Nucleophilic Substitution Catalyzed by a Supramolecular Cavity Proceeds with Retention of Absolute Stereochemistry

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Ⓢ *Supporting Information*

ABSTRACT: While the reactive pocket of many enzymes has been shown to modify reactions of substrates by changing their chemical properties, examples of reactions whose stereochemical course is completely reversed are exceedingly rare. We report herein a class of water-soluble host assemblies that is capable of catalyzing the substitution reaction at a secondary benzylic carbon center to give products with overall *stereochemical retention*, while reaction of the same substrates in bulk solution gives products with *stereochemical inversion*. Such ability of a biomimetic synthetic host assembly to reverse the stereochemical outcome of a nucleophilic substitution reaction is unprecedented in the field of supramolecular host−guest catalysis.

Figure 1. (a) Schematic representations of the Ga_4L_6 assemblies **1** and **2**, with only one ligand shown for clarity. (b) X-ray crystal structure of ΛΛΛΛ-**1** (after resolution). (c) X-ray crystal structure of ΔΔΔΔ-**2**.

As one of the fundamental transformations of organic chemistry, the nucleophilic substitution reaction can be defined as the displacement of an electron-pair acceptor (leaving group) with an electron-pair donor (nucleophile or entering group). When the reaction takes place at an sp^3-hybridized carbon atom, the mechanism is classified with reference to two canonical pathways (S_N1 and S_N2) that furnish products with different stereochemical outcomes.[1] One mechanism, favored with substrates where a developing carbocation can be stabilized through hyperconjugation or extensive π-delocalization from the neighboring substituents, is typically characterized by the initial generation of a planar sp^2-hybridized carbocation and subsequent attack by a nucleophile from either side of the intermediate to give racemized product.[1,2] In contrast, the other mechanism, involving simple primary and secondary substrates, is stereospecific, and substitution proceeds through a transition state via back-side attack of the carbon reaction center by a nucleophile to yield products with inversion of stereochemistry.[1,3,4] This includes the overwhelming majority of solvolyses at simple secondary benzylic centers.[5−7]

In recent decades, synthetic chemists have drawn inspiration from nature to design supramolecular host complexes that mimic the properties of enzymes.[8] Some of these properties include the ability to induce pK_a shifts and maintain function in aqueous environments at physiological pH.[9] More importantly, many such species contain well-defined and sterically constrictive binding pockets capable of stabilizing otherwise reactive species via encapsulation.[10,11] Such complexes can thus catalyze chemical reactions with degrees of selectivity different from those observed in bulk solution.[8c,12] We report herein an

example of a nucleophilic substitution reaction of secondary benzylic substrates catalyzed by $K_{12}Ga_4L_6$ supramolecular host complexes that proceeds with overall *stereochemical retention*.

Initially prepared by the Raymond group, complex **1** is a tetrahedral supramolecular cluster or nanovessel composed of $K_{12}Ga_4L_6$ stoichiometry (L = *N,N*-bis(2,3-dihydroxybenzoyl)-1,5-diaminonaphthalene) with metal ions occupying the vertices and bridging ligands spanning each edge (Figure 1b).[13] Mechanical coupling enforces chirality transfer between the metal vertices, leading to formation of a racemic mixture of resolvable homochiral enantiomers ΔΔΔΔ-**1** and ΛΛΛΛ-**1**. Cluster complex **1** contains a well-defined hydrophobic internal cavity, as created by the naphthalene walls of its ligands, with an approximate volume of 300−500 $Å^3$. Such a pocket has been demonstrated to cause pK_a shifts of up to 4 pK_a units, preferentially encapsulate monocationic molecules, and stabilize reactive intermediates such as the phosphine−acetone adducts and iminium cations that would otherwise decompose. Nanovessel **1** has also been applied as an effective catalyst that enhances the rate and selectivity of a variety of reactions, such as the Nazarov cyclization[14] and C−H activation of aldehydes by an encapsulated iridium complex.[15]

More recently, we reported the synthesis of a new $K_{12}Ga_4L_6$ host complex, **2** (Figure 1c), composed of a terephthalamide-based ligand bearing a chiral amide functional group that self-assembles in solution to form cationic guest-free and enantiopure clusters.[16] Complex **2**, which varies only in modification to the assembly's exterior as compared to **1**, shows increased thermal, aerobic, and low pH solution stabilities, as well as increased catalytic efficiency for enantioselective neutral guest catalysis.

