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Host-Catalyzed Cyclodehydration-Rearrangement Cascade Reaction of Unsaturated Tertiary Alcohols

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Abstract. Brønsted acidic resorcin[4]arene hexamer can be applied as an effective catalyst in the dehydrative cyclization and subsequent rearrangement of unsaturated tertiary alcohols. This is the first report on catalysing such a reaction with a Brønsted acid. Scope and limitations of this cyclopentene forming reaction sequence are presented. Furthermore, substrate-selective conversion as well as competitive inhibition are described and provide evidence that the reactions proceed within the cavity of the self-assembled structure. Additionally, a cyclobutanone forming intramolecular hydride transfer of an encapsulated cyclopropyl acetate is reported.

Keywords: carbocations; homogeneous catalysis; hydride transfer; self-assembly; supramolecular chemistry

Introduction

The last two decades have seen a remarkable advance in the development of self-assembled supramolecular host structures. Various non-covalent forces like metal–ligand interactions,[1] hydrogen bonds[2] and the hydrophobic effect[3] have been employed for the construction of these molecular assemblies. The distinct chemical environment, provided by these structures to the encapsulated substrates, has been utilized in several cases for catalytic transformations displaying a high degree of substrate and/or product selectivity.[4] Especially reactions involving cationic transition states have been catalyzed within self-assembled host structures.[1e, 5] These reactions are often accelerated by stabilization of the transition state *via* cation–π interactions[6] with the aromatic cavity walls. The increasing implementation of self-assembled supramolecular structures into homogeneous catalysis partly arises from their ease in preparation. Only smaller subunits have to be synthesized, which then spontaneously assemble to yield the desired catalyst *in situ*.

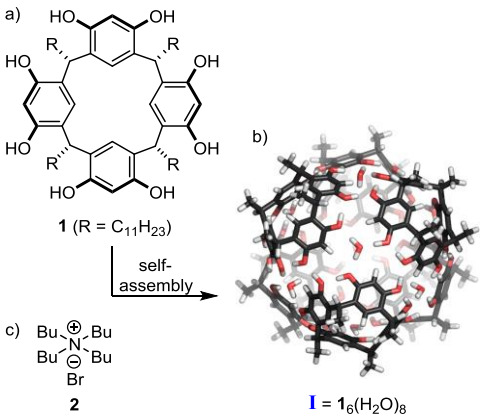
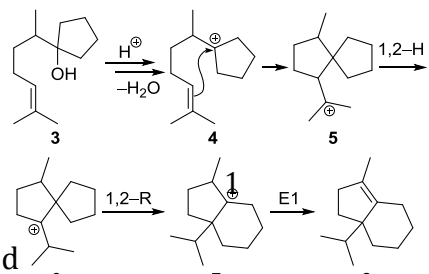


Figure 1. (a) Structure of the resorcin[4]arene monomer **1**, accessible in one synthetic step; (b) model of the hexameric resorcin[4]arene capsule **I** (C = black; O = red; H = white); alkyl groups have been omitted for clarity; (c) competitive inhibitor Bu_4NBr (**2**).

A hydrophobic cavity of about 1400 Å^3 is formed by the hexameric



resorcin[4]arene structure **I**, which self-assembles in apolar solvents like chloroform from six resorcin[4]arene units **1** and eight water molecules (Figure 1).[7] The resorcin[4]arene unit **1** can be easily prepared in multigram scale in a single step, starting from 1,3-dihydroxybenzene. The octahedral-shaped assembly is held together by a network of 60 hydrogen bonds and is capable of reversible guest encapsulation *via* a proposed pentameric intermediate.[8] Cationic species like quaternary ammonium ions (e.g. **2**) show a high affinity towards the capsule interior due to strong cation–π interactions with the aromatic cavity walls.[9] Additionally, also compounds capable of hydrogen bonding, like carboxylic acids and alcohols, are known to be encapsulated well within the capsule interior.[10] Depending on the size of the guest molecule, residual solvent molecules are coencapsulated to reach an optimum packing coefficient of approximately 0.55.[11] The hexameric assembly has been furthermore shown by our group to act as a mild phenol-based Brønsted acid (pK_a ~ 5.5–6), capable of activating suitable substrates by protonation.[12] The extended delocalization of the negative charge renders the deprotonated capsule a non-nucleophilic counter ion, which allows for the study of cationic cascade reactions. Yet the application of hexamer **I** as an acid catalyst is still limited.[12-13]

