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Supramolecular Catalysis of the Pictet-Spengler Reaction with an Endohedrally Functionalized Self-Assembled Cage Complex**

*Courtney Ngai, Colomba M. Sanchez-Marsetti, W. Hill Harman and Richard J. Hooley**

***Abstract**: An endohedrally functionalized self-assembled Fe_4L_6 cage complex can catalyze Pictet-Spengler cyclizations of tryptophols and various aldehyde derivatives, showing strong rate accelerations and size-selectivity. Selective molecular recognition of substrates controls the reactivity, and the cage is capable of binding and activating multiple different species along the multistep reaction pathway. The combination of a functionalized active site, size-selective reactivity and multistep activation, all from a single host molecule, illustrates the biomimetic nature of the catalysis.*

The confined interior spaces of self-assembled host molecules can be exploited for a variety of catalytic processes.[1] Enhanced effective concentration in a cavity confers enhanced rates, and guest confinement can force unusual regioselectivities.[2] Still, many reactions promoted and/or catalyzed by capsular hosts are, by necessity, relatively simple one or two step reactions such as cycloadditions or rearrangements.[3] More complex, multistep processes require supersized cavities that can bind many substrates. Suitable nanosized superstructures include $M_{12}L_{24}$ cages[4] and resorcinarene hexamers,[5] which can perform cationic rearrangements[5] and metal-mediated cyclizations[4b] *via* the use of cofactor-like reagents bound in the spacious inner cavities of the capsules. Smaller hosts can bind their guests more tightly, allowing size-selectivity and "enzyme-like" catalysis,[1c] but these smaller cavities have limits, either showing poor coencapsulation properties or limited turnover. The exception is Raymond's Ga_4L_6 catecholate cages, which are capable of multistep reactions exploiting organometallic reagents as cofactors.[1a],[6],[7]

While many advances in supramolecular catalysis have been achieved, enzymes are still far more capable at catalysing complex, multistep processes inside active sites. The reasons are obvious: the more complex the reaction, the more species need to be bound in the active site, either at the same time or sequentially. The enzyme provides the binding pocket, displays reactive functional groups to its substrates, and is capable of selective molecular recognition and turnover. While each of these individual traits have been achieved with supramolecular host catalysts,[1],[4b],[8] combining all of them in a single system is still a challenge. Here we show that an acid-functionalized self-assembled cage complex is capable of catalysing the multi-step Pictet-Spengler cyclization of tryptophols and various aldehyde derivatives, showing strong rate accelerations and size-selectivity. This requires the binding and activation of multiple different species along a multistep reaction pathway, which is not trivial for rigid, inflexible synthetic hosts.

