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Hydroalkoxylation Catalyzed by a Gold(I) Complex Encapsulated in a Supramolecular Host

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Supporting Information

ABSTRACT: Gold(I)−phosphine complexes are readily encapsulated by a tetrahedral supramolecular host (Ga_4L_6). We have investigated the catalytic activity of the resulting complexes for the intramolecular hydroalkoxylation of allenes. The catalytic activity of Me_3PAuBr was increased 8-fold by encapsulation, as determined by initial rate kinetics, and we observed up to 67 catalytic turnovers by Me_3PAu^+ encapsulated in Ga_4L_6.

Supramolecular host−guest chemistry has emerged as a promising method for carrying out a variety of organic and organometallic transformations.[1−3] In particular, transition-metal complexes contained in a supramolecular capsule may exhibit improved stability,[4] substrate discrimination,[5] and novel selectivity of reaction.[6] However, the goal of using such systems as true synthetic analogues of enzymes requires not just the observation of changes in the selectivity of encapsulated systems, but also the development of reactions that, like enzyme reactions, exhibit enhanced reaction rates of the encapsulated substrates. Such acceleration has been demonstrated for several organic reactions, but to our knowledge, not for reactions involving encapsulated metal catalysts. Here we report the first nanovessel-accelerated metal-catalyzed reaction that involves the synthetically important process of heterocycle formation.[7]

Raymond and co-workers have used a tetrahedral Ga_4L_6 [L = *N*,*N*′-bis(2,3-dihydroxybenzoyl)-1,5-diaminonaphthalene] cluster, **1**, to encapsulate a variety of organometallic guests (Figure 1).[8] In particular, they have observed that monocationic organometallic complexes exhibit a high affinity for binding to the interior of the cluster.[8b] As gold(I) complexes are cationic in nature and have been used in a wide range of organic reactions,[9] we hypothesized that **1** would be an ideal host for a catalytically active gold(I) guest.

We began our investigation by examining the affinity of gold(I)−phosphine complexes (PR_3AuX, where X is a halide) for **1**. Though the halide can be strongly coordinating in solution, we believed that the preference of **1** for cations would shift the equilibrium between R_3PAuX and $R_3PAu^+ + X^-$ in favor of the fully ionized form. Indeed, when Me_3PAuCl or Et_3PAuCl (1.0 equiv) was combined with the "empty" **1** (1.2 equiv) in D_2O or MeOD, encapsulation of the gold phosphine cation was observed by ^1H NMR spectroscopy (Figure S2 in the Supporting Information). A representative spectrum of Me_3PAuCl with **1** in D_2O is shown in Figure 2a. Characteristic of encapsulation, the phosphine alkyl peaks were shifted upfield from 1.64 to −1.98 ppm. We attribute the two overlapping doublets at −2.02

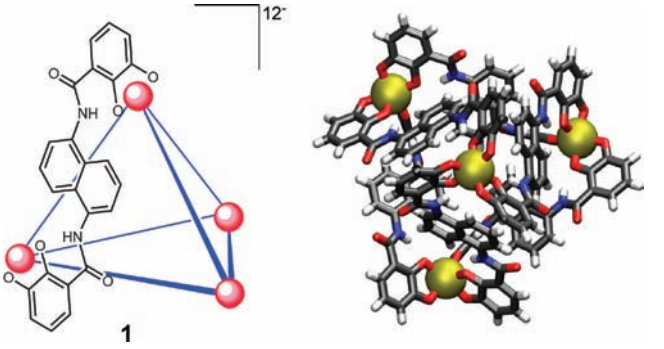

Figure 1. (right) Schematic view of **1** where each edge of the tetrahedron represents a bisbidentate ligand and each vertex represents a gallium center. (left) Stick model of **1**, looking down the C_3 axis.

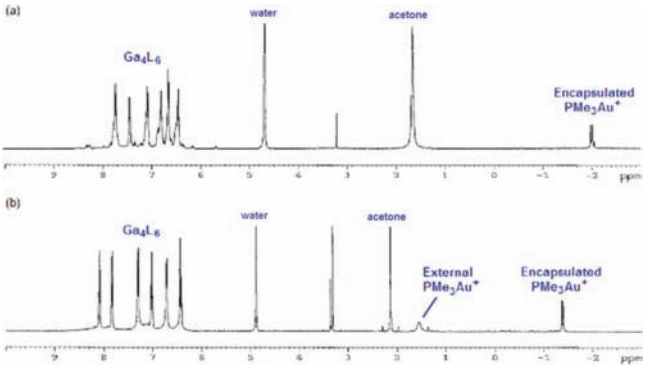

Figure 2. Encapsulation of Me_3PAu^+ by **1** in (a) D_2O and (b) MeOD. Acetone is residual from the recystallization of **1**.

and −1.98 ppm to naked PMe_3Au^+ and the aquo complex $Me_3PAu^+(OH_2)$, respectively. When MeOD was used as the solvent, peaks corresponding to both the encapsulated and freely exchanging gold complex were observed (at −1.41 and 1.65 ppm, respectively; Figure 2b), indicating that the binding constant of Me_3PAu^+ to **1** is smaller in methanol than it is in water. Interestingly, the reaction of Me_3PAuBr or $Me_3PAuNTf_2$ with **1** provided two complexes identical to those generated from Me_3PAuCl, suggesting that the counterion is fully dissociated from the encapsulated gold complex (Figure S1). This was also

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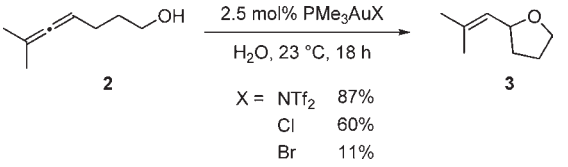
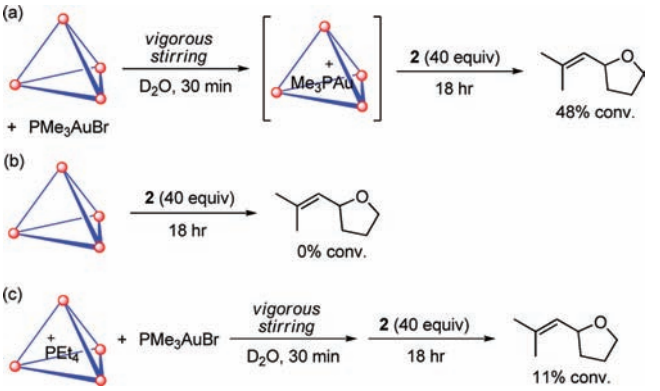
Scheme 1. Hydroalkoxylation Catalyzed by Me_3PAuX



Scheme 2. (a) Hydroalkoxylation Catalyzed by $Me_3PAu^+ \subset$ 1; (b) Background Reaction with 1 Alone; (c) Background Reaction with $Et_4P^+ \subset$ 1 and Me_3PAuBr



supported by electrospray ionization mass spectrometry data for the encapsulated gold cation (Figure S4).

The hydroalkoxylation of allenes by gold(I) in organic solvents has been well-examined,[10] and we hypothesized that this transformation would be an ideal model system for our encapsulated catalyst. This reaction system was particularly attractive to us because allenyl alcohol substrate **2** is sparingly soluble in water and is not sterically demanding. Although both Me_3PAuX and Et_3PAuX showed incorporation into the supramolecular host under aqueous conditions, we chose to use $Me_3PAu^+ \subset$ **1** (where $\subset$ denotes encapsulation) in our catalytic investigations because the smaller phosphine ligand would leave more space for substrate coordination inside the host.

We began by examining the bulk-solution reactivity of **2** with Me_3PAuX (X = Cl, Br, NTf_2) (Scheme 1). While Me_3PAuCl and $Me_3PAuNTf_2$ catalyzed the reaction to appreciable conversion, Me_3PAuBr affected the cyclization in only 11% yield after 18 h, presumably because of the relative strength of the gold−bromide bond. The low background reactivity allowed us to test whether the catalytic activity of Me_3PAuBr could be enhanced by encapsulation.

When **2** (40.0 equiv) was added to an aqueous solution of $[Me_3PAu^+ \subset Ga_4L_6]^{11-}$, we observed 48% conversion of the allene to the desired product after 18 h at room temperature (Scheme 2a).[11] No reaction was observed with **2** in the presence of Ga_4L_6 alone (Scheme 2b). To ensure that the enhanced rate of reaction observed was not due to changes in solvent polarity or counteranion effects[10a] upon addition of the anionic assembly, another control experiment with a "blocked" cluster ($PEt_4^+ \subset$ **1**) and free Me_3PAuBr was performed (Scheme 2c). The phosphonium ion has a very high binding constant for Ga_4L_6 and, not surprisingly, no exchange between PEt_4^+ and Me_3PAu^+ was observed when $Et_4P^+ \subset$ **1** and Me_3PAuBr were combined. When **2** was added to the solution containing $Et_4P^+ \subset$ **1** and