As part of our ongoing investigation of hexamer **I**-catalyzed cationic cyclizations, we became aware of an early report of the Epstein group regarding a selective cyclodehydration-rearrangement cascade reaction of hydroxy olefin **3** (Scheme 1). The report describes the use of a sevenfold excess of trifluoroacetic acid (TFA) (pK_a = 0.2) to induce the depicted reaction.[14] Indeed, similar cyclorearrangements have also been shown to require an excess of Brønsted acid and in most cases also require an excess of Lewis acid.[15] Catalytic approaches to related reactions are limited to the use of expensive transition metal catalysts.[16] We therefore decided to probe if the reaction of substrate **3** can be rendered catalytic by exploiting the unique microenvironment provided by the supramolecular hexamer **I**. Furthermore, prompted by the report of only two substrates, we set out to investigate the scope and limitations of this cationic cascade reaction.

The reaction sequence starts with an initial protonation of the hydroxy group, followed by dehydration to yield cationic intermediate **4** (Scheme 1). Subsequent 5-*exo* olefin cyclization results in cationic species **5**, which is related to the protosterol cation observed in the biosynthesis of lanosterol.[17] Next, a 1,2-hydride shift generates the thermodynamically more stable[18] endocyclic cation **6**. According to a detailed DFT study by Vrcek, the formation of intermediate **6** represents the rate determining step of the overall reaction cascade.[18] The spiro-type cation **6** then undergoes a Wagner–Meerwein ring expansion to give intermediate **7**, which eliminates to yield annulated cyclopentene **8** as the final product of the cyclorearrangement.

Scheme 1. Mechanism of the cyclodehydration-rearrangement cascade reaction of hydroxy olefin **3**.[18]

Results and Discussion

We started our investigation by adding cyclopentyl alcohol **3** to a solution of 10 mol% of hexamer **I** in $CDCl_3$. Shortly after mixing, new upfield-shifted resonances in the region of 0.5 to −0.6 ppm could be observed in the ^{1}H NMR spectrum of the reaction mixture (Figure 2). The observed upfield-shift, caused by the aromatic anisotropy of the cavity walls, indicated successful encapsulation of the alcohol substrate. In addition, the diffusion coefficient of those resonances matched the diffusion coefficient of the hexameric assembly, which further corroborated successful uptake of the substrate (see ESI Figure S3). A quantification of encapsulated guest *via* integration of the upfield-shifted resonances, however, could not be performed due to the reactivity of the guest and the unknown correlation between shifted and original resonances. In contrast to our previous studies,[12, 13b, 13c] the reaction temperature was raised to 50 °C in order to facilitate the dehydration process. Furthermore, literature data suggests an acceleration of guest encapsulation at elevated temperatures.[8, 19] According to GC analysis, complete consumption of the starting material was achieved after 2 h. The initially formed product mixture, consisting of the desired product and the two non-cyclized dehydration products (see ESI chapter 15), slowly equilibrated over 4 d to give the desired bicyclic structure **8** as the main product in 81% yield (Table 1). The slow equilibration process via reprotonation can be attributed to the low affinity of the dehydrated side products towards the capsule interior. The weak binding of the dehydrated products results from their inability to form hydrogen bonds and successfully prevents product inhibition, a problem often encountered in supramolecular catalysis.[5a, 20] The applied catalyst loading is based on one of our previous studies,[13b] which revealed a negative effect of high hydroxy olefin concentration on the overall reaction rate. This negative effect is believed to arise from the interaction of the hydroxyl group of the

