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# Molecular Capsule Catalysis: Ready to Address Current Challenges in Synthetic Organic Chemistry?

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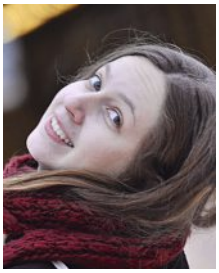
*Abstract:* Self-assembled molecular capsules, host structures that form spontaneously when their building blocks are mixed, have been known since the 1990s. They share some basic similarities with enzyme pockets, as they feature defined hydrophobic binding pockets that are able to bind molecules of appropriate size and shape. The potential to utilize such host structures for catalysis has been explored since their discovery; however, applications that solve current challenges in synthetic organic chemistry have remained limited. In this short article, we discuss the challenges associated with the use of molecular capsules as catalysts, and highlight some recent applications of supramolecular capsules to overcome challenges in synthetic organic chemistry.

**Keywords**: Catalysis · Cyclization · Host–guest chemistry · Molecular capsule · Supramolecular chemistry



***Ivana Némethová*** studied Organic chemistry at the University of P.J.Šafárika (Košice, Slovakia) focussing on the total synthesis of sphingolipids. In 2015, she started her PhD studies in the group of Prof. Radovan Šebesta at the Comenius University (Bratislava, Slovakia), developing asymmetric catalytic methods employing organozirconium species as nucleophiles. During her studies, she pursued an internship in the group of Prof. Stephen Fletcher (University of Oxford, UK). She is currently a postdoc working on supramolecular catalysis of terpene cyclizations in the group of Prof. Konrad Tiefenbacher.

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## 1. Introduction

Self-assembled molecular capsules are homogenous molecular host structures that form spontaneously when their building blocks are mixed under suitable conditions. They enclose a specific volume of space in which they are able to reversibly bind guest molecules. Ever since self-assembled molecular capsules were reported in the early 1990s,[1] they have attracted the interest of chemists working in the broad field of catalysis due to their apparent similarities to enzyme pockets. Much like an enzyme pocket, they are able to selectively isolate suitable substrates from the solvent inside their hydrophobic reaction pocket. Depending on the specific host–guest interactions, they are able to adjust the substrates' orientation towards each other, and/or their conformation, and in some cases alter or enhance the substrate's reactivity by non-covalent interactions. The first example of a reaction

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mediated by a self-assembled supramolecular capsule was reported by Rebek's group. In 1997 they reported the 200-fold acceleration of the Diels-Alder reaction between *p*-quinone and cyclohexadiene inside the dimeric 'softball' capsule.[2] Several other examples followed, and nowadays hundreds of examples for reactions taking place, or even being catalyzed, inside molecular capsules have been described.[3,4] In many cases, interesting substrate and/or product selectivities have been observed. However, most of these examples up to this day still represent proof-of-principle studies with little connection to current challenges in synthetic organic chemistry. To become a useful and widely applied tool in organic chemistry, molecular capsule catalysis has to provide solutions for current synthetic challenges that are difficult to address with other tools available. Therefore, in this short, non-comprehensive article, we want to highlight some recent examples which demonstrate that molecular capsules are able to overcome real challenges in synthetic organic chemistry. We are very optimistic that more examples will become available in the near future.

## 2. Fujita's Site-selective Functionalization of Linear Diterpenoids

In 2019, Fujita and coworkers disclosed a remarkable site-selective functionalization of linear diterpenoids by using the self-assembled supramolecular coordination cage **I** in aqueous media.[5] Cage **I** (Fig. 1a) is a positively charged assembly of six Pd(II)-ions and four tritopic organic ligands, and is soluble and stable in aqueous solutions. It features a tetrahedral shape, encloses a volume of approx. 460 Å$^3$,[6] and provides four portals of approx. 8 Å in diameter for guest uptake. It can encapsulate various guests, ranging from small aromatic compounds to large hydrophobic molecules, by forming inclusion complexes of different guest/host ratios depending on the size of the guest molecules.[7] Besides the hydrophobic effect, interactions with the electron-deficient tritopic ligands drive the encapsulation. For the large flexible polyunsaturated terpenoids **1a–d,** the group observed the formation of 1:1 inclusion complexes in which the substrates were conformationally frozen in U-shaped conformations (Fig. 1b). This was indicated by NMR spectroscopy, and

