

Catalytic Asymmetric Dihydroxylation by Gold Colloids Functionalized with Self-Assembled Monolayers

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This Letter demonstrates the design and synthesis of functional nanoparticles based on the assembly of terminally substituted alkanethiols on the surface of colloidal gold. The colloids were modified with alkanethiolates presenting methyl groups and dihydroquinidine ligands (in a ratio of 3:1) for the Sharpless asymmetric dihydroxylation of olefins. Dihydroxylation reactions were performed at room temperature in *tert*-butyl alcohol/water with functionalized colloid (0.1 equiv based on immobilized ligand) OsO₄ (0.005 equiv) and K₃Fe(CN)₆ (3 equiv) as secondary oxidant. The dihydroxylation of *trans*- β -methylstyrene proceeded in 80% yield and gave diol with an enantiomeric excess of 90%. The dihydroxylation of *trans*-stilbene and methyl *trans*-cinnamate gave similar results and compare favorably with yields and selectivities obtained using polymer-supported alkaloid ligands. The colloids could be isolated from the reaction mixture by gel permeation chromatography and used again, but with a modest loss in efficiency. This report provides an early example of a functional monolayer protected colloid and, together with other examples to follow, will define the range of applications for which these nanoparticles will find use.

The self-assembly of terminally substituted alkanethiols on colloidal gold provides a convenient and synthetically flexible method for preparing structurally well-defined particles having sizes of 5–25 nm.^{1,2} Extensive physical characterization has shown that the structure of methyl-terminated monolayers on gold colloids is similar to that for alkanethiolates assembled at the surface of planar gold in that the chains are largely *trans* extended and exhibit similar thermotropic behavior, but the faceted surface of the colloids results in a higher density of attached chains and in more complex dynamic behavior of the end groups.³ This and much other excellent work⁴ now make it routine to prepare and characterize these monolayer-protected clusters and in turn set the stage for the preparation of *functional* particles. The first examples, which have used these particles for the colorimetric detection of DNA and as a means to enhance the sensitivity in Raman and fluorescence spectroscopy of immobilized molecules, relied on the electrical and optical properties of the metallic core.⁵ The use of these particles for other

applications, including as catalysts and protein mimics, will require control over the structure of molecules attached to the monolayer. In this Letter, we show that colloidal gold particles modified with a monolayer that presents a dihydroquinidine ligand can effect the Sharpless catalytic asymmetric dihydroxylation of aromatic olefins with yields and enantioselectivities comparable to those realized with the free ligand.

We chose the Sharpless asymmetric dihydroxylation as a model reaction with which to demonstrate catalytically active colloids for several reasons. The reaction is mechanistically well understood and an important practical method for the preparation of chiral diols in high yield.⁶ The use of chiral cinchona alkaloid derivatives as catalysts to activate the oxidant osmium tetroxide gives diols with excellent enantioselectivity. Since the reaction is performed in aqueous cosolvents, rigorous exclusion of oxygen and water is not required. Previous work has demonstrated that alkaloid ligands could be modified for attachment to polymer resins, and the results from this work provide a benchmark for evaluating the performance of the colloid-supported ligands.⁷

Figure 1 shows the synthesis of an alkanethiol terminated in the dihydroquinidine ligand (**1**). The tri(ethylene glycol)-substituted undecene (**2**) was prepared as reported previously.⁸ The glycol spacer was chosen because this linker prefers an extended conformation in protic solvents and would minimize steric effects originating from the colloid. Base-promoted coupling of alcohol **2** and 1,4-dichlorophthalazine gave ether **3** in 85% yield. Analogous substitution of the remaining chloride with dihydroquinidine gave the dialkoxypthalazine (**4**). Photochemical