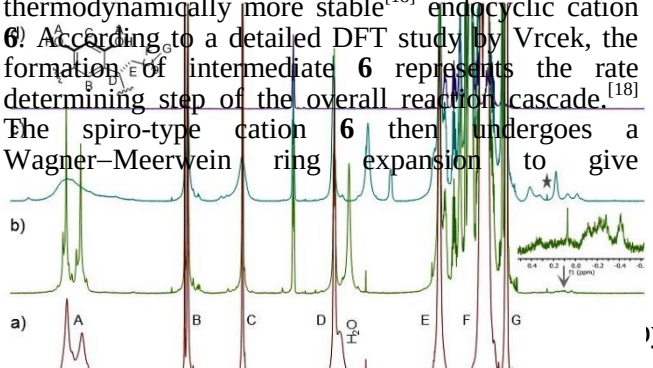


Figure 2. ^{1}H NMR spectra in $CDCl_3$ of (a) hexamer **I** (3.3 mM); (b) hexamer **I** (3.3 mM) and substrate **3** (33 mM), 10 min after mixing (area between 0.5 and −0.6 ppm enlarged); (c) hexamer **I** (3.3 mM), Bu_4NBr (**2**) (5.0 mM) and substrate **3** (33 mM); (d) substrate **3** (33 mM) (silicone grease marked with an asterisk).

substrate with the monomer units, which reduces the equilibrium concentration of operational catalyst.[21] Additionally, a low initial water content of the reaction mixture was found beneficial for the reaction rate. It appears likely that excess water molecules compete with the alcohol substrate for the protons of the hexamer.[13b] When the cavity was blocked by addition of the high affinity guest Bu_4NBr (**2**) (1.5 equiv), the yield of cyclopentene **8** was reduced to 7% after 4 d under otherwise identical reaction conditions. This control experiment provided first evidence that the reaction proceeds within the cavity of the hexameric assembly. It is noteworthy, that encapsulation of Bu_4NBr (**2**) has been shown to increase the acidity of hexamer **I**.[13c] This further enhances the quality of the performed control experiment. When the reaction was repeated in the presence of methanol, which disrupts the hydrogen-bonding network and leads to dissociation of hexamer **I**, no formation of product **8** could be observed (see ESI chapter 10.4). This indicates that substrate activation by simple hydrogen bonding from the phenolic units is not enough to accelerate the reaction. In addition, when hexamer **I** was replaced by 10 mol% of TFA, only 5% of product were formed after 4 d at 50 °C, although the acidity of TFA is about five orders of magnitude higher than that of **I**. This significant difference is likely to result from the stabilization of cationic intermediates and transition states *via* cation-π interactions in the cavity of hexamer **I**, as it has been observed in other reactions.[22]