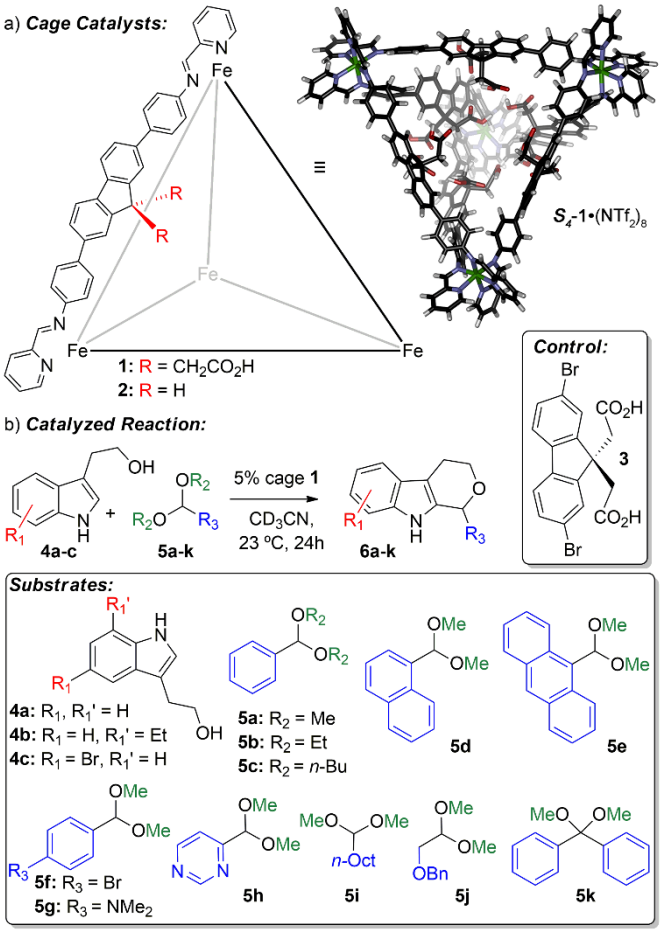

Figure 1. Cage-catalyzed Pictet-Spengler cyclizations. a) Structure of $Fe^{II}_4L_6$ acid cage **1**, unfunctionalized cage **2**, control acid **3** and a minimized structure of the S_4 isomer of **1** (SPARTAN, semi-empirical calculations); b) summary of Pictet-Spengler reaction and scope of substrates used.

Self-assembled Fe_4L_6 host complex **1** (Figure 1a), which displays twelve carboxylic acid groups towards a host cavity, is a highly effective host catalyst. [9] The complex exists as a mixture of two metal-centered isomers, and can catalyze simple acid-mediated

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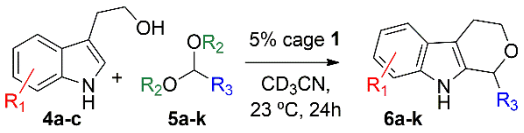
processes such as acetal solvolysis[9] and thioetherification of activated alcohols.[10] Small, neutral guests can be bound in the cavity with affinities up to 10^5 M^{-1}, and display fast in/out exchange, allowing turnover and catalysis in acetonitrile solvent. The reactions tested to date have been quite rudimentary, however, such as acid-mediated dissociative substitutions with mild nucleophiles. As such, we were interested in investigating the ability of host **1** to catalyze more complex, multistep reactivity. The choice of reaction is important: self-assembled Fe-iminopyridine complexes[11] are poorly tolerant to strong nucleophiles, coordinating anions (even some as mild as hydroxide or chloride) and strong acids. They are often insoluble in hydrocarbon solvents, and are restricted to CH_3CN, DMSO or, in some cases, water.[12]

The Pictet-Spengler reaction (Figure 1b) is the cyclization of tryptophol derivatives with aldehydes, and is readily catalyzed by strong Lewis acids such as BF_3•Et_2O or $AlCl_3$.[13] Enantioselectivity is possible with organocatalysts such as chiral amine-appended thioureas.[14] It is challenging for a host-catalyzed reaction, however. The reaction is usually performed in anhydrous, non-coordinating solvents. In addition, the catalyst must activate the substrate *twice* for reaction to proceed: both the indole and alcohol groups of the tryptophol must attack the carbonyl carbon of the electrophile. This is not a problem for small molecule Lewis acids in non-coordinating solvents, as they freely coordinate to different atoms in the system. A host must bind and activate both the small electrophile and larger intermediate in a fixed, inflexible cavity, while not suffering from product inhibition. This is not simple, nor is it common among self-assembled cage hosts.

Table 1. Pictet-Spengler Cyclization via Supramolecular Catalysis.[a]



Indole	Acetal	Catalyst	Product Yield (%)	Aldehyde Yield (%)	Control yield (with CSA catalyst, %)[b]
4a	**5a**	cage **1**	87	7	90
4a	**5a**	cage **2**	0	0	N/A
4a	**5a**	diacid **3**	0	0	N/A
4a	**5b**	cage **1**	80	11	84
4a	**5c**	cage **1**	80	10	87
4a	**5d**	cage **1**	26	25	62
4a	**5e**	cage **1**	15	13	47
4a	**5f**	cage **1**	17	9	53
4a	**5g**	cage **1**	56	22	15
4a	**5h**	cage **1**	0	0	0
4a	**5i**	cage **1**	12	14	52
4a	**5j**	cage **1**	0	0	0
4a	**5k**	cage **1**	0	8	63
4b	**5a**	cage **1**	39	19	62
4c	**5a**	cage **1**	0	29	0

[a] 293 K, CD_3CN, [**4**] = 15.8 mM, [**5**] = 19.8 mM, [**1,2**] = 0.8 mM; [**3**] = 4.74 mM. [b] 5 % camphorsulfonic acid (CSA) used as catalyst. Yield determined by integration against dioxane as standard (7.9 mM).

Fortunately, cage **1** is a promiscuous host, capable of binding and activating multiple species of various sizes,[9],[10] as has also been seen with other Fe-iminopyridine cages.[15] The host shows ~1000-fold rate accelerations of simple reactions that proceed *via* benzyl cations and oxocarbenium ions, when compared to carboxylic acids in free solution. Benzaldehyde dimethyl acetal **5a** can be activated by **1** at room temperature in acetonitrile,[9] so this was applied as the initial test case for Pictet-Spengler reaction with tryptophol **4a** as nucleophile. Both **4a** and **5a** (1:1.25 molar ratio) were combined in distilled CD_3CN with 5% cage **1**, and the reaction course monitored by ^1H NMR, using dioxane as internal standard. As can be seen from Table 1, the Pictet-Spengler cyclization between **4a** and **5a** was successfully catalyzed by only 5% **1**, with 87% yield of product **6a** present after 24 h. Control experiments show that acid cage **1** is required for catalysis. If the host is replaced with 5% unfunctionalized cage **2**, no reaction is seen after 24 h, nor is the any reaction observed with 30% of the carboxylic acid control **3**. While **3** shows some minor ability to catalyze a small amount of solvolysis of **5a**,[9] it is not active enough to catalyze the more complex Pictet-Spengler cyclization. It is notable that the hydrolysis of **5a** to benzaldehyde occurs faster than the Pictet-Spengler cyclization, and undried CD_3CN gives rise to mainly aldehyde byproduct rather than product **6a**. The cage is not capable of catalyzing cyclization between **4a** and aldehydes, and any aldehyde formed is retained throughout the reaction. Fortunately, using distilled CD_3CN is all that is needed, and the reaction can be performed in air, with no precautions taken to prevent exposure of the reaction to water. A small amount of solvolysis is seen, but as 1.25 mol.-eq. of the acetal are used, this does not limit the yield of **6a**.

Having shown the catalytic abilities of the cage, we expanded the scope of the process by varying the individual components, using the same conditions as above (distilled CD_3CN on the benchtop in air). As well as being experimentally simple, allowing small amounts of a competitive nucleophile (water) to the reaction gives additional insight into the reaction mechanism for different substrates (see below). The tryptophol and acetal reactants were varied in both size and reactivity: the structures of the reactants are shown in Figure 1b (see Supporting Information for the structures of products **6a-k** - these products were independently synthesized to corroborate the assignment). The size of the acetal can be varied at two points, the alcoholic leaving groups R_2 (**5a-c**, with R_2 = Me, Et, *n*-Bu, respectively), or the R_3 group (**5d**, **5e**, R_3 = naphthyl, anthryl). Increasing the size of the R_2 leaving groups had minimal effect on the catalysis, and 80% yield of product **6a** was observed in both cases (Table 1, entries 4, 5). However, increasing the size of the R_3 group in the acetal significantly reduced the reaction yield, with naphthyl product **6d** forming in 25% yield and anthryl product **6e** in only 15% yield after 24 h. Notably, the amount of solvolysis of **5a-e** varied as well, with 25% yield of naphthaldehyde seen, but only 13% anthraldehyde (entries 6,7), as opposed to only 7% benzaldehyde.

Aromatic dimethyl acetals with more electron poor rings than **5a** (bromophenyl **5f**, pyrimidine **5h**) were, as expected, poor substrates for the reaction. Neither Pictet-Spengler cyclization nor solvolysis were seen for the very electron poor **5h** and only minimal reaction was seen for **5f** (Table 1, entries 8, 10). Alkyl acetals **5i** and **5j** and benzophenone ketal **5k** were also poor substrates. Dimethylamino-phenyl acetal **5g** is an interesting outlier, though: the acetal is quite reactive, both towards solvolysis (22%) and Pictet-Spengler reaction, with 56% yield observed after 24 h. Finally, varying the size of the tryptophol derivatives was possible by using 5-bromo- or 7-ethyl indole. The tryptophol substrate **4c** was synthesized in two steps *via* literature methods (**4b** was commercially available)[16] and reacted with acetal **5a** and host **1** as before. The larger tryptophols were not well-tolerated by the cage, with ethyltryptophol **4b** showing only 39% reaction with **5a**, and no Pictet-Spengler reaction occurring with **4c**.

