

# Selective Monoterpene-like Cyclization Reactions Achieved by Water Exclusion from Reactive Intermediates in a Supramolecular Catalyst

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Supporting Information

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**ABSTRACT:** A polyanionic supramolecular assembly (**1**) is shown to catalytically cyclize the monoterpene citronellal (**2**) and two homologues (**6a**, **7a**). In contrast to cyclization in acidic aqueous solution, the hydrophobic interior of **1** prevents the capture of reactive intermediates by water. This effect was also observed in the gold catalyzed cycloisomerization of enyne **8**. Due to the steric confinement of the catalyst's interior, Prins cyclizations in **1** proceed cleanly both for substrates containing and lacking *gem*-dimethyl substitution. Encapsulation in **1** consequently imposes a degree of mechanistic control, which, similar to enzyme catalysis, is not observed in bulk aqueous solution.

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Terpene synthases are enzymes that generate over 60,000 small molecule natural products from simple precursors.<sup>1</sup> These enzymes catalyze cascading 1,5-diene cyclization reactions that proceed through carbenium ion intermediates.<sup>2</sup> Noncovalent interactions, such as cation- $\pi$  stabilization and steric repulsion, dictate the conformations of intermediates and resulting product distributions.<sup>3,4</sup> Although terpene synthases can be highly selective, product distributions containing multiple

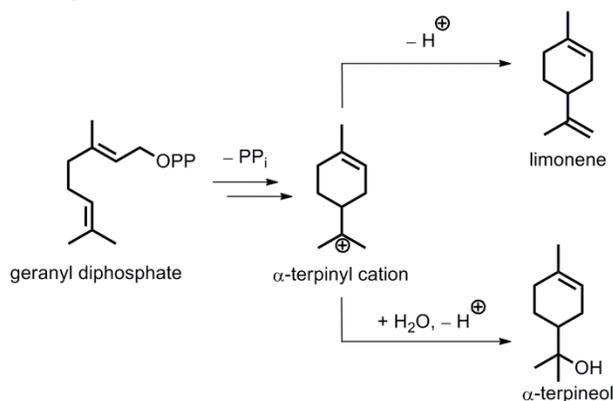
species are common. Contingent on the nature of the enzyme's active site, these intermediates may undergo eventual deprotonation or nucleophilic capture (*e.g.* by water) to furnish the final products.<sup>5-7</sup> An example is the conversion of geranyl diphosphate to limonene and  $\alpha$ -terpineol via the  $\alpha$ -terpinyl cation, as illustrated in Scheme 1.

Synthetic systems have modeled the selectivity and efficiency of enzymes.<sup>8</sup> Recent advances in supramolecular catalysis demonstrate the potential for these systems to effect high rate enhancements<sup>9-11</sup> and a capacity for regulation<sup>12</sup> reminiscent of enzyme catalysis. The Raymond group has developed a water-soluble, chiral metal-ligand assembly of  $K_{12}Ga_4L_6$  stoichiometry ( $L = N,N$ -bis(2,3-dihydroxybenzoyl)-1,5-diaminonaphthalene; polyanion (**1**) represented in Scheme 2).<sup>13</sup> Bearing analogy to the active sites of terpene synthases,<sup>14,7</sup> the constrictive steric interior of polyanion **1** is defined by cation-stabilizing aromatic moieties. Combined with the assembly's high negative charge, this property has been demonstrated to bring about  $pK_a$  shifts for encapsulated guests.<sup>15</sup> Assembly **1** has consequently been shown to catalyze proton-mediated processes in basic solution.<sup>16</sup> Notably, **1** catalyzes the Nazarov cyclization of 1,3-pentadienols with rate accelerations on the order of  $10^6$

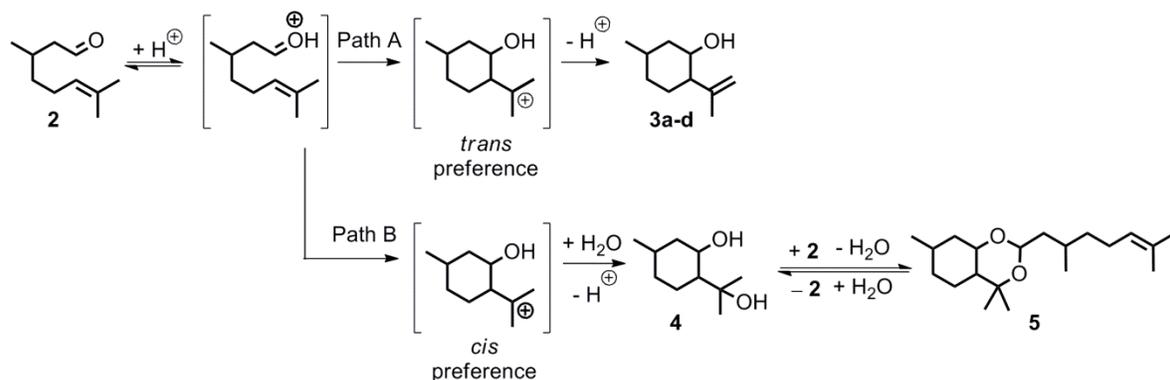
**Table 1. The cyclization of 2 to 3-5 by 1 and buffered acidic solution**

