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Iminium Catalysis inside a Self-Assembled Supramolecular Capsule: Modulation of Enantiomeric Excess

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Abstract: *The noncovalent combination of a supramolecular host with iminium organocatalysis is described. Due to cation–π interactions the reactive iminium species is held inside the host and reacts in this confined environment. The products formed differ up to 92% ee from the control experiments without added host. A model rationalizing the observed difference is presented.*

Catalysis in self-assembled supramolecular structures has attracted great interest.[1] Chemists are intrigued by the possibility of performing reactions in small spaces (nm^3 scale), in which the reactivities and selectivities differ from those in solution.[2] In artificial systems, product inhibition poses a great challenge. Nevertheless, a variety of reactions including hydroformylations,[3] hydrolysis,[4] hydrations,[5] hydroalkoxylations,[6] aza-Cope rearrangements,[7] Diels–Alder reactions, Nazarov[8] and, Prins[9] cyclizations, isomerizations,[10] and terpene cyclizations[11] were catalyzed successfully. The majority of these examples involve monomolecular reactions, or reactions catalyzed by an encapsulated metal catalyst. We herein report the catalysis of a complex multimolecular reaction inside the supramolecular host **I**. Capsule **I**, first reported by the Atwood group,[12] self-assembles from six resorcinarene units **1** and eight water molecules (Figure 1).[13] Its behavior in solution was studied extensively.[14]

Recently, we reported that **I** acts as a Brønsted acid[4g] and is able to catalyze cationic reactions.[6c,11] We now explored the possibility of controlling iminium reactions[15] inside this host. If the reaction is to occur inside the cavity of **I**, rapid encapsulation of the reactive iminium species **4** (Figure 2) is essential. Since capsule **I** displays a high affinity towards ammonium ions due to cation–π interactions,[14b,c,e–h,m] we speculated that a suitably sized iminium species would also be an excellent guest to yield complex **A**. After uptake of a nucleophile (complex **B**) and reaction (complex **C**), hydrolysis would regenerate the catalysts amine **2** and capsule **I**.

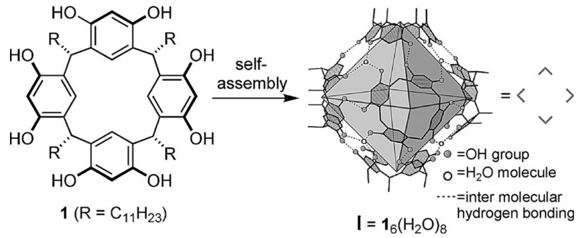

Figure 1. Structure of resorcinarene **1** and capsule **I**.

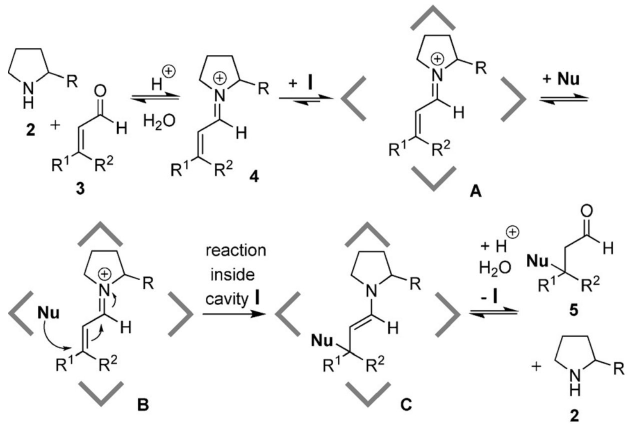

Figure 2. Proposed pathway of the iminium-catalyzed reaction inside capsule **I**.

To the best of our knowledge, no iminium catalysis has been reported inside supramolecular structures. The Rebek group reported the acceleration of a Knoevenagel reaction by an amine catalyst bound to a cavitand, where the reaction took place outside of the open cavity.[16] The Bergman and Raymond groups reported the stabilization of an iminium ion inside a supramolecular container but no conversion.[17] The fact that intramolecular cation–π interactions can play a significant role in iminium catalysis was demonstrated by the Gilmour group.[18] We herein show that intermolecular cation–π stabilization and the resulting encapsulation inside a supramolecular host can dramatically influence the reaction.