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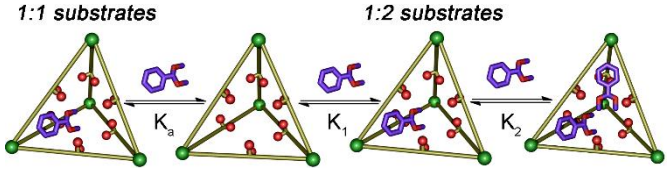
These results were then compared to the reaction with a strong small molecule acid as catalyst, camphorsulfonic acid (CSA, see Table 1 and S-1). The reaction conditions were chosen so that the conversion of **5a** + **4a** was identical under both conditions, allowing a comparison of relative conversion between the cage and a "free" acid as catalyst. The reactivity with CSA was far less dependent on structure than with cage **1**. The phenyl acetals **5a-c** were most reactive, giving 84-90% (± 3%) yield under the chosen conditions. The unreactive acetals **5h** and **5j** again gave no conversion. The rest of the acetals mostly cyclized with yields between 47-63%, irrespective of size, stabilizing groups, etc.

The most interesting observations were with the larger acetals: electrophiles **5d-5f** were cyclized with **4a** in 47-62% yield with CSA, far more than the 12-26% yield seen with the cage. The alkyl acetal **5i** was cyclized much more slowly in the cage, in only 12% yield, whereas 52% yield was obtained with CSA. The larger tryptophol **4b** was a more effective nucleophile outside the cage, reacting with **5a** in 62% yield (as opposed to 39% in the cage). The most surprising observation was with acetal **5g**, which showed accelerated reaction with **4a** in the cage: whereas 56% yield was seen with 5% **1**, only 15% yield was observed with 5% CSA. The clearest example of selectivity was with the large ketal **5k**: this is a perfectly good partner for cyclization with **4a** and CSA, with 63 % yield seen after 24 h, but showed absolutely no Pictet-Spengler reactivity in cage **1**. A small amount of solvolysis was seen, but no cyclization.

Table 2. Binding affinities between substrates and cage **1**.[a]



1:2 Substrate	K_1 x 10^3 M^{-1}	K_2 x 10^3 M^{-1}	α ($4K_2/K_1$)
5a	8.6 ± 0.8	0.08 ± 0.002	0.04
5b	20.0 ± 0.7	0.03 ± 0.001	0.06
5c	34.0 ± 1.3	0.40 ± 0.01	0.05
5d	4.7 ± 0.4	0.70 ± 0.04	0.60
1:1 Substrate	**K_a x 10^3 M^{-1}**	**1:1 Substrate**	**K_a x 10^3 M^{-1}**
4a	3.9 ± 0.1	**5h**	9.6 ± 0.4
4b	4.1 ± 0.1	**5i**	12.0 ± 1.0
4c	7.4 ± 0.3	**5j**	8.3 ± 0.3
5e	4.0 ± 0.2	**5k**	4.4 ± 0.5
5f	12.0 ± 0.6	**6a**	6.2 ± 0.3
5g	1.9 ± 0.04	**6e**	2.9 ± 0.1

[a] in CH_3CN, [**1**] = 3 μM, absorbance changes measured at 300/330nm.[10],[18]

These results indicate that cage-catalyzed process is strongly affected by size and shape matching in the cavity. As such, we investigated the binding affinities of the substrates **4**, **5** and some of the products **6** with **1** *via* UV/vis absorbance titrations. This is an effective method of interrogating binding in porous hosts such as **1** and **2**, which show rapid in/out exchange of neutral guests.[9],[10],[17] Guests were titrated into a CH_3CN solution of **1**, and absorbance changes at 300nm and 330 nm were fitted using the Nelder-Mead method with both 1:1 and 2:1 binding models,[18] to determine the affinity and stoichiometry of the process. The results are shown in Table 2. The errors in each binding model were assessed to determine whether 1:1 or 2:1 binding was most likely. It is clear that most of the substrates were *capable* of binding in the host in a 2:1 manner, but that only four guests clearly favored 2:1 binding over 1:1. As would be expected, the smallest guests **5a-5d** fit best to a 2:1 model, whereas larger species fit best to a 1:1 model. Some guests such as the large anthryl product **6e** had very high errors in the 2:1 fit and were clearly only bound in a 1:1 manner, whereas "intermediate-sized" species were more ambiguous. The binding affinities of the various substrates were all strong (> 10^3 M^{-1}), and varied in magnitude between ~2-12 x 10^3 M^{-1} for the 1:1 substrates. The 2:1 substrates showed a 7-fold variation in the first binding affinity K_1, with butyl acetal **5c** bound most strongly. The coencapsulation process was negatively cooperative in each case.[18] In general, the affinities of the components are all quite similar, which is to be expected as they are of broadly similar sizes and do not have any strongly coordinating groups. This (along with the rapid rate of in/out exchange) aids effective catalysis, as one species does not dominate the binding in **1** at any one time.