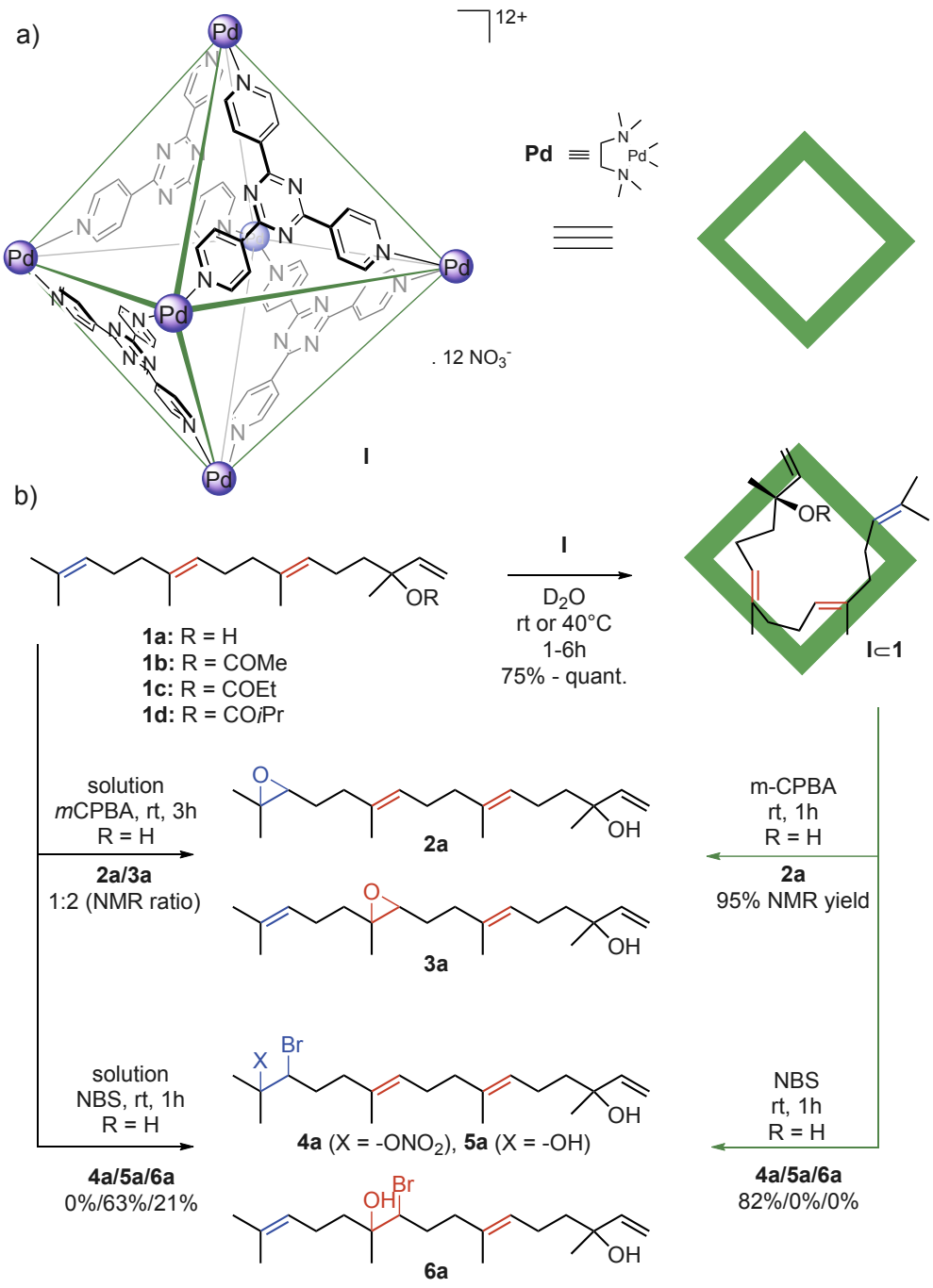



Fig. 1. a) Structure of Fujita's cage **I** that self-assembles from six Pd(II)-ions and four tritopic organic ligands. b) Examples of the selectivity differences observed when comparing the functionalization of **1a–d** in solution and inside cage **I**.