As a model reaction, the organocatalytic reduction of α,β-unsaturated aldehyde **3a** (Figure 3) was investigated.[19] The

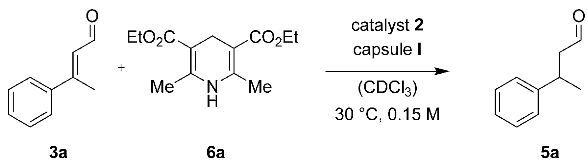

Figure 3. Iminium-catalyzed 1,4-reduction investigated.

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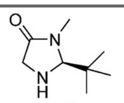
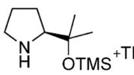
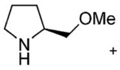
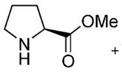
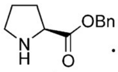
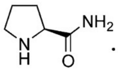
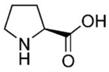
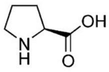
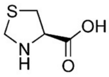
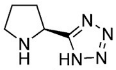
reactions were carried out with and without 26 mol % capsule **I**. Reactions with catalysts carrying a sterically shielding group in α-position (entries 1 and 2, Table 1) did not display significant differences when capsule **I** was present. However, catalysts with hydrogen-bond acceptor groups (entries 3–5, Table 1) provided products with different enantiomeric excess when the capsule was present. For instance, with proline benzyl ester **2e** a Δ*ee* value of 32 % was observed. Employing catalysts with hydrogen-bond acceptor and donor functionalities (entries 6 and 7, Table 1), resulted in even higher Δ*ee* values. In the case of proline **2g** (entry 7, Table 1), 67 % *ee* (*S*) was obtained in the presence of **I**, while only 23 % *ee* (*S*) were observed in its absence.

Control experiments (Supporting Information (SI) chapters 8.1–8.6) with a very large Hantzsch ester, amine catalyst, and aldehyde were performed. Due to their size, the formation of the reactive complex **B** (Figure 2) is prevented and, therefore, the reaction has to occur outside in solution.

Table 1: Results of the iminium-catalyzed 1,4-reduction of aldehyde **3a** utilizing different catalysts.

Entry	Catalyst	Capsule **I** present?	Yield [%][a]	*ee* [%][b]	Δ*ee*
1	 · TFA **2a**	yes	72±15	1±0% *ee* (*R*)	4%
		no	66±5	5±2% *ee* (*R*)	
2	 +TFA **2b**	yes	51±7	47±4% *ee* (*R*)	5%
		no	41±3	52±2% *ee* (*R*)	
3	 + TFA **2c**	yes	52±12	0±2% *ee*	35%
		no	54±1	35±1% *ee* (*R*)	
4	 + TFA **2d**	yes	61±3	22±0% *ee* (*S*)	31%
		no	65±8	9±1% *ee* (*R*)	
5	 · TFA **2e**	yes	72±2	30±0% *ee* (*S*)	32%
		no	92±4	2±0% *ee* (*R*)	
6	 · TFA **2f**	yes	54±3	48±1% *ee* (*S*)	45%
		no	41±2	3±2% *ee* (*S*)	
7	 + TFA **2g**	yes	79±1	67±0% *ee* (*S*)	44%
		no	69±3	23±0% *ee* (*S*)	
8	 **2g**	yes	93±1	74±0% *ee* (*S*)	65%
		no	27±0	9±2% *ee* (*S*)	
9	 **2h**	yes	85±1	46±0% *ee* (*S*)	43%
		no	22±7	3±1% *ee* (*S*)	
10	 **2i**	yes	78±5	41±1% *ee* (*S*)	51%
		no	82±3	10±1% *ee* (*R*)	

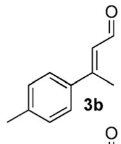
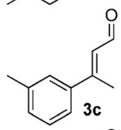
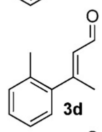
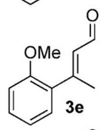
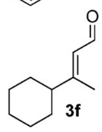
[a] Determined by GC analysis. [b] Determined by GC analysis on a chiral stationary phase. Bn = benzyl, TFA = trifluoroacetic acid, TMS = trimethylsilyl.