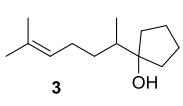
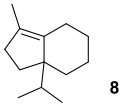
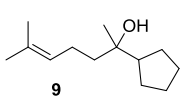
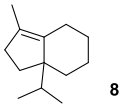
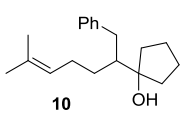
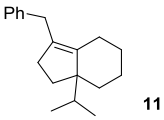
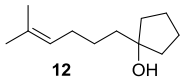
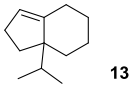
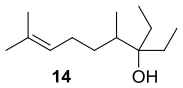
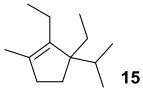
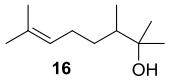
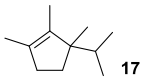
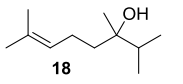
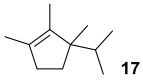
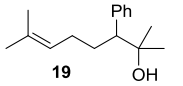
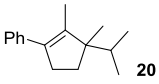
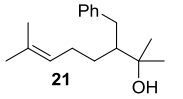
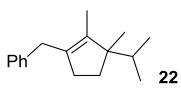
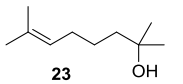
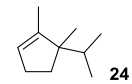
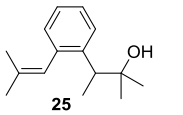
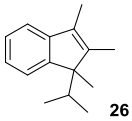
Next, we investigated the formation of product **8** starting from hydroxy olefin **9**, the only other substrate reported by Epstein *et al.*.[14] The structure of substrate **9** requires a hydride shift after protonation and cleavage of water or a deprotonation–reprotonation sequence of an intermediary formed alkene prior to cyclization. Similar to exocyclic cation **5**, the initial hydride shift lowers the energy of the system by locating the positive charge within the ring, as indicated by DFT calculations.[18] Indeed, treatment of substrate **9** with hexamer **I** for 3 d yielded product **8** in 75% yield. Reaction monitoring *via* GC furthermore excludes substantial deprotonation, favoring a 1,2-hydride shift mechanism. After having proven the applicability of hexamer **I** as a catalyst, the tolerance of the reaction sequence towards β-residue variation was probed utilizing substrate **10**. In this case, the desired product **11** was formed in moderate yield. Additionally, no significant amounts of electrophilic aromatic substitution products could be observed. When the β-residue was completely omitted, the reaction still proceeded, yielding annulated cyclopentene **13** in good yield from hydroxy olefin **12**. Following this, we investigated the influence of the substituents geminal to the hydroxy group. An initial attempt, utilizing a cyclobutyl analogon of substrate **3**, failed to give a selective transformation, probably due to the complex mesomeric nature of the cyclobutyl cation.[23] Also a cyclopropyl analogon of substrates **3** failed to undergo the desired rearrangement process, apparently forming the corresponding cyclic ether instead. Employing substrate **14**, which features two ethyl groups, restored the desired reactivity, giving cyclopentene **15** in moderate yield. The corresponding methyl substrate **16** performed even better, despite the reduced migratory aptitude of methyl groups.[24] In this case, the desired product **17** was formed together with a cyclohexene side product, which is assumed to result from an intramolecular proton transfer step (see ESI Scheme S7).[25] Derivative **18**, which requires a 1,2-hydride shift after protonation and cleavage of water, gave a reduced yield of product **17**, due to increased formation of the cyclohexene side product. In both cases, only traces of an acyclic diene intermediate could be detected during reaction monitoring. Additionally, no substantial amounts of other intermediates could be observed, which indicates a 'non-stop' reaction mechanism. This can to some extent be attributed to the high stabilization of the generated phenolate anion. The negative charge can freely shift through the entire hydrogen bond network *via* proton migration, resulting in high stabilization and therefore low nucleophilicity. Changing the β-residue led to substrates **19** and **21**, which cyclized in satisfactory yields to the corresponding cyclopentenes **20** and **22**. To showcase a possible derivatization of the obtained cyclopentenes and further confirm the rearranged structure, the crude mixture of product **20** was subjected to catalytic Sharpless alkene cleavage conditions,[26] giving the corresponding diketone in 56% isolated yield over two steps (see ESI chapter 8). An attempt to induce polycycle formation, by employing a substrate carrying a second homoprenyl group in the β-position, failed, resulting only in unselective conversion of the starting material (see ESI chapter 12). Subsequent investigation of alcohol **23** illustrated the influence of the β-methyl group on the 1,2–methyl migration. The expected product **24** was formed in only 45% yield, together with 32% of a cyclopentene that was formed by direct elimination after the 1,2–hydride shift. A prolonged reaction time did not lead to an increased formation of product **24** by reprotonation of the side product, but led to a slow

consumption of both products. The 1,2-methyl migration appears to be favored by a β-substituent *via* hyperconjugative stabilization of the partial positive charge in the transition state. An equilibrium between the two products could be excluded by subjecting isolated product **24** to the standard reaction conditions. Interestingly, when the β-position was blocked by introduction of a second methyl group, an entirely different pathway was followed, resulting in the formation of a cyclohexene structure in high selectivity (see ESI chapter 13). Finally, the influence of preorganization was probed by employing substrate **25**. In this case, the bicyclic product **26** was formed in good yield after 5 d of equilibration.