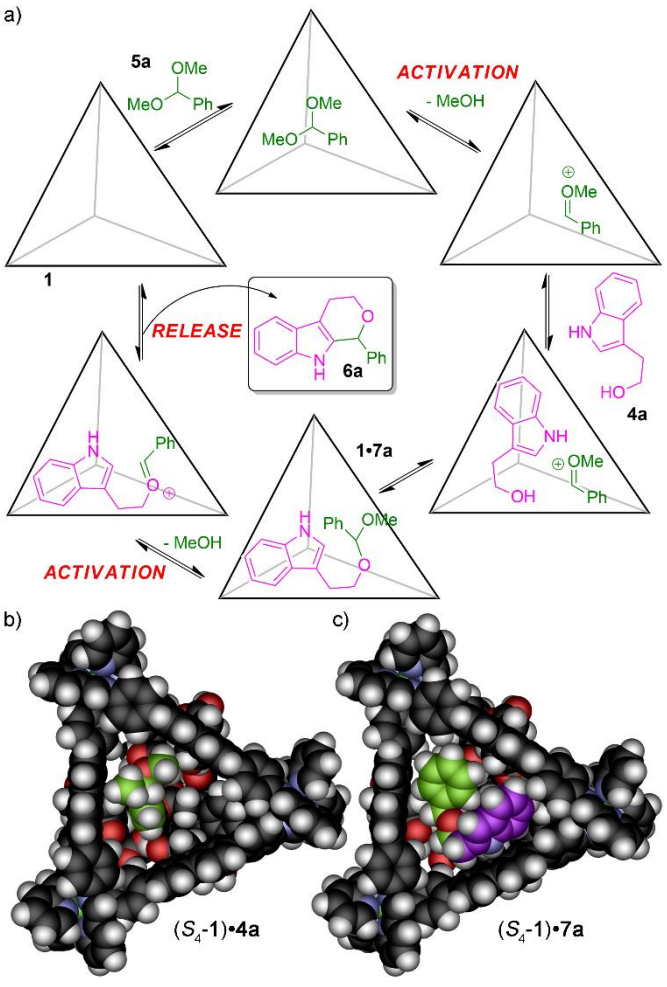


Figure 2. a) Proposed mechanistic cycle of the cage-catalyzed Pictet-Spengler cyclization; minimized structures (SPARTAN, semi-empirical calculations) of host **1** binding: b) substrate **4a** (incompletely filling the cavity); c) intermediate **7a**.

The takeaway from the fitting data is that cage **1** is a promiscuous host, capable of binding each substrate. In addition, the host is large enough to bind the products, any intermediates and, most importantly,

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both substrates at once. This allows some mechanistic analysis, as shown in Figure 2. At the beginning of the reaction, any of the substrates can bind in cage **1**. Binding the acetal **5a** allows loss of methanol after protonation, giving the oxocarbenium ion intermediate. This is possible for all substrates, but the selectivity is seen in the next step: Pictet-Spengler cyclization is only possible if the acetal ***and*** the tryptophol nucleophile **4** can be bound in the cavity. Small acetals allow this, but larger acetals such as **5d**, **5e**, **5i** and especially **5k** are too big to allow further reaction to give intermediate **7a**. Once the mixed acetal **7a** is formed, it must then bind inside **1** and be activated a second time, forming a second oxocarbenium intermediate, which can then cyclize to form product **6a** and be released, allowing turnover. Figures 2b and c show minimized structures of the S_4 isomer of cage **1** binding tryptophol **4a** and the putative intermediate **7a**. Each guest can fit inside the spacious cavity, and **4a** does not fully fill the host by itself.

