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# A supramolecular approach to combining enzymatic and transition metal catalysis

Z. Jane Wang, Kristen N. Clary, Robert G. Bergman*, Kenneth N. Raymond* and F. Dean Toste*

**The ability of supramolecular host–guest complexes to catalyse organic reactions collaboratively with an enzyme is an important goal in the research and discovery of synthetic enzyme mimics. Herein we present a variety of catalytic tandem reactions that employ esterases, lipases or alcohol dehydrogenases and gold(I) or ruthenium(II) complexes encapsulated in a $Ga_4L_6$ tetrahedral supramolecular cluster. The host–guest complexes are tolerated well by the enzymes and, in the case of the gold(I) host–guest complex, show improved reactivity relative to the free cationic guest. We propose that supramolecular encapsulation of organometallic complexes prevents their diffusion into the bulk solution, where they can bind amino-acid residues on the proteins and potentially compromise their activity. Our observations underline the advantages of the supramolecular approach and suggest that encapsulation of reactive complexes may provide a general strategy for carrying out classic organic reactions in the presence of biocatalysts.**

A long-standing goal of supramolecular chemistry is the construction of assemblies that mimic the desirable qualities of protein catalysts[1–4]. These qualities include the ability to operate in an aqueous solution at a physiological pH, to provide a well-defined cavity for reaction that is chemically distinct from the bulk solvent and to select one substrate, on the basis of size or shape, from a pool of structurally related molecules[4]. The first complexes to be termed 'artificial enzymes' were based on cyclodextrins modified with transition-metal complexes and reported by Breslow over four decades ago[5]. Since these seminal reports, research on supramolecular enzyme mimics has been directed largely towards developing scaffolds that model enzyme binding and, in a smaller number of examples, showcase selectivity of the reaction as a result of preferential binding. The frameworks reported as a result of these efforts[2,6–12] operate as molecular flasks, in analogy to the binding site of proteins.

Despite these reports, one hallmark of catalysis by true enzymes in a complex metabolic pathway is explored much less frequently: the ability of synthetic enzyme mimics to catalyse transformations in the presence of many other biocatalysts. In nature, enzymes contain highly substrate-selective reactive sites that allow for a series of chemically incompatible reactions to be performed in tandem[13]. The integration of enzymatic and chemocatalysis in one-pot sequences can result in powerful transformations[14,15]. However, this combination is often challenging as it extends beyond the ability of synthetic complexes to copy catalytic behaviour and requires that the catalysts be compatible with each other when operating under similar conditions and rates[16–22]. Although a few interesting examples of transition-metal catalysts working in parallel with enzymes are reported[16–24], the number of transformations amenable to these processes represents a small subset of the catalytic reactions reported in organometallic chemistry or synthetic biology. The ability to unify the pool of enzymatic and synthetic reactions is important in the construction of a truly biomimetic pathway.

A supramolecular approach to the problem of tandem catalysis has many advantages. First, the ability of supramolecular assemblies to stabilize reactive metal centres on the formation of host–guest complexes may improve the lifetime of the organometallic complex[25,26]. Second, supramolecular hosts that demonstrate high water solubility can 'pull' metal complexes bearing relatively hydrophobic organic ligands into the aqueous solution such that reactions traditionally performed in an organic solvent can be achieved in water[27]. Third, the cluster itself can prevent the reactive metal catalyst from diffusing into solution, where it can interact directly with residues on a protein, negating the need for a high enzyme loading. These advantages make supramolecular host–guest complexes an attractive target for the development of synthetic catalysts that can work collaboratively with true enzymes.

## Results and discussion

Recently, we reported organometallic complexes encapsulated in a tetrahedral $Ga_4L_6$ (L = *N*,*N*′-bis(2,3-dihydroxybenzoyl)-1,5-diaminonaphthalene) cluster (**1**, Fig. 1) that is stable at neutral pH in water and provides a well-defined cavity for reaction[28,29]. In particular, the gold(I)–$Ga_4L_6$ host–guest complex ($Me_3PAu^+ \subset$ **1**) exhibits an eightfold rate enhancement relative to that of the free gold complex in the hydroalkoxylation of allenes, and shows a higher reactivity towards unsubstituted substrates like **2** than to those that bear substitution along the alkyl chain[28]. We hypothesized that this assembly would be an excellent platform to test whether a $Ga_4L_6$ host–guest complex could function in a multistep reaction that contained an enzyme-mediated step. Lipases and esterases are robust enzymes that are used often by synthetic chemists for carrying out regio- and chemoselective reactions[30]. We reasoned that these enzymes would be good partners for our supramolecular cluster in a tandem process. This overall transformation is shown in Table 1: starting from allenic acetate **4**, enzymatic hydrolysis reveals the alcohol substrate **2**, which can then be cyclized to give substituted tetrahydrofuran **3**.