All substrates were tested in the presence of the competitive inhibitor Bu_4NBr (**2**), giving only a low yield (≤ 13%) of the desired product (see Table 1). An exception regarding this observation was substrate **25**, which formed product **26** in 55% despite the presence of Bu_4NBr (**2**), presumably caused by its preorganization-based tendency for cyclization. Bu_4NBr (**2**) has recently been shown to be encapsulated as an ion pair,[27] which means the overall charge of the assembly does not change upon encapsulation. Furthermore, control experiments in the absence of catalyst **I** were performed with substrates **3**, **14** and **16**, representing the three different migrating groups employed. This was done in order to exclude a background reaction, induced by trace amounts of HCl/DCl, potentially generated by photodegradation of $CDCl_3$. In those cases, almost no conversion (≤ 1%) could be detected *via* GC analysis. Additionally, all products were isolated and successfully enriched employing column chromatography utilizing $AgNO_3$-impregnated silica gel. The highly-substituted, quaternary carbon center bearing products, which are difficult to prepare via other routes, represent useful precursors for further functionalizations using the installed double bond as a reactive handle.

To complete the study of this cascade reaction, the influence of the leaving group was tested for substrates showing no or diminished product formation. Based on our terpene cyclization studies,[13c] the acetate leaving group was chosen as a leaving group displaying a reduced nucleophilicity. The reduced nucleophilicity of the leaving group can result in less interception of intermediates and therefore provide a more 'non-stop' reaction process. Unfortunately, neither an increased yield nor a change in selectivity was observed when employing the corresponding acetates of substrate **16** and **23**. However, when cyclopropyl acetate **27** (Scheme 2) was subjected to the standard reaction conditions, the formation of an unexpected product in 80% yield was detected *via* GC analysis. The product was subsequently identified as cyclobutanone **28**, and further confirmed by X-ray crystal structure analysis of the corresponding semicarbazone **29**. The postulated mechanism for product formation is depicted in Scheme 2, assuming an intramolecular 1,5-hydride transfer after initial protonation of the double bond. Intramolecular hydride transfers have been recently reviewed in detail as an attractive approach to C–H bond functionalization.[28] To the best of our knowledge, a 1,5-hydride transfer induced ring expansion of a substituted cyclopropane to a cyclobutanone has not been described so far. The observed change in reactivity can be explained by the high energy barrier to generate a highly unstable cyclopropyl cation. In a control experiment, the reaction was completely

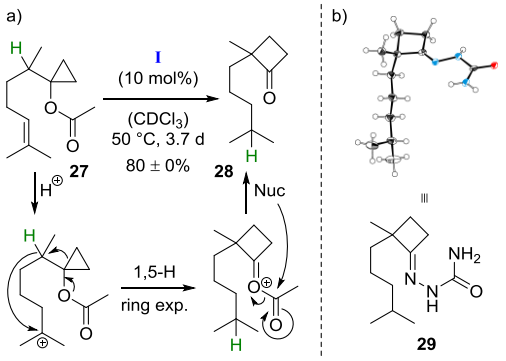
Table 1. Substrate scope of the cyclodehydration-rearrangement tandem reaction.[a]

Entry	Substrate	Product	Yield[b] (%) (+Bu_4NBr)[c]	Yield[b] (%) (Time (d))
1	 **3**	 **8**	7	81 ± 1 (4)
2	 **9**	 **8**	12	75 ± 1 (3)
3	 **10**	 **11**	12	54 ± 1 (7)
4	 **12**	 **13**	3	77 ± 1 (2)
5	 **14**	 **15**	13	55 ± 0 (2)
6	 **16**	 **17**	10	72 ± 1 (3)
7	 **18**	 **17**	3	60 ± 2 (3)
8	 **19**	 **20**	1	68 ± 1 (2)
9	 **21**	 **22**	6	66 ± 1 (2)
10	 **23**	 **24**	0	45 ± 0 (1)
11	 **25**	 **26**	55	73 ± 1 (5)