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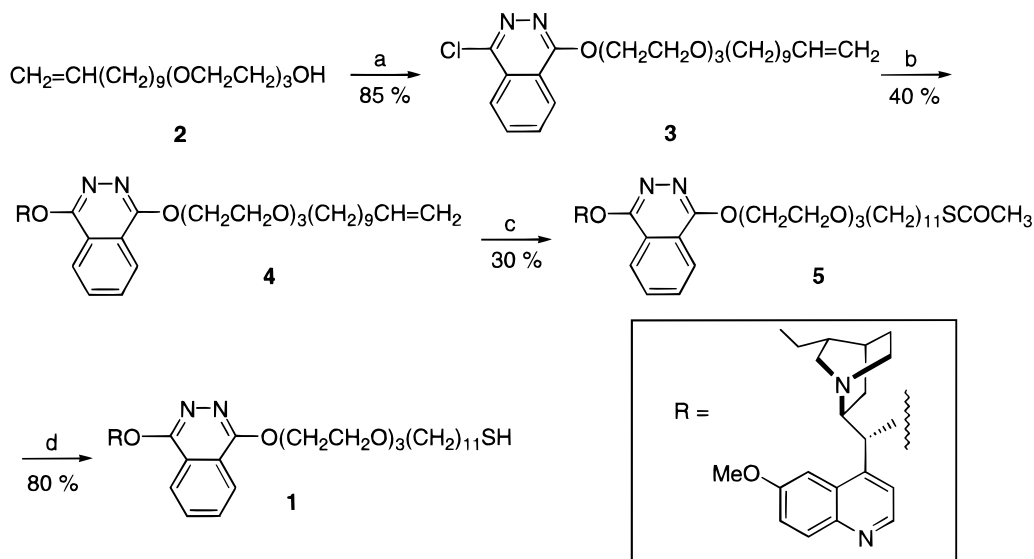


Figure 1. Synthesis of dihydroquinidine-terminated alkanethiol **1**. The following conditions were employed in the synthesis: (a) 1,4-dichlorophthalazine, KOH, K_2CO_3 ; (b) dihydroquinidine, KOH, K_2CO_3 ; (c) CH_3COSH , AIBN, *h\nu*; (d) NaOMe, Rexyn 101 resin.

addition of thiolacetic acid to the terminal olefin was followed by basic hydrolysis to give the desired alkanethiol **1**.

We prepared gold colloids that were modified with a monolayer of octanethiolate by the organic-phase reduction of AuCl_4^- with sodium borohydride in the presence of octanethiol.^{2a,4a} With this method, the size of the colloids is determined by the ratio of octanethiol to AuCl_4^- : the ratio of 2:1 used here produced colloids with a diameter of 2.5 nm.⁹ The colloids were purified by repeated precipitation from toluene with ethanol before alkanethiol **1** was introduced by the place exchange methodology described by Murray and co-workers.^{4a} The colloids (2 mg/mL) were stirred in a solution of **1** (1.5 mM) in methylene chloride for 2 days at room temperature. The resulting functionalized colloids were purified by several cycles of precipitation with hexanes. The structure of this monolayer-protected colloid is illustrated in Figure 2. The ratio of **1**:octanethiolate was 1:3 as determined by ^1H NMR.¹⁰

Asymmetric dihydroxylation of β -methyl styrene was performed in the presence of colloid (0.10 equiv based on immobilized ligand) in 1:1 *tert*-butyl alcohol:water with OsO_4 (0.005 equiv) and $\text{K}_3\text{Fe}(\text{CN})_6/\text{K}_2\text{CO}_3$ (3 equiv) as secondary oxidant. The mixture was allowed to stir for 5 h at room temperature and then terminated by adding excess sodium sulfite (12 equiv). The reaction mixture was concentrated and the diol was purified by silica gel chromatography in 81% yield and with 90% ee. The results for asymmetric dihydroxylation of two other β -substituted styrenes using the same conditions gave comparable results (Table 1). In all cases, the yields were in the range of 80% and compare favorably with reactions catalyzed by soluble monomeric ligands.⁶ The reaction gave diols with enantiomeric excess of 85–90%, and while slightly lower than those observed in reactions catalyzed by soluble ligand, they are similar to those obtained using polymer-supported alkaloid ligands.⁷