When the acetylated substrate **4** was combined with 25 units of rabbit liver esterase in Tris buffer at pH 8 and 10 mol% of $Me_3PAu^+ \subset$ **1**, a 12% conversion into the cyclized product was observed after 20 hours. The addition of 5% dimethyl sulfoxide (DMSO) or MeOH to the reaction mixture greatly improved the solubility of **4** and resulted in a dramatic improvement in conversion to 88% after 20 hours. Increasing the temperature to 37 °C allowed the reaction to proceed to complete conversion and excellent yield using only six units of enzyme. Significantly, the reaction of **4** with rabbit liver esterase under identical conditions, but without

Division of Chemical Sciences, Lawrence Berkeley National Laboratory, and Department of Chemistry, University of California, Berkeley, California 94720-1460, USA. *e-mail: rbergman@berkeley.edu; raymond@socrates.berkeley.edu; fdtoste@berkeley.edu

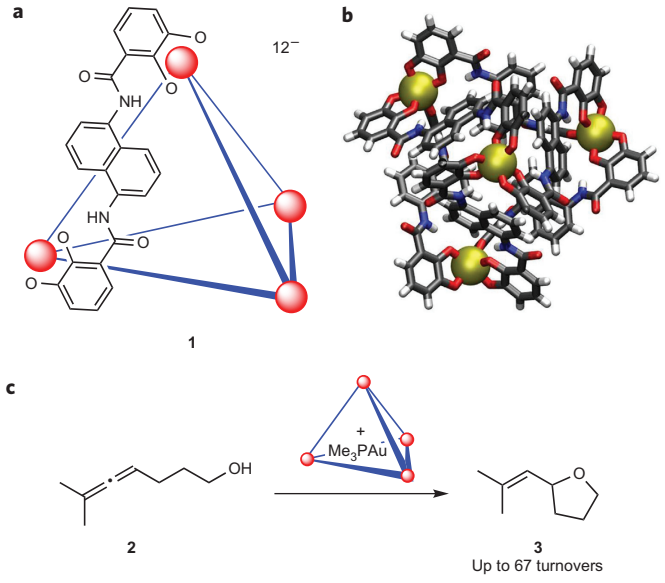


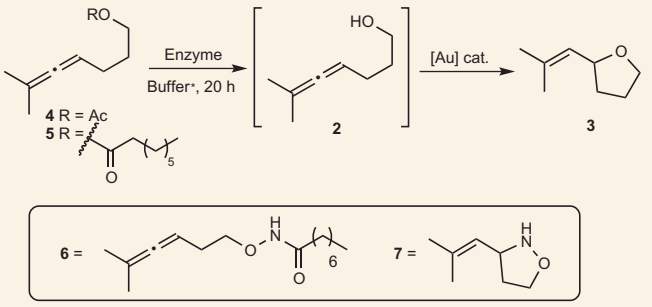

**Figure 1 | Host–guest complexes of $Ga_4L_6$ with Au(I) complexes can facilitate the hydroalkoxylation of an allene in water. a**, A schematic view of the $Ga_4L_6$ tetrahedral supramolecular assembly (**1**) in which each edge of the tetrahedron represents a bisbidentate ligand and each vertex represents a gallium centre. **b**, A stick model of **1**, viewed down the C3 axis. **c**, Hydroalkoxylation reaction catalysed by $Me_3PAu^+ \subset$ **1**.

any gold catalyst, afforded only the alcohol product **2**, and subjecting **4** to 10 mol% of $Me_3PAu^+ \subset$ **1** alone led to no reaction. Thus, catalytic formation of the cyclized product **3** required both rabbit liver esterase and $Me_3PAu^+ \subset$ **1**.

Following this initial result, we examined the tandem reaction sequence with a variety of esterases. Good-to-excellent conversion into the desired product **4** was observed in most cases (Table 1) with only 1–6 units of enzyme. Additionally, a few lipases are known to cleave amide bonds[31] and we were able to exploit this property to furnish **6** in good yield after amide hydrolysis and $Me_3PAu^+ \subset$ **1**-mediated hydroamination. Interestingly, tandem reactions with $Me_3PAu^+ \subset$ **1** and rabbit, hog or horse liver esterase proceeded more readily than the analogous reactions with $Me_3PAuCl$. In these reactions, a small-to-moderate amount of starting material was present after 20 hours when $Me_3PAuCl$ was used, which suggests that $Me_3PAuCl$ may inhibit the activity of the esterase.

