMI of 26.4 could be achieved in a continuous flow synthesis.[19] In the case of the commercial synthesis of the active pharmaceutical ingredient of Viagra, sildenafil citrate, a PMI value of 60 has been calculated.[xx] By comparison, the PMI value for narrow dispersity Brust type nanoparticles of 16,095 represents a tremendous amount of waste. A more than 600 fold greater chemical footprint can be attributed to the nanoparticles compared to ibuprofen, resulting in more waste. Similarly, an analysis of The assumptions made about the relative risks of preparation, use, and release should be scaled accordingly.

Not all green chemistry metrics are well suited to analysis of nanoparticle synthesis. The main weakness of AE is that is does not include considerations of yield, solvent, or additional auxialliary reagents, while these are often the most wasteful parts of a procedure. The similarity of all the calculated AEs described in this work arises from the fact that a common set of reactants are used to prepare all of the gold nanoparticles. This includes tetrachloroaurate as a gold source and typically an alkanethiol of some kind. For each gold atom from tetrachloroaurate that is incorporated into the product, four chlorines are lost to waste. Therefore the more gold that is included in the structure of a

nanoparticle, the poorer the AE. The thiol does not cause much of a decrease in AE, because only a proton is wasted during its incorporation into the product. As a result there is a minor dependence on the size of the nanoparticles but little reason to think that larger nanoparticles are more efficient.

Another metric poorly suited to nanoparticle evaluation is ME. Molar Efficiency expresses the efficiency of a reaction based on the ratio of the number of moles of product created to the sum of the number of moles of inputs. This makes additive reactions appear very inefficient, because many moles of reagents come together to form one mole of product. This results in a very large denominator, giving a small ME value. This is the reason why nanoparticle preparations have low ME values. However, the molecularity of a reaction should not count against it. In fact, many organic reactions that are highly efficient[21] would also have a poor ME because they result from the combination of multiple reagents. The inclusion of a correction for the molecularity of a reaction would be necessary prior to using this metric in analyzing nanoparticle synthesis and this would also improve its use for organic reactions.

The mass based metrics, PMI[22] and E-factor,[23] work best to reveal the actual inefficiency in a nanoparticle reaction as they reveal the impact of mass intensive steps. PMI seems to be one of the better metrics because it uses almost all aspects of a reaction procedure to quantify the efficiency in a ratio. Furthermore, they can be adapted to account for dispersity as demonstrated here. This makes these metrics well-suited for making realistic comparisons of routes as demonstrated in the case study. As has been noted previously, E-factor and PMI differ only by a single unit.[22] For the syntheses discussed here, the difference between the two values is trivial and for simplicity we

report the E-factor in supporting information. RME provides limited information on reaction conditions, is formulated on a percentile scale, and likewise is reported in the supporting information. RME quantifies the efficiency of a reaction based on the ratio of the product mass to the sum of the masses of the stoichiometric reactants. The drawback of RME is that it does not include solvent masses or other additive masses, which can be wasteful portions of reaction procedures.

The relative efficiency of nanoparticle synthetic routes involving multiple steps, such as the size focusing reactions discussed here, is not immediately evident from literature. In fact the results obtained were opposite to our initial assumption that the two-step reactions would be less efficient. In fact, both the Jin and Murray methods that add a chemically intensive size focusing step, have a better efficiency than using crude Brust nanoparticles. While the Brust method, with or without a dispersity correction, ranks as having the best AE, this has little predictive power if assessing waste generation. In contrast, the Murray method ranks as having the highest ME, although this is largely an artifact of the average size obtained. The PMI, which we argue is the most accurate assessment of efficiency, ranks the Jin method as most efficient. The Brust method would come in a close second, however, only if no correction is applied. If one compares the Jin method to the use of a Brust method where one discards the unwanted nanoparticles, the Brust method moves to a distant third place behind Murray. If the cost of purifying out that small band of nanoparticles were included for situations where the excess material could not be tolerated, the rating would be even worse.

The metrics used here are not yet optimal for evaluating nanoparticles and this comparison is not meant to provide a final answer about the best possible efficiency of

these routes as each of these routes could be improved. In fact, the inefficiency in the method of Murray largely arises from the initial synthesis of phosphine-stabilized nanoparticles using the method of Schmid.[17] Other methods for this material have been optimized[13] that would improve the overall efficiency of Murray's method to rank better than Jin's. We anticipate that the application of these modified metrics to other nanoparticles, such as carbon nanodots,[24] especially in the early stages will avoid large amounts of waste generation.

Experimental

Atom economy was calculated according to the equation:

$$Atom\ Economy\ (AE) = \left(\frac{MW\ of\ Product\ Structure}{Sum\ of\ the\ MW\ of\ Reactants}\right) \times 100$$

The product structure was assumed to be the major product reported for the nanoparticle preparation, or determined by finding the weighted average nanoparticle size according to a size histogram provided in the literature. The molecular weight was determined according to a molecular weight calculator (supporting information). The denominator includes only the reactants whose structure ends up in the structure of the product. This does not include species that are labeled as solvents, catalysts, acids, bases, or reducing agents as is common practice.[4]

Process mass intensity was calculated according to the equation:

$$Process\ Mass\ Intensity\ (PMI) = \frac{Sum\ of\ Mass\ of\ Reactants\ and\ Recovered\ Product}{Mass\ of\ Recovered\ Product}$$

and the mass of the solvent (excluding water) was included in calculations of PMI.

The adjustment factor is calculated from the mass percent data in the histogram by adding up the mass percent value of each desirable bin and dividing the sum by 100. The original PMI value is then divided by this adjustment factor to give a corrected PMI value.

Molar efficiency was calculated according to the equation:

$$Molar\ Efficiency\ (ME) = \left(\frac{Moles\ of\ Recovered\ Product}{Sum\ of\ Moles\ of\ Reactants}\right) \times 100$$

A weighted average nanoparticle size was determined within the size window of the histogram. The molecular weight of this nanoparticle size was determined from the calculator and a new calculation of moles of product is produced from the original reported mass recovered. The adjustment factor was calculated from the histogram by adding up the frequency value of each desirable bin and dividing by the total number of particles counted in the entire sample expressed in the histogram. The ME value was then multiplied by this adjustment factor to give a corrected ME value.

The histogram of nanoparticle sizes was recreated from a previously published TEM analysis.[15] A chart expressing the percent that each discrete nanoparticle size contributed to the total mass was prepared from this literature histogram. A molecular weight calculator was used to estimate the molecular weight (MW) of each nanoparticle size (supporting info). The frequency of a given nanoparticle size was then multiplied by the estimated MW to give the mass fraction that a given nanoparticle size contributes to the total mass of the product. The mass that the nanoparticle size contributes to the mass of the product was then divided by the sum of all the masses and multiplied by 100. This provides the percent that a given nanoparticle size contributes to the total mass.

Conflict of interest

The authors declare no competing financial interests.

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