To assess the robustness of the colloidal reagents, we isolated the colloids from the reaction mixture and used

them in subsequent reactions.¹² Entry 2 in Table 1 shows that the recycled colloid effected the dihydroxylation of β -methylstyrene with only modest losses in yield and enantioselectivity. The use of the colloid after a second recovery, however, showed a substantial loss in enantioselectivity. We presume that the decrease in efficiency is due to desorption of the alkanethiolates from the colloids.¹³ We have observed by NMR the liberation of dialkyl disulfides from the monolayer-protected colloids and are now characterizing the rates and extent of desorption.¹⁴ Additional support for this interpretation comes from previous studies that have shown gold powder can effect the oxidation of aromatic thiols to the corresponding disulfides and that the mechanism involves an intermediate wherein thiulates are adsorbed to the gold surface.¹⁵ It will be important to determine the extent to which the spontaneous loss of alkanethiolates from the gold may place a limitation on the use of these colloids in applications.

Although these colloids were not optimized in any way, they do compare favorably with several previous reports that used polymer-bound ligands to effect the dihydroxylation of aromatic olefins.⁷ Han and Janda, for example, used a poly(ethylene glycol) bound alkaloid to effect the dihydroxylation of β -methylstyrene in 80% yield and 85%

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(12) The reaction mixture was partitioned between water and ethyl acetate. The organic phase was concentrated, applied to a column packed with styrene divinylbenzene copolymer beads (BIO-RAD S-X12 GEL), and eluted with THF. The colloids eluted with the front volume; the diol eluted in later fractions and was further purified by silica gel chromatography. Gel permeation chromatography is a convenient and effective method for purifying monolayer-protected colloids.

(13) We have ruled out the possibility that the oxidant used in the dihydroxylation reaction consumed the gold colloids. UV-vis spectra of colloids that were isolated from the reaction mixture revealed that the size-dependent surface plasmon resonance band at 520 nm did not shift or decrease in intensity. See: Alvarez, M. M.; Khoury, J. T.; Schaaff, T. G.; Shafiqullin, M. N.; Vezmar, I.; Whetten, R. L. *J. Phys. Chem. B* **1997**, *101*, 3706–3712.

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(16) In ref 7e, these authors reported a polymer that gave diol in 83% yield and 99% ee. The polymer was substituted with a bisalkaloid ligand, which is far more effective in terms of enantioselectivity and therefore cannot be compared directly to our results.

(9) The mean diameter of colloids was determined by imaging with TEM. More than 100 particles were sized to give a mean diameter of 2.5 nm with a standard deviation of 20%.

(10) The ratio of 1:3 was determined by comparing the integrated areas for the aromatic protons of **1** and the poly(methylene) chains for both **1** and octanethiolate.