Other experiments support this mechanistic postulate: the intermediate **7a** can be observed during the reaction. The reaction between tryptophol **4a** and acetal **5a** with 5% **1** was monitored at discrete time intervals by ^{1}H NMR. The acetal region of the spectra is shown in Figure 3, and the full spectra are shown in Figure S-11. After only 30 mins reaction time, two new peaks appear in the δ 5.2-6.0 ppm region, corresponding to the benzylic proton (red dot) in product **6a** and a small amount of an intermediate product that can be assigned as the mixed acetal **7a**. Over time, acetal **5a** is converted to product **6a**, and the mixed acetal concentration slowly lowers, until it is negligible after 24 h. Finally, the reaction was tested in the presence the PF_6^- ion as competing guest. The cyclization of **4a**/**5a** in the presence of 5% **1** and 50% (i.e. 10-fold excess with respect to cage) of $NaPF_6$ still occurred, but only gave 46% yield of **6a**, as opposed to 87% in the absence of the anion. While the anion does not block the cavity, adding a competitive guest slows the desired reaction.

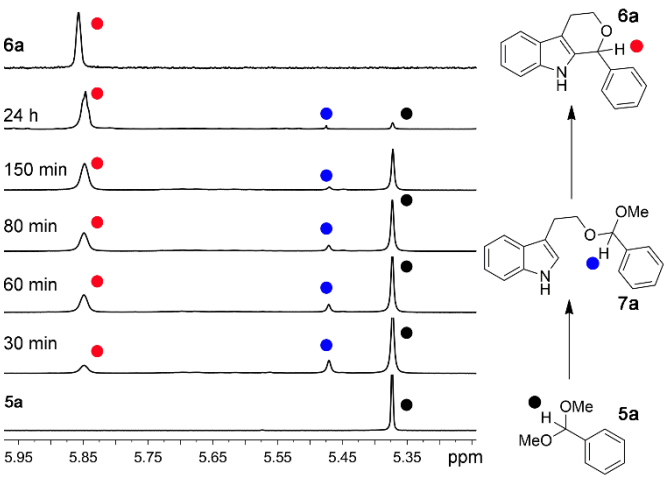

Figure 3. *In situ* monitoring of the reaction between **4a** and **5a**. Acetal region of the ^{1}H NMR spectrum shown, CD_3CN, 293 K, 400 MHz, [**4a**] = 15.8 mM, [**5a**] = 19.8 mM, [**1**] = 0.8 mM.

These studies help explain some of the selectivity shown by cage **1**. The guests bind with short lifetimes, allowing rapid equilibration between host:guest complexes, which allows turnover and limits product (or substrate) inhibition. The internalization of the reactive functional groups in the cavity confers large rate enhancements on the reaction, when compared to small molecule acid analogs. While the host can bind many species, proper size matching between both electrophile and nucleophile is essential for effective cyclization. While the flexible alkyl chains on the acetals (R_2) are not important, larger R_3 groups disfavor the cyclization reaction and species such as ketal **5k** are unable to react with tryptophol in the cage at all, despite being good substrates for reaction in free solution. Increasing the size of the tryptophol also disfavored the reaction in the cage. Size and shape matching in the intermediate does not explain everything, however. Why acetal **5g** is more reactive in the cage than with CSA is not clear at all, and these observations indicate that the multistep process is affected by more than just shape-fitting. This delicate sensitivity to structure illustrates the "enzymatic" behavior of host **1**. It can bind and activate two *different* substrates in a single active site, and shows differential reactivity that is dependent on proper size and shape fitting of the intermediate — not necessarily the "base" reactivity of the substrate.

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Biomimetic Catalysis

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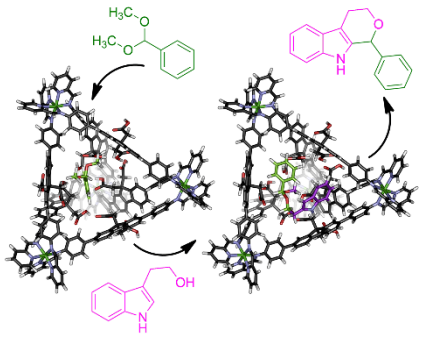
Supramolecular Catalysis of the Pictet-Spengler Reaction with an Endohedrally Functionalized Self-Assembled Cage Complex



An endohedrally functionalized self-assembled Fe_4L_6 cage complex can catalyze Pictet-Spengler cyclizations of tryptophols and various aldehyde derivatives,