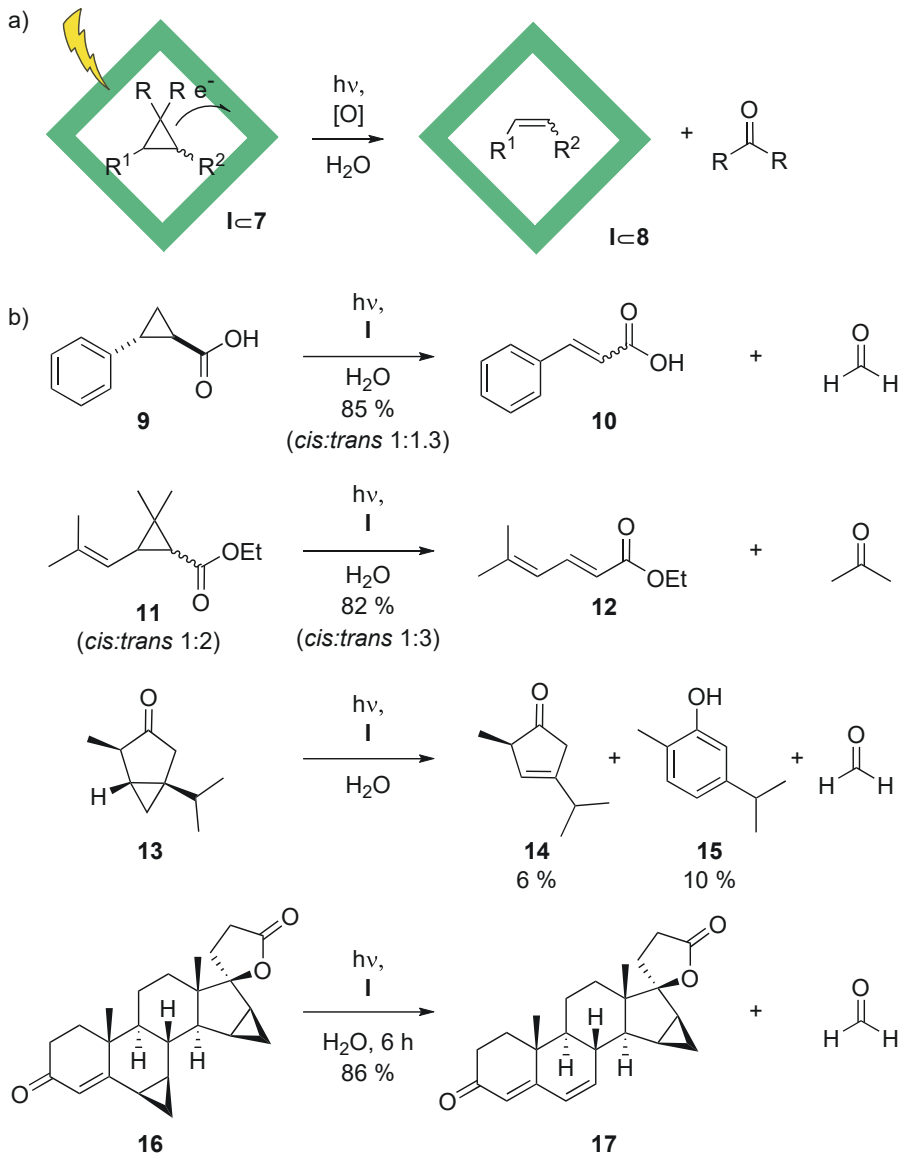
confirmed by solid-state X-ray studies. Stacking of the internal alkenes onto the panels of **I** and carbonyl-π interactions stabilize the conformation.

The folded binding mode stands in contrast to earlier findings by the authors about the binding of linear hydrocarbons which lack strong specific guest–host interactions. The restricted binding mode shielded several reactive sites of the substrates **1a–d**, which enabled the site-selective functionalization of the unshielded protruding terminal prenyl moiety (Fig. 1b, in blue) either *via* mCPBA or NBS. A related mono functionalization of less complex dialkenes was recently reported by the Rebek group utilizing a water-soluble cavitand.[8] The oxidation of the complex **I⊂1a** with 1 equiv. of mCPBA cleanly yielded the terminal epoxide **2a** in 95% NMR yield as the only observed product. The control experiment in organic solvent without cage **I** yielded a 1:2 ratio of products **2a** and **3a**. Furthermore, experiments with the separate cage components (ligand or Pd-salt) led to more complex mixtures, highlighting the directing role of cage **I** in the selective epoxidation. The functionalization of the encapsulated substrates **1a–d** with NBS, interestingly, did not provide the usual bromohydrin **5** but the nitratobrominated product **4** (Fig. 1b). Its formation likely stems from the high local concentration of $NO_3^-$ ions that intercept the bromonium intermediate. For instance, compound **4a** was formed selectively and was isolated in 82% yield. The control experiment in solution delivered bromohydrins **5a** and **6a** in a 3:1 ratio. The experiments with the separate cage components (ligand or Pd-salt) also led to bromohydrin product mixtures, again highlighting the directing role of cage **I** in these functionalizations.