[a] Reaction conditions: substrate (33 mM), catalyst **I** (3.3 mM), $CDCl_3$, 50 °C, 1–7 d. [b] Determined *via* GC. [c] Identical reaction conditions and reaction time, but in the presence of Bu_4NBr (**2**) (1.5 equiv).

suppressed in the presence of Bu_4NBr (**2**), indicating that the hydride transfer proceeds within the cavity of

hexamer **I**. Variation of the β-residue of the cyclopropyl acetate led to substrates that were either unselective or did not undergo hydride transfer. This highlights the sensitivity of hydride transfers towards structural variations.

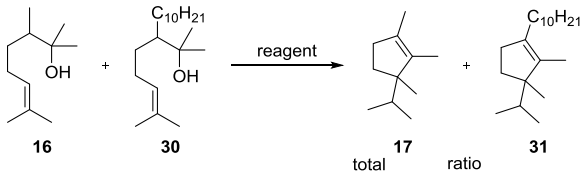


Scheme 2. (a) Mechanism of the cyclobutanone formation; (b) crystalline derivative of the formed cyclobutanone.

After having investigated the scope and limitations of the catalyzed cascade reaction, the possibility of substrate-selective conversion using hexamer **I** was explored in a competition experiment utilizing substrate **16** and its large derivative **30**. For this purpose, a mixture of **16** and **30** (5 equiv each; Scheme 3) was added to a solution of catalyst **I** (1 equiv) in $CDCl_3$ (3.3 mM) and the reaction was monitored *via* GC. In accordance with previous findings,[12] the reaction proceeded highly selectively in favor of the smaller substrate due to its more efficient encapsulation. After 3 h, the small substrate showed almost complete conversion (95%), while substrate **30** remained nearly untouched by the catalyst (4%). This corresponds to a 96:4 ratio of conversion (see ESI chapter 11). In contrast, when the reaction was performed with an excess of TFA, no significant differentiation of the two substrates could be observed. As a result, the ratio of conversion changed to 45:55 (73% conversion of **16** and 91% conversion of **30**). This size-selectivity[29] achieved with catalyst **I** marks a conceptual advantage of encapsulation-based supramolecular catalysis,[4] which can be utilized for multicatalyst tandem reactions[30] and working with complex substrate mixtures. The observation furthermore provides strong evidence that the reaction indeed proceeds within the cavity of the supramolecular assembly.

Conclusion

In conclusion, we herein presented the efficient catalysis of a cyclodehydration-rearrangement cascade reaction utilizing supramolecular assembly **I**. A reaction which so far was only observed with excess of a strong Brønsted acid. The scope and limitations of this reaction sequence were investigated in detail for the first time by systematic variation of the substitution pattern of the starting material. In this process, several highly substituted



reagent	total conv.	ratio of conv.
395 equiv TFA	82%	45:55
0.1 equiv I	50%	96:4

Scheme 3. Selectivities observed with TFA (–5 °C, 10 s (CH_2Cl_2)) and catalyst **I** (50 °C, 3 h ($CDCl_3$)) in a competition experiment towards cyclopentenes **17** and **31**.

cyclopentenes could be obtained in moderate to good yield. Additionally, substrate-selectivity could be achieved starting from a mixture of differently sized hydroxy olefins. Thus, the reaction was shown to proceed within the cavity of the hexamer after encapsulation of the substrate. The cationic intermediates and transitions states of the reaction are believed to be stabilized *via* cation– π interactions with the surrounding cavity walls. In addition, this study led to the discovery of an unprecedented cyclobutanone formation through an intramolecular 1,5-hydride transfer within the cavity of **I**. Altogether, this study further corroborates the important role of supramolecular structures in the long term goal of controlling cationic olefin cyclizations in an enzymatic fashion. This future goal will require the rational modification of the capsule interior to induce selective interactions between the catalyst and the encapsulated substrate.