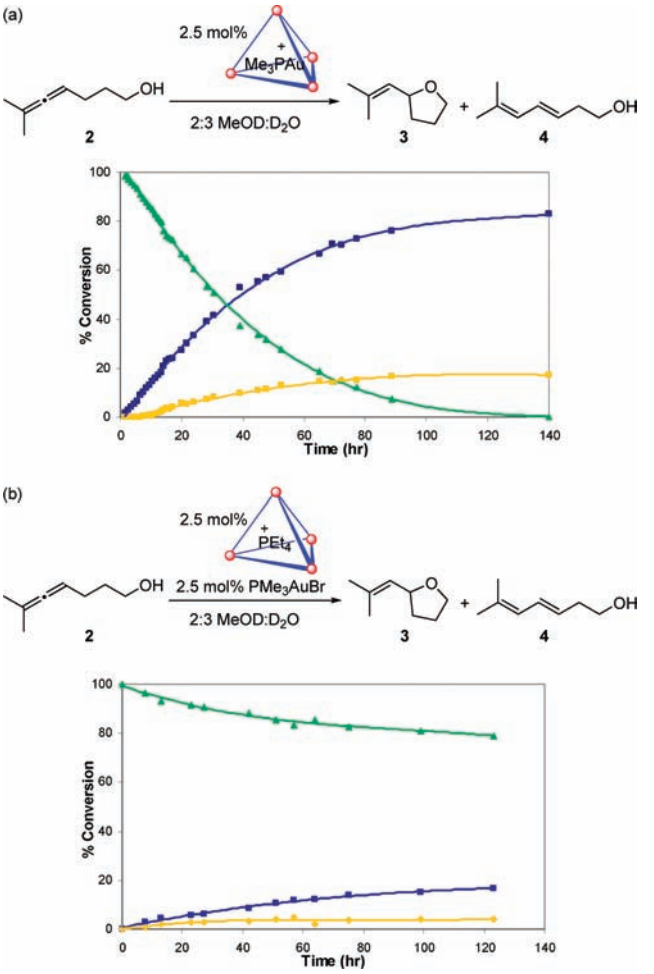


Figure 3. (a) Monitoring of the hydroalkoxylation reaction of **2** catalyzed by $Me_3PAu^+ \subset$ **1**. (b) Monitoring of the reaction of **2** catalyzed by Me_3PAuBr in the presence of the blocked assembly. Green, blue, and gold traces represent the decay of starting material, formation of **3**, and formation of **4**, respectively.

Me_3PAuBr, only 11% conversion to the cyclized product was observed after 18 h. This experiment demonstrated that the enhanced rate cannot be attributed to Me_3PAu^+ bound to the exterior of the cluster. Thus, encapsulation in the cluster must have been responsible for the rate enhancement observed.

To measure the relative rate acceleration, the hydroalkoxylation reaction was monitored by NMR spectroscopy in 2:3 MeOD/D_2O solvent. The mixed solvent system was used because the substrate is soluble up to 16.5 mg/mL in this combination and no externally bound or exchanging Me_3PAu^+ is observed. When the homogeneous reaction mixture was protected from air oxidation, the $Me_3PAu^+ \subset$ **1** complex maintained catalytic activity over 6 days and completely consumed the starting allene (Figure 3a). Complete conversion to a 4.8:1 ratio of **3** to **4** was observed, where **4** is a side product from allene isomerization.

Monitoring the background reaction with the blocked assembly and Me_3PAuBr (Figure 3b) showed that encapsulation of the gold catalyst produced an (8.0 ± 0.9)-fold acceleration of the catalysis,[12] based on the measured initial rates (see the Supporting Information). In addition, the lifetime of the catalyst in water was enhanced by encapsulation, as we think catalyst decomposition is responsible for the tapering of the rate of the background reaction

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after 2 days.[13] To probe the turnover number of the $Me_3PAu^+ \subset$ **1** catalyst, we added 250 equiv of **2** to a solution of the catalyst in 2:3 MeOD/D_2O. After 6 days of vigorous stirring of the biphasic mixture, **3** was isolated in 27% yield, corresponding to 67 turnovers. Although more sterically demanding substrates can also be employed in the reaction, the rate enhancement observed for these substrates is smaller than that with **2**.[14]

In conclusion, we have shown that gold−phosphine complexes are readily encapsulated in **1** in both methanol and water. Notably, the encapsulation of Me_3PAu^+ (generated from Me_3PAuBr in water) led to an enhancement in the catalytic activity in the hydroalkoxylation of allenes. This reaction constitutes the first example of acceleration of a gold-catalyzed process in which the reactivity and lifetime of the catalyst were enhanced by supramolecular encapsulation. Moreover, encapsulation of the gold catalyst allowed us to perform reactions that previously required organic solvents in water.[9] Studies directed toward taking further advantage of this strategy are ongoing.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and additional spectroscopic and kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) In comparison, the same reaction catalyzed by $Et_3PAu^+ \subset$ **1** proceeded to only 2% conversion after 18 h. We believe this to result from the increased steric demand of the cation, which leaves less space available inside the cluster for the substrate.

(12) The reported rate enhancement is in comparison to Me_3PAuBr and applies only to this catalyst. For instance, as Me_3PAuCl is already a relatively active catalyst, catalysis with the encapsulated species led to 52% conversion after 18 h, which is comparable to the rate of reaction for the unencapsulated catalyst.

(13) At low conversion (0−12%), $[\mathbf{2}]_0 \approx [\mathbf{2}]_t$, and thus, there should be a pseudolinear correlation between conversion and time.

(14) For example, cyclization of **5** proceeded to 28% conversion in the presence of $Me_3PAu^+ \subset$ **1** but to only 14% conversion with Me_3PAuBr alone.