This was confirmed further when substrates **8** and **9** were subjected to tandem enzymatic kinetic resolution and $Me_3PAu^+ \subset$ **1**-mediated cyclization, to afford tetrahydrofurans **10** and **11** (Table 2). The configurations assigned to **10** and **11** are based on the $^{19}F$ and $^1H$ NMR $\delta$ values of the Mosher's acid derivatives of the alcohol generated from hydrolysis of acetate **10** (Supplementary Information). This is also in agreement with the known enantiopreference of the lipase from *Burkholderia cepacia*[32]. The major diastereomers were identified as shown based on one-dimensional selective nuclear Overhauser enhancement spectroscopy experiments. In reactions with Amano lipase PS from *B. cepacia* the conversion increased by 12% for substrate **8** when the supramolecular assembly was present, but the enantioselectivity remained constant. However, when hog liver esterase catalysed the hydrolysis, the conversions were similar in both cases, but the addition of the supramolecular assembly improved the enantioselectivity by 26% in the case of the methyl-substituted analogue **8** and 19% with the ethyl substrate **9**. Amino acids like cysteine, histidine and asparagine are known to coordinate free gold(I) ions[33,34] and we hypothesize that the observed decreases in the rate of hydrolysis could be a result of direct interactions

**Table 1 | Tandem esterase- or lipase-mediated acetate hydrolysis followed by $Me_3PAu^+ \subset$ 1- or $Me_3PAuCl$-catalysed hydroalkoxylation.**



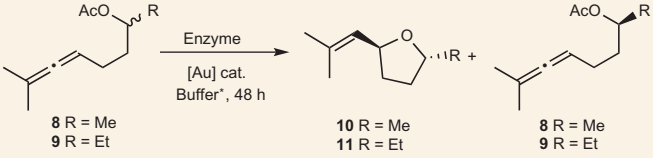

| Substrate | Product | Enzyme | [Au] cat. | Product ratio (4:2:3)† |
|---|---|---|---|---|
| 4 | 3 | Rabbit liver esterase‡ | $Me_3PAu^+ \subset$ 1 | (0:0:100) |
| | | | $Me_3PAuCl$ | (14:24:62) |
| 4 | 3 | Hog liver esterase§ | $Me_3PAu^+ \subset$ 1 | (2:4:94) |
| | | | $Me_3PAuCl$ | (35:22:44) |
| 4 | 3 | Horse liver esterase§ | $Me_3PAu^+ \subset$ 1 | (4:43:53) |
| | | | $Me_3PAuCl$ | (11:35:54) |
| 5 | 3 | *Mucor miehei* lipase‖ | $Me_3PAu^+ \subset$ 1 | (0:0:100) |
| | | | $Me_3PAuCl$ | (15:0:65) |
| 6 | 7 | *Mucor miehei* lipase‖ | $Me_3PAu^+ \subset$ 1 | (38:2:60) |
| | | | $Me_3PAuCl$ | (32:2:66) |

*Tris buffer pH 8 was used in the esterase reactions and phosphate buffer pH 7 was used in the lipase reactions. 5% DMSO or MeOH was also used in all the reactions to increase the solubility of **4** in aqueous buffer. The substrate concentration was 2.2 mM. †Determined by proton NMR spectroscopy (see the Supplementary information for NMR yields relative to internal standard). ‡Six units of enzyme used at 37 °C. §One unit of esterase used at 23 °C. ‖Three units of enzyme used at 37 °C. cat = catalyst.

between gold(I) and amino-acid residues on the esterase. In contrast, the encapsulated gold complex sequesters $Me_3PAu^+$ and prevents it from diffusing into the bulk solvent, where it can complex to the protein.

To further explore this hypothesis, fluorinated substrate **12** was prepared and subjected to tandem reaction conditions with hog liver esterase and both $Me_3PAu^+ \subset$ **1** and $Me_3PAuCl$. The fluorinated ester allowed us to monitor the rate of the hydrolysis step (step 1, Fig. 2) in the tandem transformation by $^{19}F$ NMR spectroscopy (Fig. 2)[35,36]. The reaction traces in Fig. 2 reflect the effect