Entry	Catalyst	pH	Conv. (%)	Selectivity (%)		
				3a-d	4	5
1 <sup>a</sup>	1	7.50	71	97	3	< 1 <sup>c</sup>
2 <sup>b</sup>	KH <sub>2</sub> PO <sub>4</sub>	3.20	91	9	91	< 1

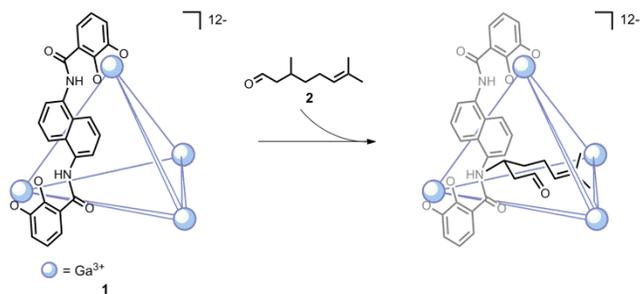
Conversion and selectivity assessed by <sup>1</sup>H NMR. Selectivity determined as a proportion of the identified product. Aqueous solutions contained 50 mM phosphate buffer for both trials. Conditions: <sup>a</sup>10 mol % 1, 60 °C, 28 h; <sup>b</sup>50 °C, 8 h; <sup>c</sup>Product not observed by <sup>1</sup>H NMR or GC-MS. relative to background reactivity, which has been attributed to transition state binding as well as substrate conjugate acid stabilization.<sup>17</sup>



**Scheme 1.** Biosynthesis of limonene and  $\alpha$ -terpineol from geranyl diphosphate (PP<sub>i</sub> = diphosphate). While limonene is obtained through a deprotonation route, capture of the  $\alpha$ -terpinyl cation with water affords  $\alpha$ -terpineol.<sup>4, 5-7</sup>



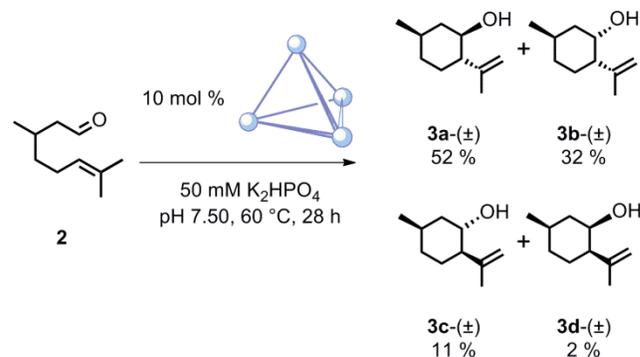
**Scheme 3.** Proton mediated cyclization of 2 to products 3-5. Under catalysis by acidic solution, 3-5 are observed with 4 as the major product by Path B. Catalysis with 1 affords 3a-d as the major class of products, demonstrating that Path A is instead favorable.



**Scheme 2.** Encapsulation of 2 by host 1; spheres represent a Ga<sup>3+</sup> center and bisbidentate ligands are depicted as lines.

Given the cation-stabilizing and hydrophobic properties of both the interior of 1 and the active sites of terpene synthases, we were eager to investigate a monoterpene cyclization in 1. The monoterpene ( $\pm$ )-citronellal (2) has been shown to cyclize in the presence of Brønsted acids and is a relevant industrial intermediate in the manufacture of menthol.<sup>18</sup> We hypothesized that 1 would stabilize the conjugate acid of encapsulated 2, driving protonation at the aldehyde oxygen and subsequent cyclization, the latter process being accelerated by the constrictive interior of 1. Herein we report our studies of a catalytic cyclization of 2 and two homologues (6a, 7a) in a water-soluble supramolecular assembly at moderate temperatures and physiological pH.

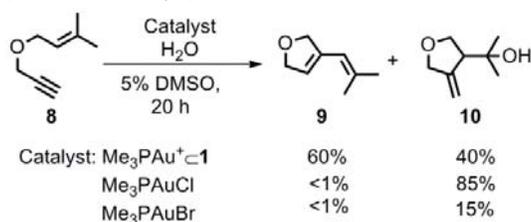
It has been reported that three classes of products are formed when 2 is treated with buffered acidic solution, as depicted in Scheme 3.<sup>19-21</sup> We confirmed this experimentally: in addition to minor products 3a-d, a mixture of four stereoisomeric *p*-menthane-3,8-diols (4) is observed as the major class of products. Once formed, 4



**Scheme 4.** Selectivity of alkene products from the cyclization of 2 by 1.



The *trans* product selectivity of **6a** in acidic solution is presumably the result of a 1,3-diaxial repulsion between the aldehyde oxygen and axially oriented  $\beta$ -methyl group in the transition state leading to *cis* product. The complex product mixture observed upon treating **7a** with acidic buffer demonstrates that in acidic solution, alternate reaction pathways are competitive with cyclization when *gem*-dimethyl substitution is absent at the  $\beta$ -position. In light of the very different product selectivity observed between **6a** and **7a** following acidic solution treatment, the tendency for these substrates to stereoselectively form alkene products in **1** is surprising, given that both bulk solution and cluster catalysis are proton mediated processes. While the presence of *gem*-dimethyl substitution vastly improves the product selectivity obtained from acidic solution catalysis, this discrepancy is eliminated with **1**. In the latter case, overriding steric repulsion experienced by the guest during encapsulation confers high selectivity toward *trans* alkene products, regardless of whether *gem*-dimethyl substitution is present at the  $\beta$ -position.



**Scheme 6.** Gold catalyzed cycloisomerization of enyne **8** to products **9** and **10**.

Having established enzyme-like selectivity in the Prins cyclizations of **2**, **6a** and **7a**, we then investigated whether **1** would impart similar selectivity during transition-metal-mediated transformations. We have recently reported the gold (I) host-guest complex  $\text{Me}_3\text{PAu}^+\text{c1}$  (where **c** denotes encapsulation) to be a viable catalyst for the hydroalkoxylation of allenes in water.<sup>28</sup> Gold catalyzed cycloisomerizations of 1,6-enynes have been well documented to result in different products depending on reaction conditions and substituent effects.<sup>29</sup> In the absence of assembly **1**,  $\text{Me}_3\text{PAuCl}$  catalyzed the cycloisomerization of **8** to **10**, which was obtained in 85% yield.<sup>30</sup> When the cavity of **1** was blocked by strongly bound  $\text{NEt}_4^+$ , compound **10** was likewise observed as the sole product. Use of  $\text{Me}_3\text{PAuBr}$  as a catalyst resulted in a lower yield of **10**, an observation that is presumably due to the relatively strong gold-bromide bond. However, following treatment of **8** with  $\text{Me}_3\text{PAu}^+\text{c1}$ , **9** was instead produced as the major product. Preparing the encapsulation complex  $\text{Me}_3\text{PAu}^+\text{c1}$  from  $\text{Me}_3\text{PAuBr}$  instead of  $\text{Me}_3\text{PAuCl}$  did not have a significant effect on the selectivity of this process and again 60:40 mixtures of products **9:10** resulted. The tendency for **1** to exclude water from reactive intermediates was thus demonstrated for a gold catalyzed cycloisomerization of enyne **8**.

In conclusion, we report the first example of a terpene cyclization by a water-soluble supramolecular catalyst at physiological pH. In analogy with the active sites of many terpene synthases, **1** directs the cyclization of monoterpene **2** toward deprotonation instead of nucleophilic capture by water.<sup>31</sup> The generality of this property was demonstrated in the gold catalyzed cycloisomerization of enyne **8**. We attribute this effect to the hydrophobic environment of the assembly's cavity, which prevents water from capturing carbenium ion intermediates during catalysis. Identification of **3a-d** is of interest, as these compounds are frequently used in the asymmetric synthesis of complex natural products.<sup>32</sup> Formation of **3a** as the major product is also important, as this compound is a direct industrial precursor to menthol, a fine chemical of multi-ton yearly production.<sup>18</sup> The synthesis of **3a** from **2** is conventionally accomplished using organic solvents and Lewis acids, where dehydration and dimerization products are often observed.<sup>33,34</sup> In contrast, catalysis by **1** provides an environmentally benign method to afford products of synthetic and economic utility without the byproducts often observed from Lewis acid treatment.<sup>35</sup> Also, in contrast to cyclization in acidic solution, assembly **1** affords product selectivity both in the presence and absence of *gem*-dimethyl substitution. This effect attests to the high degree of substrate conformational control provided by **1**. Both conformational control and the exclusion of water from reactive intermediates are characteristic properties of terpene synthases, to which the activity of **1** presented here bears analogy.

## ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and <sup>1</sup>H NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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