### 2.1 *Fujita's Demethylenation of Cyclopropanes*

When irradiated, the Pd-coordinated triazine ligands of cage **I** can accept an electron from an encapsulated guest molecule, oxidizing it to the corresponding radical cation.[9] Making use of this reactivity, the group previously demonstrated the oxidation of adamantane[10] and triquinacene,[11] as well as the anti-Markovnikov hydration of alkynes.[12] Following these reports, the group showed that irradiation of cyclopropanes **7** encapsulated in cage **I** results in demethylenation to produce the corresponding alkene (Scheme 1a).[13] Photomediated demethylenation reactions of cyclopropanes are known.[14] However, these are mechanistically different from Fujita's study as they do not involve an electron transfer process, but rather a cycloelimination to generate an alkene and a carbene; in these cases the demethylenation process often competes with alternative pathways such as ring opening.

Substrates **9** and **11** react to give the corresponding alkenes in good yields (85% and 82%, respectively, Scheme 1b). Mixtures of *cis* and *trans* isomers were formed in these cases (1:1.3 *cis*/*trans* for **10**, 1:3 *cis*/*trans* for **12**). The authors present evidence that these mixtures are due to light-mediated isomerization of the alkene product. Substrates that do not contain an alkene or a phenyl group adjacent to the cyclopropane represent a potential limitation



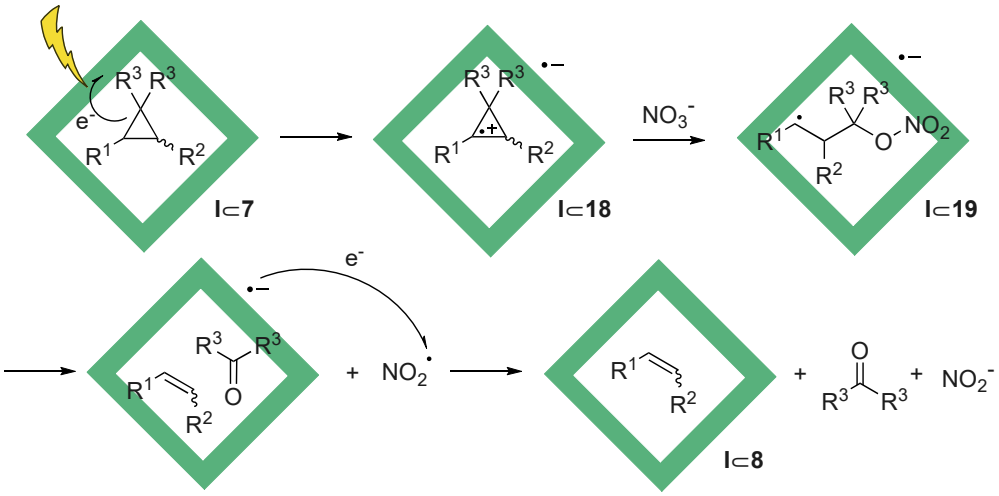

Scheme 1. a) Photomediated demethylenation reaction of cyclopropanes inside cage **I**, and b) specific examples.

of the method: the use of thujone (**13**) as the substrate was found to form the alkene product **14** in only low yield.

The authors propose that the reaction proceeds *via* a light-mediated host-to-guest electron transfer[9] to give a cyclopropyl radical cation together with the radical anion of the cage (**I⊂18**, Scheme 2). This is followed by opening of the cyclopropane radical cation by a nucleophilic attack by the nitrate counterion of cage **I**. Fragmentation of the resulting radical **19** gives the alkene product **8**, formaldehyde, and a nitrite radical. The latter is finally reduced to nitrite anion by accepting an electron from the cage radical anion.

An interesting application of this methodology is presented by the reaction of the steroid drospirenone (**16**), which reacts selectively to give the mono-demethylenated product **17** in 86% isolated yield (Scheme 1b). Control experiments without cage **I**, or in the presence of only its subcomponents (ligand or Pd-salt) did not lead to the formation of **8**. Furthermore, a modified cage, in which the triazine part of the ligand was replaced by a benzene, also failed to produce the demethylenated product **8**. The high yield and selectivity obtained within cage **I** is certainly remarkable, and indicates its applicability for the late-stage modification of complex molecules.

Scheme 2. Proposed mechanism for the photomediated demethylenation reaction of cyclopropanes inside cage **I**.




### 2.2 *Bergman-Raymond-Toste's Site-selective Hydrogenation*

In the example discussed in the beginning of this article, encapsulation resulted in the site-selective functionalization of the alkene exposed to the solvent. In contrast, Bergman-Raymond-Toste's selective catalytic hydrogenation of alkenes takes place inside the cage **II** (Fig. 2a).[15] This self-assembled system consists of four Ga(III) ions and four naphthalene-based catecholate ligands forming a negatively charged tetrahedral host.[16] It has excellent water solubility and provides a hydrophobic cavity of up to 450 Å$^3$ capable of encapsulating various neutral or cationic guest molecules.[3a,17] Since the host does not feature large portals like cage **I**, guest exchange has to take place *via* deformation of the host.[16b,18] Moreover, a larger version of this cage, assembly **III**, featuring pyrene ligands has also been reported (Fig. 2a).[19] Inspired by the Reek group's selective supramolecular and Rh-mediated hydroformylation[20] and based on their previous reports of host-encapsulated Rh- and Ru-catalysts used for the isomerization[21] of allyl alcohols, the authors demonstrated that a Rh-precatalyst encapsulated in the cage **II** is able to hydrogenate olefins in polyene structures site-selectively (Fig. 2b). As a model substrate, they employed hexene-1-ols **20**–**23** with a double bond positioned in various places in the aliphatic chain. In solution control experiments with the Rh-precatalyst, all substrates **20**–**23** were reduced quickly (1 h). However, if the **II**⊂Rh-precatalyst complex was employed, only substrates **20** and **21** featuring a terminal or methyl-substituted alkene were affected (Fig. 2b). Experiments with substrates carrying a negatively charged carboxylate group that prevents complete uptake into the negatively charged cage, indicated that a complete substrate encapsulation is not required for the reaction to proceed inside the cage. The excellent site-selectivity was confirmed in competition experiments using mixtures of various isomeric alkenes as well as mixtures of alkene/alkyne compounds (Fig. 2c). When *E*-**21** and *E*-**22** were used in a competition experiment, good conversion of *E*-**21** was observed (91% yield of **24**), while *E*-**22** was fully recovered. Similarly, when the mixture of two alkynes **25** and **26** was used, only the one with the methyl-substituted triple bond (**25**) was reduced. Even more interestingly, in the case of alkene *Z*-**21** and alkyne **26**, only *Z*-**21** was reduced, in contrast to the inherent reactivity of the precatalyst.

Utilizing the same concept in the larger host **III**, a spectacular site-selectivity was achieved in the reduction of the polyenol **28**, derived from the fatty acid α-linolenic acid. The site-selective reduction of any of the three alkenes is highly challenging due to their similar reactivity, and the lack of a directing group. Reaction with the free precatalyst gave mixtures of different products after a short reaction time, which all converged to the fully saturated product over time. However, in accordance with the results obtained with the smaller host, the alkene able to enter the cavity of host **III** was reduced selectively. The product **29** was obtained in a preparatively useful yield of 74%, highlighting the potential of selectively reducing alkenes in complex molecules (Fig. 2d).

### 2.3 *Our Four-step Biomimetic Synthesis of Presilphiperfolan-1β-ol and Unnatural Derivatives*

Our group has demonstrated the remarkable capacity of the hexameric resorcinarene capsule **IV** (Scheme 3a) to act as an artificial terpene synthase by catalyzing the tail-to-head terpene (THT) cyclization.[3n,o,22,23] The hydrogen-bonded capsule **IV** is formed by the self-assembly of the monomer **30** in apolar solvents, encompassing a cavity of approximately 1400 Å$^3$.[24–26] The aromatic walls of this cavity interact with cationic guests *via* cation-π interactions. In this way, the capsule is capable of complexing cationic guests (for instance, tetraalkylammonium ions),[26,27] and presumably stabilizing cationic intermediates and transition states involved in the terpene cyclization cascade. Guest encapsulation is believed to occur *via* the dissociation of one unit from the assembly.[28] The potential for catalysis of capsule **IV** was first reported by the Scarso group,[29,30] and has been explored by our group[3n] and the Gaeta-Neri group.[3r]