**Table 2 | Tandem enzymatic kinetic resolution and cyclization with $Me_3PAu^+ \subset$ 1 or $Me_3PAuCl$.**




| Product | Enzyme | [Au] cat. | Conversion (%)† | d.e (%)† | e.e. (%)† |
|---|---|---|---|---|---|
| 10 | Amano lipase *PS*§ | $Me_3PAu^+ \subset$ 1 | 32 | 26 | 89‡ |
| | | $Me_3PAuCl$ | 20 | 21 | 88‡ |
| 10 | Hog liver esterase‖ | $Me_3PAu^+ \subset$ 1 | 32 | 15 | 64‡ |
| | | $Me_3PAuCl$ | 30 | 20 | 38‡ |
| 11 | Amano lipase *PS*§ | $Me_3PAu^+ \subset$ 1 | 33 | 30 | 96 |
| | | $Me_3PAuCl$ | 32 | 37 | 89 |
| 11 | Hog liver esterase‖ | $Me_3PAu^+ \subset$ 1 | 19 | 29 | 46 |
| | | $Me_3PAuCl$ | 22 | 38 | 27 |

*Moderate diastereoselectivity and good-to-excellent enantioselectivity are exhibited. Tris buffer pH 8 was used in the esterase reactions and phosphate buffer pH 7 was used in the lipase reactions. 5% DMSO was used in all the reactions and the substrate concentration was 2.2 mM. †Determined by gas chromatography analysis. ‡Determined from the minor *cis* diastereomer, ±5%; §2.5 mg of Amano lipase PS (>30,000 units per gram) were used at room temperature (r.t.). ‖Two units of enzyme were used at r.t. d.e. = diastereomeric excess, e.e. = enantiomeric excess.

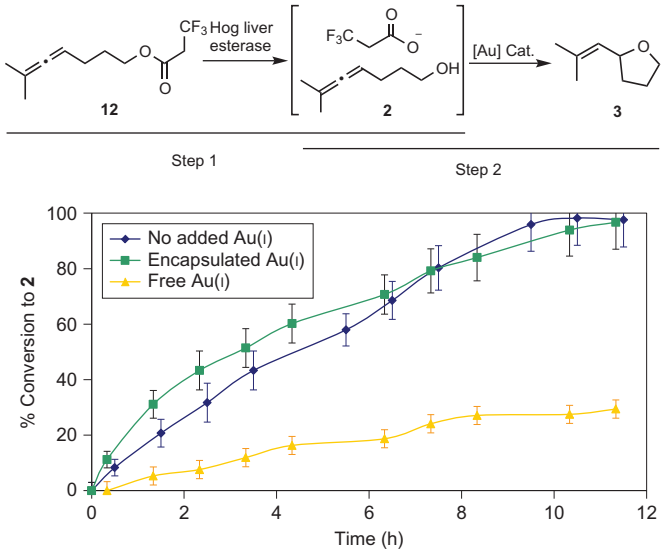



**Figure 2 | Reaction progress of the hydrolysis of 12 with hog liver esterase in the presence of $Me_3PAu^+ \subset$ 1, $Me_3PAuCl$ (free Au) or no additional gold complex.** Free gold(I) complexes significantly reduce the activity of hog liver esterase, but encapsulated gold(I) complexes have no measurable effect on the rate of enzyme catalysis. Error bars represent the error inherent in the integration of $^{19}F$ NMR signals used to determine conversion.

of the catalyst in the cyclization step (step 2, Fig. 2) on the kinetics of the first step in the sequence. Although the rate of hydrolysis in the presence of $Me_3PAu^+ \subset$ **1** is within the error of the inherent rate of hydrolysis in the absence of any gold species, the rate of esterase catalysis is significantly reduced when $Me_3PAuCl$ is used as the catalyst. This result provides evidence that the supramolecular host–guest complex has little effect on enzyme activity, and the free $Me_3PAuCl$ is deleterious to enzyme catalysis. We conclude that the supramolecular cluster may prevent undesired direct interactions between the enzyme and gold catalysts, and so preserve the activity of both.

After our progress with the hydrolysis–cyclization tandem reaction, we turned our efforts towards developing a process in which an alcohol dehydrogenase (ADH) could be employed in a sequence with an encapsulated transition-metal catalyst. Although a few methods that employ transition-metal catalysts in tandem with esterases are known, to the best of our knowledge only one instance of one-pot reactions with transition metals and ADHs has been reported[37]. Recently, we reported a method for the isomerization of allylic alcohols into the corresponding aldehydes with $(Me_3P)CpRu(NCMe)_2^+$ encapsulated in **1** (ref. 29). We hypothesized that this transformation could be incorporated into an enzymatic pathway in which the aldehyde product from the reaction could be reduced by ADH. A general scheme that depicts this transformation is shown in Fig. 3. To avoid using a stoichiometric amount of nicotinamide adenine dinucleotide phosphate (NADPH) cofactor, we posited that the reduction could be coupled to oxidation of sodium formate by formate dehydrogenase (FDH)[1] such that NADPH could be regenerated *in situ*. Thus, the overall transformation requires that the supramolecular catalyst works well in concert with both dehydrogenases.