No significant Δ*ee* values were observed in these cases, providing strong evidence that encapsulation is indeed responsible for the strong modulation of the *ee*. Further evidence is provided by a control experiment, in which the cavity was blocked by a strongly binding inhibitor. Evidence for the encapsulation of an iminium species of **2g** was obtained by NMR spectroscopy (SI chapters 8.7–8.10).

Furthermore, we found that in the case of the carboxylic acid **2g** the addition of acid additive is not necessary. Without TFA, even a higher modulating effect of capsule **I** was observed (Δ*ee* of 65 %). Also other catalysts with acidic protons, thioproline (**2h**) and proline tetrazole **2i**,[20] exhibited relatively large Δ*ee* values (43 % and 51 %, respectively).

Inside the confined environment of **I**, strong substrate selectivity is to be expected. Therefore, a series of unsaturated aldehydes were investigated with **2g** as the catalyst (Table 2).

Table 2: Results of the iminium catalyzed 1,4-reduction of different aldehydes **3** utilizing proline (**2g**).

Entry	Aldehyde	Capsule **I** present?	Yield [%][a]	*ee* [%][b]	Δ*ee*
1	 **3b**	yes	67±2	18±1% *ee* (*S*)	9%
		no	26±2	9±2% *ee* (*S*)	
2	 **3c**	yes	89±3	61±1% *ee* (*S*)	41%
		no	37±2	20±5% *ee* (*S*)	
3	 **3d**	yes	12±0	73±1% *ee* (*S*)	92%
		no	10±1	19±2% *ee* (*R*)	
4	 **3e**	yes	96±4	78±2% *ee* (*S*)	69%
		no	28±12	9±1% *ee* (*S*)	
5	 **3f**	yes	89±8	63±1% *ee* (*S*)	26%
		no	73±1	37±1% *ee* (*S*)	

[a] Determined by GC analysis. [b] Determined by GC analysis on a chiral stationary phase.

The addition of a methyl group at different positions of the phenyl substituent of the substrate (entries 1–3, Table 2) had a pronounced influence on the reaction inside the capsule: the Δ*ee* value observed increased from 9 % (*para*-) to 92 % (*ortho*-substitution). Similarly, the *ortho*-methoxy substrate was also converted much more selectively in the presence of capsule (Δ*ee* of 69 %). To gauge the influence of the phenyl group, the cyclohexyl derivative was investigated. Only a reduced modulating effect of capsule **I** was observed (Δ*ee* of 26 %), indicating that interactions of the phenyl ring contribute to the phenomenon observed.

Inspection of all experiments reveals that the enantiomeric distribution of the product tends towards an *S* configuration inside **I**, when compared to the corresponding results in

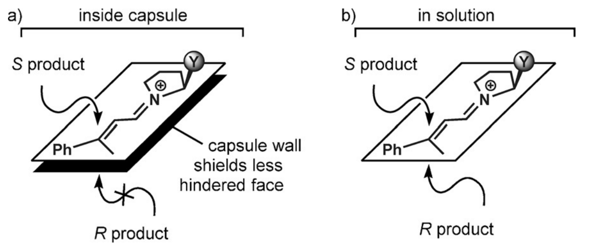


Figure 4. Hypothesis for the different selectivity inside capsule **I**.

solution. We propose that the iminium species binds to the interior wall of the cavity via cation–π interactions from the less hindered side (Figure 4a). Therefore, the hydride is preferentially delivered *syn* to group Y. In the case of directing groups[15a,21] (groups that can act as hydrogen-bond donors, Table 1 entries 6–10), modest to good selectivities for the *S* enantiomer were obtained inside capsule **I**. In the case of a sterically shielding group Y, the orientation of the substrate inside capsule **I** reduces the selectivity for the *R*-configured product. It is further noteworthy that the described reactions differ from catalysis observed previously[4g,5,6c,11] in capsule **I**. The reaction is not accelerated inside the container (SI chapter 6.2). This is due to the fact that the reactive iminium species is sequestered from the nucleophile by encapsulation.

