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Enantioselective Catalysis of the Aza-Cope Rearrangement by a Chiral Supramolecular Assembly

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Nanoscale molecular flasks have increasingly been used to promote novel reactivity or impart powerful selectivity through precise, noncovalent interactions with substrate molecules. Encapsulation of substrate molecules within these host structures may stabilize reactive species[1] or, conversely, promote substrate reactivity.[2] The confined environment within these supramolecular hosts has also been demonstrated to impart remarkable size and shape selectivity.[3]

Employing these supramolecular assemblies in asymmetric catalysis remains an important challenge.[4] Chiral building blocks may be used to construct chiral supramolecular assemblies, in some cases generating additional elements of chirality during the assembly of these structures. While chiral supramolecular assemblies have been shown to carry out enantioselective stoichiometric reactions or catalyze reactions with modest ee, a highly enantioselective catalytic transformation has not been demonstrated to date.[5] We now report such catalysis.

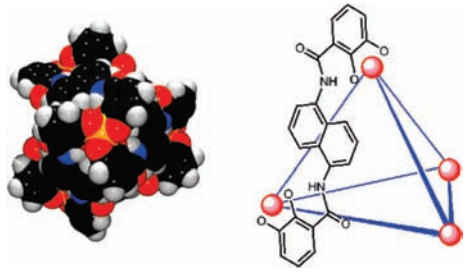

Figure 1. (left) Space-filling model of $[Ga_4L_6]^{12-}$ assembly **1**, viewed down the threefold axis. (right) Schematic of assembly **1**. For clarity, only one ligand is shown.

Raymond and co-workers[6] developed $[Ga_4L_6]^{12-}$ assembly **1**, a self-assembling supramolecular structure. In collaboration with the Bergman group, they have shown that this cluster is capable of catalyzing a variety of chemical transformations with low catalyst loadings and enzyme-like kinetics, including the aza-Cope rearrangement and the hydrolysis of orthoformates and acetals.[7] Importantly, **1** is chiral as a result of the three bidentate catecholates coordinating each gallium center (Figure 1). Mechanical coupling of the four vertices enforces the same helical configuration (Δ or Λ) at each metal center.[8] As a result, two enantiomeric forms of **1** exist: $\Delta\Delta\Delta\Delta$-**1** and $\Lambda\Lambda\Lambda\Lambda$-**1**. Though **1** is synthesized as the racemate, addition of (−)-*N*′-methylnicotinium iodide (S-nicI) causes the spontaneous resolution of the two enantiomers, allowing access to pure $\Delta\Delta\Delta\Delta$-(S-nic $\subset$ **1**) and pure $\Lambda\Lambda\Lambda\Lambda$-(S-nic $\subset$ **1**), where $\subset$ denotes encapsulation. Ion exchange chromatography allows isolation of the two enantiomers as the tetramethylammonium salts.[9]

For this study, the aza-Cope rearrangement of enammonium substrates (Figure 2) was selected to evaluate **1** as an enantioselective catalyst.[7c] Encapsulation of enammonium substrates within **1** enforces a reactive conformation. The product iminium ions are vulnerable to hydrolysis, producing neutral aldehydes that are not encapsulated in **1**. As long as $R_1 \neq R_2$, the rearrangement generates a chiral center and potentially is enantioselective within chiral assembly **1**. Since obtaining suitable quantities of enantiopure K_{12}**1** is not practical, reactivity compatible with $(NMe_4)_{12}$**1** is required. Enammonium substrates **2** are more tightly bound than NMe_4^+, enabling efficient catalysis within $(NMe_4)_{12}$**1**. We describe here the application of enantiopure **1** in catalyzing the aza-Cope rearrangement, achieving enantioselectivities for host−guest catalysis that are remarkable in view of the fact that *the cavity bears no reactive or coordinating functional groups.*

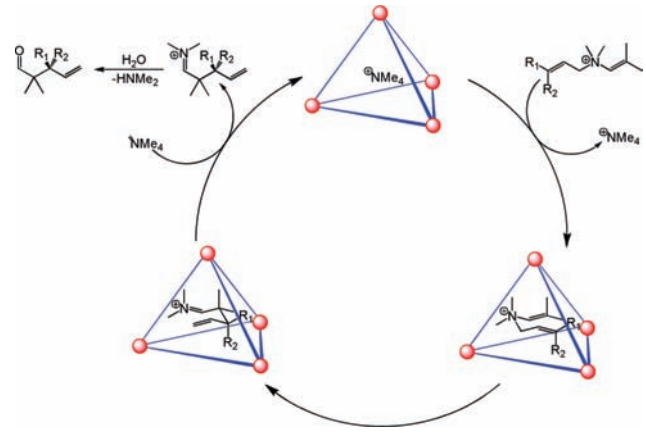

Figure 2. Catalytic cycle for the aza-Cope rearrangement within supramolecular assembly **1**.

A series of prochiral enammonium tosylates (**2a**−**g**) were treated with catalytic amounts of $(NMe_4)_{12}[\Delta\Delta\Delta\Delta$-**1**] to explore the possibility of asymmetric induction in the host-catalyzed aza-Cope rearrangement. High catalyst loadings were used to avoid precipitation of the catalyst−substrate complexes. Lower catalyst loadings (3%) could be used in a mixed MeOH/DMSO solvent system, with identical yields and selectivities. Longer reaction times and difficulty in separating the products from the reaction mixtures, however, made this less desirable. The chiral product aldehydes were extracted into toluene-d_8 solution and analyzed by chiral GC (Figure S1 in the Supporting Information). Enantioselectivities greater than 60% were observed for the *cis*-ethyl (**2b**) and *trans*-isopropyl (**2f**) salts (Table 1).