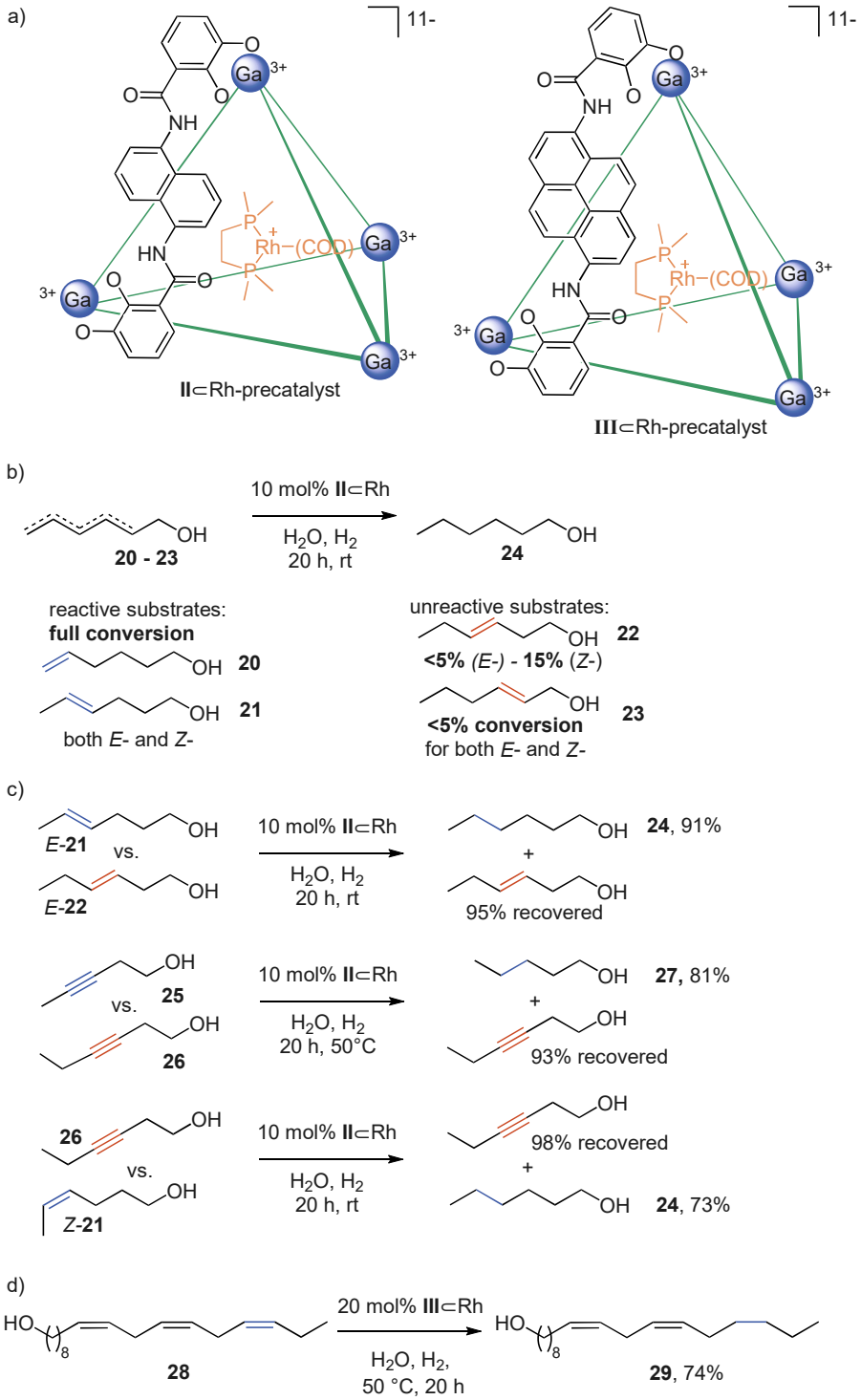
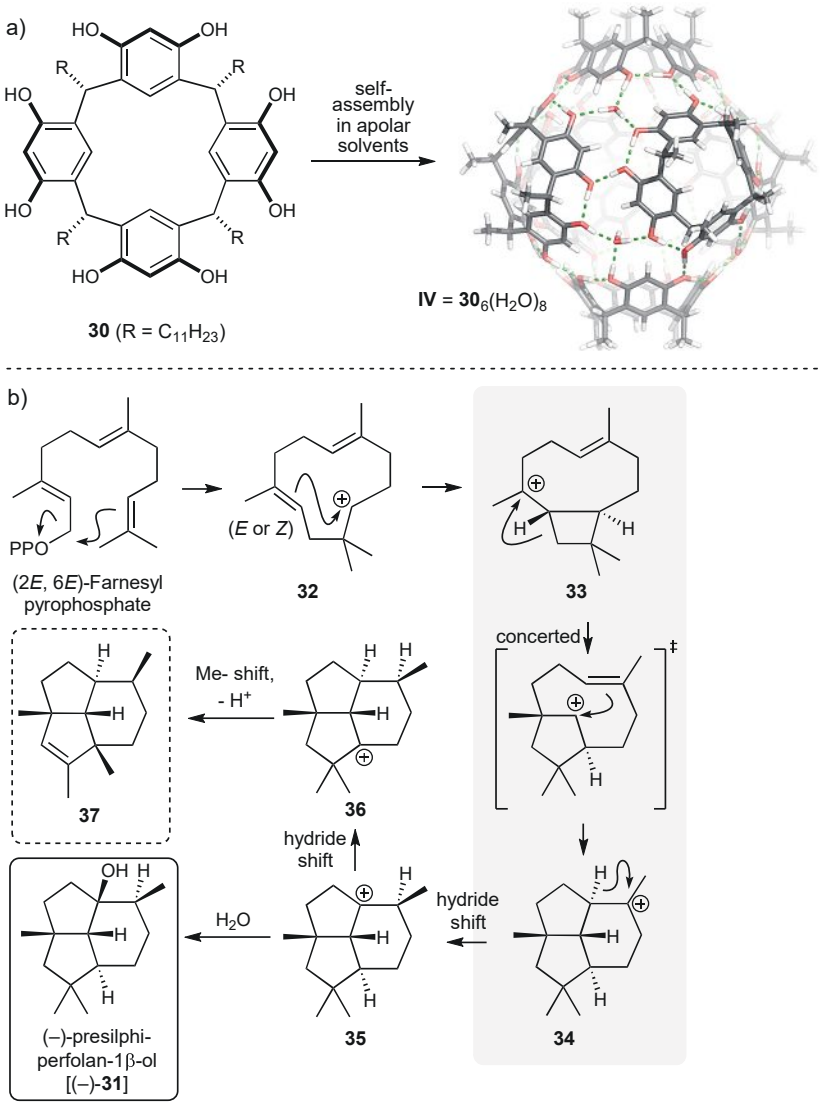



Fig. 2. a) Structure of the Raymond cages **II** and **III** that self-assemble from four Ga(III)-ions and four naphthalene- or pyrene-based catecholate ligands. b) In contrast to the free catalyst, the encapsulated catalyst **II**⊂Rh reduces substrates **20** and **21** selectively. c) Competition experiments, highlighting the selectivity displayed by **II**⊂Rh. d) Highly selective reduction of a trialkene utilizing **III**⊂Rh.

We applied the capsule **IV** to the THT cyclization of monoterpenes[3n,o,22] and sesquiterpenes,[23] in the latter case achieving the selective synthesis of isolongifolene. While **IV** is a mild Brønsted acid,[31] the use of HCl as a cocatalyst is necessary to initiate the cascade.[22b,32] The THT cyclization has been very hard to achieve in solution due to premature quenching of reactive intermediates;[33,34] therefore these reports represented significant advances. However, isolongifolene is a commercially available compound, and it is not known to display any interesting biological activity. Applications of this capsule catalyst to the synthesis of valuable natural products, difficult to access by other means, is certainly a desirable next step.

The recent report of the biomimetic synthesis of presilphiperfolan-1β-ol (**31**, Scheme 3b) represents the first such example.[35] Presilphiperfolan-1β-ol (**31**) is a tricyclic sesquiterpene that displays antimycobacterial properties;[36] other members of the family act as insect antifeedants.[37] Its complex structure makes it a challenging target for total synthesis: the only previous total synthesis consisted of 13 steps.[38]

The biosynthesis of presilphiperfolan-1β-ol (**31**) involves cyclization of farnesyl pyrophosphate into caryophyllenyl cation **33** *via* humulenyl cation **32** (Scheme 3b). Cation **33** undergoes an 1,2-alkyl shift/cyclization cascade to form the presilphipefolanol skeleton as cation **34**; a hydride shift and capture by water then gives the natural product **31**.[38–40] We demonstrated that it is possible to mimic this process by generating the key caryophyllenyl cation intermediate **33** within the confines of the capsule. Alcohol **39** (Scheme 4), prepared in three steps from commercially available caryophyllene oxide **38** using a literature procedure,[41] was used as the substrate. Reaction of this compound

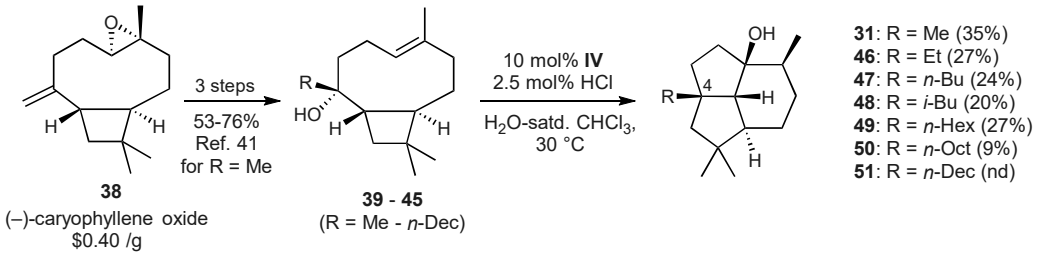



Scheme 3. a) Structure of the hydrogen-bonded capsule **IV** that self-assembles from six resorcinarene units **30** in apolar solvents. b) Proposed biosynthesis of the natural product presilphiperfolan-1β-ol (**31**) and formation of rearranged alkene **37**.

with 10 mol% of capsule **IV** and 3 mol% HCl at 30 ºC in $CDCl_3$ gave presilphipefolan-1β-ol (**31**) along with rearranged alkene **37** (Scheme 3b). Under the reaction conditions presilphiperfola-1β-ol was slowly converted into **37**, but it was found that this reaction could be suppressed by using water-saturated chloroform as the solvent. Employing optimized conditions (2.5 mol% HCl, water-saturated chloroform), the reaction was carried out in large scale to give the natural product in 35% isolated yield, thus accomplishing its total synthesis from commercial starting materials in four steps and 26.6% overall yield.

Control experiments in the absence of capsule or HCl failed to form products **31** or **37**. The same was true for reactions with the capsule blocked by a strongly binding tetrabutylammonium guest, providing evidence that the reaction takes place within the capsule's cavity. The unique capacity of the catalyst to accomplish this transformation was further demonstrated by assaying a number of Lewis and Brønsted acids, all of which failed to provide **31**. This is in line with previous literature reports on acidic treatment of caryophyllene or its derivatives, all of which failed to produce a natural presilphiperfolanol.[41–43]

Furthermore, the formation of unnatural derivatives of presilphiperfolan-1β-ol (**31**) in the C4 position was achieved using this approach, starting from appropriately substituted precursors **40**–**44**. Derivatives bearing Et-, *n*-Bu, *i*-Bu and *n*-Hex substituents provided the corresponding presilphiperforlan-1β-ol derivatives **46**–**49** in 20–27% yield. *n*-Oct-substituted substrate **44** provided a significantly reduced yield, while *n*-Dec-substituted substrate **45** failed to react, likely due to the size limit for the reaction inside the capsule's cavity. These results, as well as the preparation of the novel rearranged alkene **37**, are important as they demonstrate a potential advantage of supramolecular catalysts over enzymes. The natural cyclase enzyme, which has not been isolated and char-




Scheme 4. Four-step total synthesis of the natural product presilphiperfolan-1β-ol (**31**), utilizing the capsule **IV**-catalyzed cyclization of **39** as key step. Furthermore, access to novel derivatives **46**–**50**, which cannot be formed by natural enzymes, was achieved.

acterized yet, would most likely not be able to provide access to these products.

## 3. Discussion and Outlook

The examples presented highlight the applicability of molecular capsules in overcoming some first limitations in synthetic organic chemistry. Nevertheless, the examples are still scarse. What are the limitations of the applicability of molecular capsules? We believe that several points are noteworthy. First, the number of molecular capsules is still limited, especially when considering the volume required to encapsulate small- to medium-sized organic molecules containing approx. ten carbon atoms (approx. ≥ 400 Å$^3$). Second, the guest uptake ability of novel hosts is not fully predictable, especially in organic solvents that lack the strong hydrophobic effect that drives encapsulation in aqueous solutions. Understanding and being able to predict the encapsulation behavior of novel hosts will be important for streamlining future work. Third, and even more importantly, many capsular hosts turn out to be catalytically inactive. Whether a given host exhibits catalytic activity remains very hard to predict *a priori*. Fourth, most host structures are of very high symmetry. This is not surprising since they are formed by a self-assembly process of smaller building blocks, but it certainly limits their applicability. For illustration, less symmetric hosts would allow better control over the conformation of flexible substrates, for instance terpenes, and potentially increase the selectivities obtained in their conversion. Therefore, the development of less symmetric, heteromeric assemblies will be important in driving the applicability to current challenges in synthetic organic chemistry. Ideally such hosts would be modifiable concerning size and shape; certainly a very challenging demand for a self-assembly process. Fifth, product inhibition, observed since the first capsule catalyzed reaction, is still challenging for many capsular catalysts; this is especially the case when working in aqueous media, and when performing bimolecular fusion reactions such as intermolecular Diels-Alder reactions. Very clearly, many challenges remain to be solved in the field of capsule catalysis. However, it is very encouraging that recently more examples have started to appear that demonstrate the applicability to current challenges in synthetic organic chemistry. We are convinced that the growing interest in molecular capsule catalysis, and the increasing understanding of the processes involved, will catalyze a surge in useful applications.

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