In summary, it has been demonstrated that an iminium-catalyzed 1,4-reduction can be performed inside a supramolecular host. The intermolecular, noncovalent interactions inside the host system dramatically improve the enantioselectivity for several amine catalysts. As expected for a reaction inside a confined environment, a high substrate selectivity was observed. To some extent, the presented system mimics natural amine reductases, in which NADH binds as a reducing cofactor inside an enzyme pocket. Conceptually, this novel approach opens up new avenues for organocatalysis.

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Keywords: enantioselectivity · host–guest systems · iminium catalysis · organocatalysis · supramolecular chemistry

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[1] a) M. Yoshizawa, J. K. Klosterman, M. Fujita, *Angew. Chem. Int. Ed.* **2009**, *48*, 3418–3438; *Angew. Chem.* **2009**, *121*, 3470–3490; b) J. Meeuwissen, J. N. H. Reek, *Nat. Chem.* **2010**, *2*, 615–621; c) L. Marchetti, M. Levine, *ACS Catal.* **2011**, *1*, 1090–1118; d) M. J. Wiester, P. A. Ulmann, C. A. Mirkin, *Angew. Chem. Int. Ed.* **2011**, *50*, 114–137; *Angew. Chem.* **2011**, *123*, 118–142; e) M. Raynal, P. Ballester, A. Vidal-Ferran, P. W. N. M. van Leeuwen, *Chem. Soc. Rev.* **2014**, *43*, 1734–1787; f) C. J. Brown, F. D. Toste, R. G. Bergman, K. N. Raymond, *Chem. Rev.* **2015**, *115*, 3012–3035; g) S. H. A. M. Leenders, R. Gramage-Doria, B. de Bruin, J. N. H. Reek, *Chem. Soc. Rev.* **2015**, *44*, 433–448; h) S. Zarra, D. M. Wood, D. A. Roberts, J. R. Nitschke, *Chem. Soc. Rev.* **2015**, *44*, 419–432; i) L. Catti, Q. Zhang, K. Tiefenbacher, *Synthesis* **2016**, *48*, 313–328.

[2] a) D. Ajami, L. Liu, J. Rebek, Jr., *Chem. Soc. Rev.* **2015**, *44*, 490–499; b) K. I. Assaf, W. M. Nau, *Chem. Soc. Rev.* **2015**, *44*, 394–418; c) K. Hermann, Y. Ruan, A. M. Hardin, C. M. Hadad, J. D. Badjic, *Chem. Soc. Rev.* **2015**, *44*, 500–514; d) J. H. Jordan, B. C. Gibb, *Chem. Soc. Rev.* **2015**, *44*, 547–585; e) J.-N. Rebilly, B. Colasson, O. Bistri, D. Over, O. Reinaud, *Chem. Soc. Rev.* **2015**, *44*, 467–489.

[3] For recent examples see: a) P. Dydio, R. J. Detz, B. de Bruin, J. N. H. Reek, *J. Am. Chem. Soc.* **2014**, *136*, 8418–8429; b) C. García-Simón, R. Gramage-Doria, S. Raoufmoghaddam, T. Parella, M. Costas, X. Ribas, J. N. H. Reek, *J. Am. Chem. Soc.* **2015**, *137*, 2680–2687.