The observed enantioselectivities displayed a large variation with subtle changes in substrate size and shape. The enantioselectivity obtained with substrate **2b** (64% ee) eroded rapidly with addition of a single carbon (**2d**, 9% ee) or a change in the geometry of the double bond (**2c**, 25% ee). The shape selectivity is further

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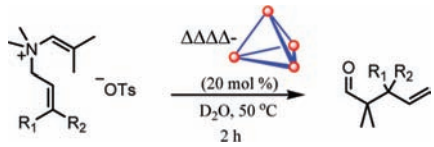
exemplified by the different selectivities observed for isopropyl-substituted substrate **2f**, which exhibited much higher enantioselectivity than *n*-propyl-substituted substrate **2e**.[10]

Table 1. Evaluation of Asymmetric Induction in the Aza-Cope Rearrangement Catalyzed by **1**



substrate	R_1	R_2	yield (%)[a]	ee
2a	H	Me	45	0
2b	Et	H	58	64
2c	H	Et	69	25
2d	Pr	H	68	9
2e	H	Pr	21	23
2f	H	iPr	74	60
2f[b]	H	iPr	49	78
2g[c]	H	nBu	82	6

[a] Yields measured by ^{1}H NMR spectroscopy using $CHCl_3$ as an internal standard. [b] Reaction conducted at 5 °C over 8 days. [c] Catalyst loading was 50%.

Conducting the rearrangement at lower temperatures improves the enantioselectivity. With substrate **2f**, the rearrangement was tested down to 5 °C. Lower temperatures resulted in lower yields and extended reaction times, but the enantioselectivities improved, reaching 78% ee.

These enantioselectivities are much higher than the product-binding diastereoselectivities (de's) observed earlier using racemic **1**. In the absence of NMe_4^+ cations, the product iminium ion concentrations can build up without the ions being hydrolyzed. For the prochiral substrates **2a**−**g**, none of the product iminium ions is encapsulated in racemic **1** with de greater than 20%.[7c] Chiral discrimination by **1** is therefore much stronger than that of product binding alone.[11]

To gain insight into the basis for enantioselectivity in this transformation, torsional sampling of substrate **2f** was carried out within the cavity of **1** (Figure 3). The prochiral carbon bearing the isopropyl substituent is in each case directed toward one of the four helically chiral vertices of **1**. Close contact with the chiral element of the host may be responsible for the selectivity of the rearrangement. The two calculated structures shown differ in energy by 2.2 kcal/mol, appropriate to the degree of selectivity observed in the transformation neglecting transition-state effects.

Pericyclic reactions present a special challenge for asymmetric catalysis. Ordinarily, coordinating groups on the substrate are required, driving complexation of a chiral Lewis acid.[12] Assembly **1** is able to render this pericyclic reaction enantioselective simply by confining the reaction to a chiral space rather than interacting specifically with a moiety on the substrate. This is an attractive feature of supramolecular reaction vessels and an important virtue of this complementary catalytic strategy.

The enantioselectivity achieved here (78% ee) is the highest observed from catalysis by a synthetic chiral supramolecular host to date. While the cavity of **1** is primarily bounded by rigid, achiral naphthalenes, the helically chiral metal centers produce good asymmetric induction in this rearrangement. As with enzymes, precise structural control of the active site is achieved indirectly through noncovalent interactions. These results demonstrate the promise of using chiral supramolecular assemblies in asymmetric catalysis.

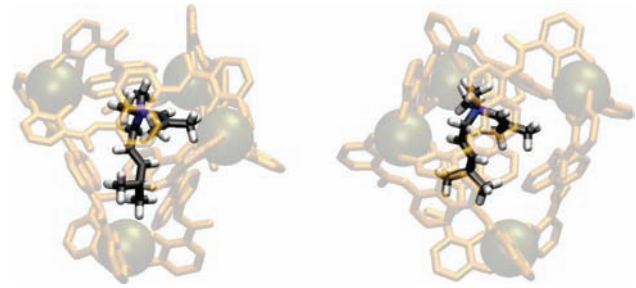


Figure 3. Prochiral conformations of substrate **2f** within **1** likely to result in enantiomeric products. Structures were modeled by torsional sampling in the OPLS_2005 force field. The structure at the right is predicted to be 2.2 kcal/mol higher in energy. Animations of these structures are included in the Supporting Information for clarity.

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Supporting Information Available: Experimental procedures, structural proofs, and spectral data for all new compounds and structure files (PDB) and movies (MPG) illustrating the structures shown in Figure 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) High shape specificity in chiral recognition by **1** has also been observed in the C−H activation of aldehydes by prochiral iridium half-sandwich complexes (see ref 5a), but the earlier system was not catalytic and was not designed to allow isolation of enantioenriched product.
(11) The low diastereoselectivity observed in racemic **1** (see ref 7c) should be attributed to equilibration to a lower thermodynamic selectivity of product binding. Rapid exchange of the product iminium ions masks the enantioselectivity of the rearrangement when racemic Ga_4L_6 is used.
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