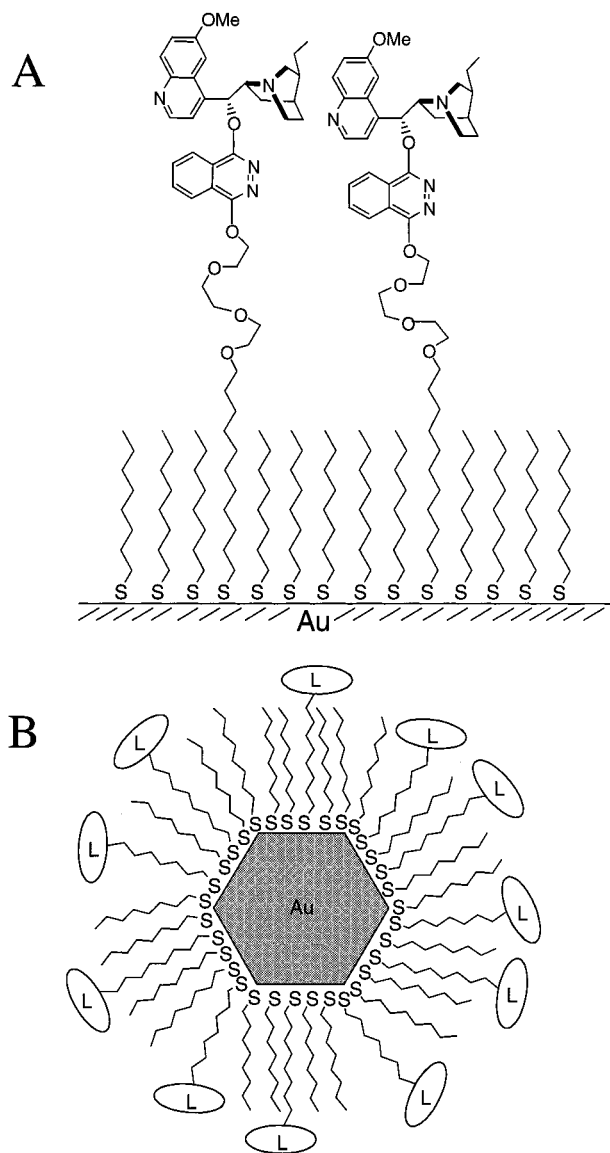


Figure 2. (A) Representation of the structure of a mixed monolayer presenting dihydroquinidine ligands and methyl groups on planar gold. This structure does not illustrate common defects in the monolayer. (B) A drawing for the structure of this monolayer assembled on colloidal gold, where L represents the alkaloid ligand.

ee.^{7d,16} That and other polymer bound reagents are being developed as retrievable catalysts for combinatorial syntheses. The model colloids described in this report do not offer any advantages over the polymers now in use, but they do have characteristics that may be important

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Table 1. Homogeneous Asymmetric Dihydroxylation of Olefins

entry	R	yield (%) ^a	ee (%)
1 ^b	Me	81	90 ^c
2 ^b	Me	79	86 ^c
3 ^b	Me	72	79 ^c
4	CO ₂ Me	78	84 ^d
5	Ph	83	88 ^d

^a Isolated yields following purification by silica gel chromatography. ^b Reactions reported under entries 1–3 were effected with the same colloids. The colloids were recovered by gel permeation chromatography and used in entry 2 and recovered a second time and used in entry 3. ^c ee was determined by chiral HPLC analysis. ^d ee was determined by comparison of optical rotation with literature values.¹¹

to optimizing the catalytic activity. Because they are structurally more ordered, the environment in which the ligand is presented is better defined and can be rationally modified. The importance of controlling the presentation of immobilized catalysts was emphasized in a recent report that used planar lipid substrates to demonstrate that the molecular order of immobilized rhodium complexes has an important effect on the activity of this catalyst.¹⁷ In another recent report, Tremel and co-workers showed that a ruthenium catalyst that was immobilized to gold colloids showed better turnover frequencies for a ring-opening metathesis polymerization.¹⁸

Monolayer-protected colloids are being studied extensively because of the opportunities they offer for designing functional nanostructured materials. The interest in these particles stems from two important features. First, because the structure of the chemisorbed monolayer of alkanethiols is reasonably well-ordered, it is possible to control the environments and densities of molecules presented on the surface. These particles are also amenable to characterization by many techniques that normally do not have sufficient sensitivity to characterize the same monolayers supported on planar gold. Second, the preparation of the modified colloids (including use of the place-exchange reaction) is straightforward and allows wide flexibility in tailoring both the size and the chemical functionality of the particles. The example described in this report, together with several other recent reports of functional monolayer protected colloids, begin to define the scope of applications (and the inherent limitations) for which these nanoparticles will be important.

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