[4] a) M. D. Pluth, R. G. Bergman, K. N. Raymond, *Science* **2007**, *316*, 85–88; b) M. D. Pluth, R. G. Bergman, K. N. Raymond, *Angew. Chem. Int. Ed.* **2007**, *46*, 8587–8589; *Angew. Chem.* **2007**, *119*, 8741–8743; c) M. D. Pluth, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2008**, *130*, 11423–11429; d) M. D. Pluth, R. G. Bergman, K. N. Raymond, *J. Org. Chem.* **2009**, *74*, 58–63; e) J. L. Bolliger, A. M. Belenguer, J. R. Nitschke, *Angew. Chem. Int. Ed.* **2013**, *52*, 7958–7962; *Angew. Chem.* **2013**, *125*, 8116–8120; f) A. G. Salles, S. Zarra, R. M. Turner, J. R. Nitschke, *J. Am. Chem. Soc.* **2013**, *135*, 19143–19146; g) Q. Zhang, K. Tiefenbacher, *J. Am. Chem. Soc.* **2013**, *135*, 16213–16219.

[5] a) A. Cavarzan, A. Scarso, P. Sgarbossa, G. Strukul, J. N. H. Reek, *J. Am. Chem. Soc.* **2011**, *133*, 2848–2851; b) G. Bianchini, G. L. Sorella, N. Canever, A. Scarso, G. Strukul, *Chem. Commun.* **2013**, *49*, 5322–5324; c) A. Cavarzan, J. N. H. Reek, F. Trentin, A. Scarso, G. Strukul, *Catal. Sci. Technol.* **2013**, *3*, 2898–2901.

[6] a) Z. J. Wang, C. J. Brown, R. G. Bergman, K. N. Raymond, F. D. Toste, *J. Am. Chem. Soc.* **2011**, *133*, 7358–7360; b) Z. J. Wang, K. N. Clary, R. G. Bergman, K. N. Raymond, F. D. Toste, *Nat. Chem.* **2013**, *5*, 100–103; c) L. Catti, K. Tiefenbacher, *Chem. Commun.* **2015**, *51*, 892–894.

[7] a) D. Fiedler, R. G. Bergman, K. N. Raymond, *Angew. Chem. Int. Ed.* **2004**, *43*, 6748–6751; *Angew. Chem.* **2004**, *116*, 6916–6919; b) D. Fiedler, H. van Halbeek, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2006**, *128*, 10240–10252; c) C. J. Hastings, D. Fiedler, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2008**, *130*, 10977–10983; d) C. J. Brown, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2009**, *131*, 17530–17531.

[8] a) C. J. Hastings, M. D. Pluth, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2010**, *132*, 6938–6940; b) C. J. Hastings, M. P. Backlund, R. G. Bergman, K. N. Raymond, *Angew. Chem. Int. Ed.* **2011**, *50*, 10570–10573; *Angew. Chem.* **2011**, *123*, 10758–10761; c) C. J. Hastings, R. G. Bergman, K. N. Raymond, *Chem. Eur. J.* **2014**, *20*, 3966–3973.

[9] a) W. M. Hart-Cooper, K. N. Clary, F. D. Toste, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2012**, *134*, 17873–17876; b) C. Zhao, Q.-F. Sun, W. M. Hart-Cooper, A. G. DiPasquale, F. D. Toste, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2013**, *135*, 18802–18805; c) W. M. Hart-Cooper, C. Zhao, R. M. Triano, P. Yaghoubi, H. L. Ozores, K. N. Burford, F. D. Toste, R. G. Bergman, K. N. Raymond, *Chem. Sci.* **2015**, *6*, 1383–1393.

[10] D. H. Leung, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2007**, *129*, 2746–2747.

[11] Q. Zhang, K. Tiefenbacher, *Nat. Chem.* **2015**, *7*, 197–202.

[12] L. R. MacGillivray, J. L. Atwood, *Nature* **1997**, *389*, 469–472.