In a continuing effort to better understand the enzyme-like behavior of our synthetic nanovessels and explore their application as catalysts for organic synthesis, we initially sought to investigate the ability of **2**'s cavity to stabilize carbocations and affect their asymmetric nucleophilic addition. We envisioned that compound **3** would be an ideal substrate to test our hypothesis, since the trichloroacetimidate functional group is an acid-activated leaving group. While the protonation of such a functional group in bulk solution requires the use of strong organic acids, such as 4-nitrobenzenesulfonic[17] and phosphoric acids,[18] we recently showed that host **2** is capable of both encapsulating and protonating trichloroacetimidate-containing molecules.[16] Initial reaction between substrate **3** and 5 mol% of ΔΔΔΔ-**2** in CD_3OD at room temperature for 124 h gave the desired benzyl ether product **4** in high yield but only 15% ee (Scheme 1). Reaction catalyzed by ΛΛΛΛ-**2** gave product with

Scheme 1. Solvolytic Substitution Reaction of Racemic 3 Catalyzed by Enantiopure ΔΔΔΔ-2

85% yield, 15% ee
after 72h: 48% yield, 16% ee of **4**, 8% ee of **3**
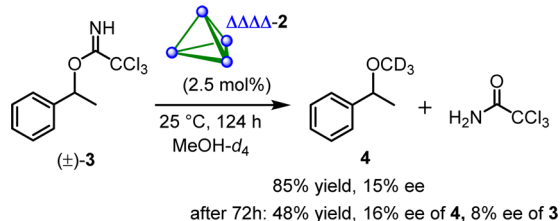
the same level of enantioselectivity, but in the opposite direction. Though no encapsulated species were observed by ^{1}H NMR spectroscopy during the course of the reaction, experiments with either PEt_4-blocked **2** or no catalyst gave only trace amounts of **4**, strongly suggesting that the formation of enantioenriched benzyl ether **4** from racemic **3** is catalyzed by the cavity of **2**.

The low enantioselectivity of the cluster-catalyzed solvolysis reaction prompted us to examine the possibility of a concerted back-side attack mechanism since substitution reactions of trichloroacetimidate have been reported to proceed by such pathways.[17] Indeed, the reaction of enantiopure (S)-**3** with 5 mol% of the achiral phosphoric acid **5** in CD_3OD at room temperature gave the desired benzyl ether **4** in quantitative yield with an expected 84% inversion of stereochemistry, or a 5.25:1 ratio of (R)-**4** to (S)-**4**, at the substituted carbon center (Scheme 2). Surprisingly, repeating the substitution reaction of (S)-**3** in the presence of 5 mol% of ΔΔΔΔ-**2** at 50 °C produced **4** in high yield with 74% *retention of stereochemistry*. Control experiments using (S)-**3** with either PEt_4-blocked **2** or no catalyst gave only trace amounts of product **4** with *inversion of stereochemistry*. While supramolecular host complexes have been shown to alter reactivity and selectivity via encapsulation during the course of the reaction, the ability of complex **2** to completely change the stereochemical outcome of a canonical S_N2 reaction to give products with high levels of overall retention is unprecedented.

Scheme 2. Catalyst-Controlled Divergent Stereospecific Substitutions of (S)-3
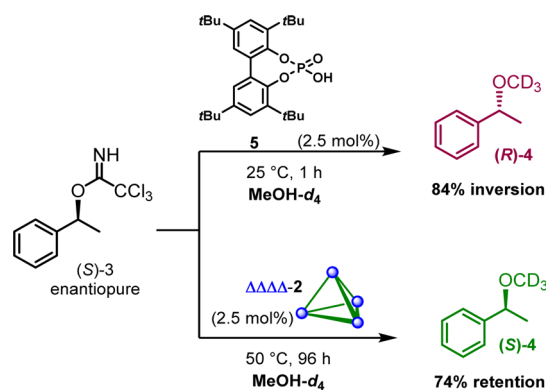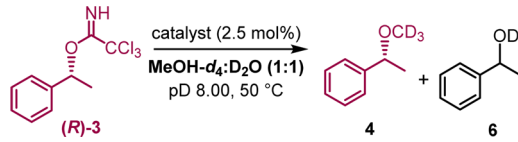
Table 1. