

TERPENE FUNCTIONALIZATIONS USING SUPRAMOLECULAR CATALYSTS

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INTRODUCTION

Terpenoids are structurally complex natural products that perform diverse functions within biological settings.¹ Nearly all terpenoids are derived from only two building blocks: dimethylallyl pyrophosphate (DMAPP) and isopentyl pyrophosphate (IPP).² The biosynthesis of terpenoids starts with the coupling of IPP and DMAPP to yield geranyl pyrophosphate (GPP). The carbon skeleton of GPP can then be extended by terpene synthases or the linear precursors can be cyclized by terpene cyclases.²

In either case, the functionalization of terpene molecules, whether modification of linear precursors or cyclization, represents a major synthetic challenge for the scalable synthesis of terpenoids.

For example, the cyclization of a simple monoterpene, GPP, generates a highly reactive α -terpinyl cation that is prone to many low energy pathways such as rearrangements, eliminations, and substitution reactions.²

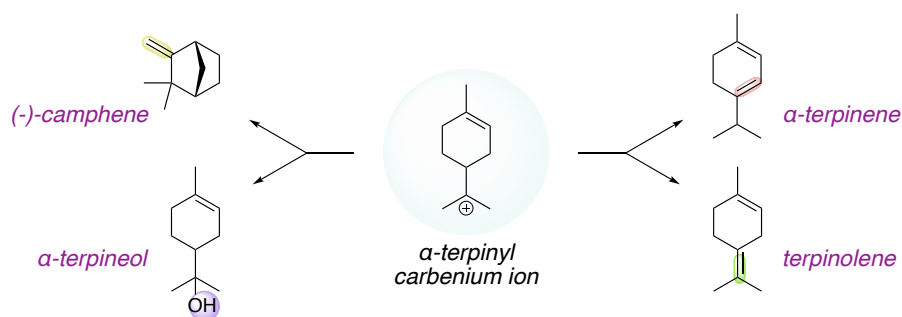


Figure 1. Controlling the Product Forming Step from a Reactive Intermediate

SUPRAMOLECULAR ASSEMBLIES AS BIOMIMETIC CATALYSTS

The use of supramolecular assemblies as catalysts presents an attractive approach for modifying linear terpenes. Supramolecular assemblies are known to desolvate guest molecules to prevent premature quenching of reactive intermediates.³ Many supramolecular assemblies contain aromatic linkers that can stabilize cations such as the α -terpinyl carbenium ion by cation- π interactions.³ In addition, these molecular assemblies have defined cavities that can stabilize transition states by electrostatic and hydrophobic interactions that would not be possible in bulk solution³. All of these characteristics not only give supramolecular catalysts a competitive edge over small molecule catalysts, but also draw many parallels with terpene cyclases. Mimicking natural terpene cyclases using supramolecular assemblies can potentially lead to a general approach for the scalable synthesis of terpenes in a regioselective, stereoselective, and site-selective fashion.

CONTROLLING PRODUCT SELECTIVITY INSIDE A SUPRAMOLECULAR ASSEMBLY

Bergman, Raymond, and Toste reported the first monoterpene-like cyclization inside a polyanionic, supramolecular catalyst by cyclizing citronellal.⁴ Only elimination products were produced

inside the capsule from citronellal and it was further demonstrated that supramolecular assemblies may impose conformational control on substrates and/or transition states that is not observed in bulk solution.⁴

CONFORMATIONAL CONTROL INSIDE A SUPRAMOLECULAR ASSEMBLY

Fujita recently reported a complementary approach, in which the structures of several linear diterpenoids bound to a supramolecular assembly were determined.⁵ The internal olefins of the diterpenoids were identified to be shielded by the triazine ligands of the catalyst, whereas the terminal prenyl group was exposed in the cavity, which ultimately led to site-selective electrophilic additions to linear terpenes.⁵

'NON-STOP' CYCLIZATIONS USING SUPRAMOLECULAR CATALYSTS

A landmark study for the functionalization of terpenes was reported by Tiefenbacher, in which geranyl acetate and related terpenes were cyclized inside a resorcinarene capsule.⁶ Mechanistic investigations led to the proposal that product selectivity can be controlled by simply changing the leaving group.⁷ Thus, the production of a given cyclic monoterpene can be turned on inside a supramolecular assembly by judicious choice of the leaving group.⁷

PARTIAL GUEST ENCAPSULATION TO OVERCOME HOST-GUEST SIZE LIMITATIONS

A possible limitation in using a supramolecular assembly as a catalyst for terpene functionalization is that each assembly size must be optimized for guest encapsulation. However, not all reactions within supramolecular assemblies require the entire guest molecule to be encapsulated. Bergman, Raymond, and Toste recently reported the site-selective catalytic hydrogenation of polyenes with a rhodium(I) complex inside a supramolecular catalyst.⁸ In contrast to previous studies,⁴⁻⁷ the results of this study illustrate that only the functional group to be modified needs to be encapsulated.⁸ Partial guest encapsulation can prove to be a general strategy for further site-selective modifications of linear terpenes such as geraniol and farnesol.

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