[13] a) J. L. Atwood, L. J. Barbour, A. Jerga, *Chem. Commun.* **2001**, *0*, 2376 – 2377; b) L. Avram, Y. Cohen, *Org. Lett.* **2002**, *4*, 4365 – 4368.
[14] a) L. Avram, Y. Cohen, J. Rebek, Jr., *Chem. Commun.* **2011**, *47*, 5368 – 5375; b) A. Shivanyuk, J. Rebek, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 7662 – 7665; c) L. Avram, Y. Cohen, *J. Am. Chem. Soc.* **2002**, *124*, 15148 – 15149; d) A. Shivanyuk, J. Rebek, *J. Am. Chem. Soc.* **2003**, *125*, 3432 – 3433; e) L. Avram, Y. Cohen, *J. Am. Chem. Soc.* **2003**, *125*, 16180 – 16181; f) L. Avram, Y. Cohen, *Org. Lett.* **2003**, *5*, 1099 – 1102; g) M. Yamanaka, A. Shivanyuk, J. Rebek, *J. Am. Chem. Soc.* **2004**, *126*, 2939 – 2943; h) L. Avram, Y. Cohen, *J. Am. Chem. Soc.* **2004**, *126*, 11556 – 11563; i) L. C. Palmer, A. Shivanyuk, M. Yamanaka, J. J. Rebek, *Chem. Commun.* **2005**, *0*, 857 – 858; j) T. Evan-Salem, I. Baruch, L. Avram, Y. Cohen, L. C. Palmer, J. Rebek, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 12296 – 12300; k) E. S. Barrett, T. J. Dale, J. Rebek, *J. Am. Chem. Soc.* **2007**, *129*, 3818 – 3819; l) E. S. Barrett, T. J. Dale, J. Rebek, *J. Am. Chem. Soc.* **2008**, *130*, 2344 – 2350; m) L. Avram, Y. Cohen, *Org. Lett.* **2008**, *10*, 1505 – 1508; n) S. Slovak, L. Avram, Y. Cohen, *Angew. Chem. Int. Ed.* **2010**, *49*, 428 – 431; *Angew. Chem.* **2010**, *122*, 438 – 441; o) S. Slovak, Y. Cohen, *Supramol. Chem.* **2010**, *22*, 803 – 807; p) S. Slovak, Y. Cohen, *Chem. Eur. J.* **2012**, *18*, 8515 – 8520.
[15] a) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416 – 5470; b) M. Mahlau, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 518 – 533; *Angew. Chem.* **2013**, *125*, 540 – 556.
[16] O. B. Berryman, A. C. Sather, A. Lledó, J. Rebek, *Angew. Chem. Int. Ed.* **2011**, *50*, 9400 – 9403; *Angew. Chem.* **2011**, *123*, 9572 – 9575.
[17] V. M. Dong, D. Fiedler, B. Carl, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2006**, *128*, 14464 – 14465.
[18] a) M. C. Holland, S. Paul, W. B. Schweizer, K. Bergander, C. Mück-Lichtenfeld, S. Lakhdar, H. Mayr, R. Gilmour, *Angew. Chem. Int. Ed.* **2013**, *52*, 7967 – 7971; *Angew. Chem.* **2013**, *125*, 8125 – 8129; b) M. C. Holland, J. B. Metternich, C. Muck-Lichtenfeld, R. Gilmour, *Chem. Commun.* **2015**, *51*, 5322 – 5325.
[19] a) J. W. Yang, M. T. H. Fonseca, B. List, *Angew. Chem. Int. Ed.* **2004**, *43*, 6660 – 6662; *Angew. Chem.* **2004**, *116*, 6829 – 6832; b) J. W. Yang, M. T. H. Fonseca, N. Vignola, B. List, *Angew. Chem. Int. Ed.* **2005**, *44*, 108 – 110; *Angew. Chem.* **2005**, *117*, 110 – 112; c) S. G. Ouellet, J. B. Tuttle, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 32 – 33.
[20] A. J. A. Cobb, D. M. Shaw, S. V. Ley, *Synlett* **2004**, *2004*, 558 – 560.
[21] B. List, R. A. Lerner, C. F. Barbas, *J. Am. Chem. Soc.* **2000**, *122*, 2395 – 2396.

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