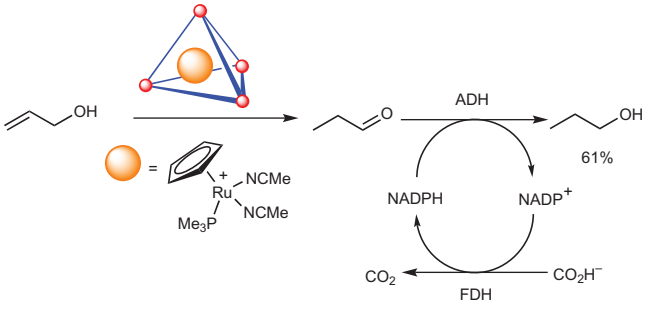



**Figure 3 | Ru(II)-mediated olefin isomerization of allyl alcohol to give propanal followed by reduction to propanol via ADH.**

Treatment of 1-propenol with horse-liver alcohol dehydrogenase (HLADH), NADPH, yeast FDH, sodium formate and $(Me_3P)CpRu(NCMe)_2^+ \subset$ **1** led to the formation of propanol in 61% yield after six hours at 37 °C, as determined by $^1H$ NMR spectroscopy using water-suppression parameters. Once again, neither the enzyme couple nor the encapsulated ruthenium catalyst alone could carry out both reactions in the sequence.

## Conclusions

The examples reported herein demonstrate the ability of enzymes to catalyse reactions in one pot with a $Ga_4L_6$ supramolecular enzyme mimic. Notably, this combination is viable independently of whether the enzymatic or metal-catalysed reaction proceeds first. Furthermore, we found that the encapsulation of a gold(I) catalyst can improve the enantioselectivity or the rate of catalysis of the enzyme relative to that in the presence of the free cationic complex. Although the mechanism of interaction between the free gold cation and hog liver esterase is not well understood at this time, the ability of free gold(I) to coordinate strongly to a variety of amino acids led us to believe that a direct coordination of gold(I) to the enzyme is responsible for the significant decrease in catalytic activity observed in the presence of $Me_3PAuCl$. These results suggest that encapsulation can prevent adverse interactions from occurring and provides a method for tandem catalysis with reactive transition-metal complexes. Our studies have important implications for the development of new supramolecular hosts for catalysis and demonstrate a key advantage of supramolecular catalysis in integrated chemical and biological synthetic sequences.

## Methods

Chloro(trimethylphosphine) gold(I) (0.50 mg, 1.6 μmol) was combined with $K_{12}[Ga_4L_6]$ (**1**) (7.0 mg, 1.6 μmol) in Tris buffer pH 8 (0.7 ml) in an oxygen-free glove box. The solution was stirred rapidly at room temperature for 20 minutes and then filtered through a microsyringe filter. A portion of the filtered catalyst solution (1.2 μmol, 500 μl) was added to a second vial equipped with a silicon septum cap and stir bar, and removed from the glove box. A stock solution of the allene substrate and internal standard (in a 3:1 ratio) in degassed MeOH or DMSO was made. A second stock solution of the enzyme in buffer solution was made such that the final concentration of the enzyme was one unit per 10 μl. To the solution of $Me_3PAu^+ \subset$ **1**, the enzyme (1–6 units) and substrate solutions (12.0 μmol of substrate in 25 μl MeOH or DMSO) were added. Additional buffer was added such that the final volume of the reaction mixture was 550 μl and the resulting solution was stirred gently (60–100 rounds per minute) for 20 hours. The aqueous reaction mixture was extracted three times with $CDCl_3$ (0.5 ml each), dried with $Na_2SO_4$ and the $^1H$ NMR spectrum of the organic solution was recorded to determine the conversion (relative to the remaining starting material) and yield (relative to the internal standard).

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## Author contributions

Z.J.W. conceived and designed the initial experiments and performed the kinetic studies. K.N.C. performed the kinetic resolution experiments and measured the diastereoselectivity and enantioselectivity of the transformations. Z.J.W. prepared the manuscript with help from K.N.C. All the authors discussed the results and commented on the manuscript.

## Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permission information is available online at http://www.nature.com/reprints. Correspondence and requests for materials should be addressed to R.G.B., K.N.R. and F.D.T.

## Competing financial interests

The authors declare no competing financial interests.