Experimental Section

General Information

^1H and ^{13}C NMR spectra were recorded at 300 MHz, 400 MHz or 500 MHz, using a Bruker AVHD 300, AVHD 400 and AVHD 500 spectrometer respectively. Chemical shifts of ^1H NMR and ^{13}C NMR (measured at 298 K) are given in ppm by using $CHCl_3$ and $CDCl_3$ as references (7.26 ppm and 77.16 ppm respectively). GC analyses were done on an Agilent GC6890 instrument equipped with a FID detector and a HP-5 capillary column (length = 29.5 m). Hydrogen was used as the carrier gas and the constant-flow mode (flow rate = 1.8 mL min^{-1}) with a split ratio of 1:20 was used. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} glass-baked plates, which were analyzed after exposure to standard staining reagents. All chemicals were used without further purification. $CDCl_3$ was purchased from Deutero GmbH and Sigma Aldrich and used as received.

Catalyst, Substrates and Products

Resorcin[4]arene **1** was synthesized according to modified literature procedures.[31] After dissolving **1** (11.0 mg) in $CDCl_3$ (0.50 mL), a water content of 9-10 eq. H_2O/hexamer **I** was determined *via* integration of the ^1H NMR spectrum. The employed substrates were synthesized according to the procedures reported in the Supporting Information. All cyclodehydration-rearrangement products were isolated and purified using $AgNO_3$-coated silica, prepared according to Cert *et al.*.[32] Full characterization data and copies of relevant spectra of all new products, as well as X-ray crystallographic analysis data of compound **29**[33] are provided in the Supporting Information.

Catalytic Studies

An aliquot of a stock solution containing 11.0 mg *C*-undecylcalix[4]resorcinarene (**1**) (9.95 μmol, 6.0 eq.) was transferred to a GC vial. Next $CDCl_3$ was added to adjust an overall $CDCl_3$ volume of 0.50 mL. To this solution, *n*-decane (internal standard) (2.59 μL, 13.3 μmol, 8.0 eq.) and the substrate (16.6 μmol, 10.0 eq.) were added successively in one portion and the mixture was immediately sampled after 30 s of vigorous agitation. The small sample (approximately 10 μL) was diluted with *n*-hexane (0.1 mL) containing 0.08% (v/v) DMSO, centrifuged, decanted and subjected to GC analysis (initial sample). The GC vial was kept at 50 °C (±1 °C) using a thermostated heating block made from alumina. Based on preliminary studies regarding reaction time optimization, a second sample (final sample) was taken after a given time frame. All substrates were tested in triplicate. In order to precisely calculate the conversion and yield, GC-response factors to *n*-decane as internal standard (IS) were determined for the investigated substrates and their corresponding products.

Control Experiments with Inhibitor 2

To a solution of *C*-undecylcalix[4]resorcinarene (**1**) (11.0 mg, 9.95 μmol, 6.0 eq.) in $CDCl_3$ (0.46 mL), 40 μL of Bu_4NBr (**2**) (2.49 μmol, 1.5 eq.) stock solution in $CDCl_3$ (62.3 mm) were added. Next, the sample was heated using a heat gun to ensure complete uptake of the inhibitor. After allowing the solution to cool to rt, *n*-decane (internal standard) (2.59 μL, 13.3 μmol, 8.0 eq.) and the substrate (16.6 μmol, 10.0 eq.) were added and the reaction was subsequently monitored as described above.

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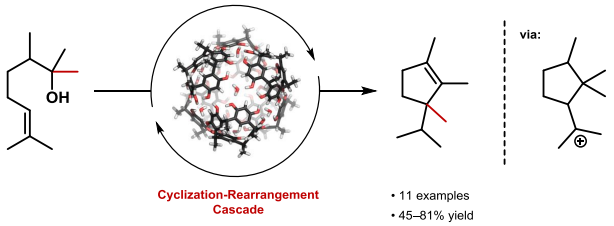
[33] CCDC-1520534 contains the supplementary christallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Host-Catalyzed Cyclodehydration-Rearrangement Cascade Reaction of Unsaturated Tertiary Alcohols



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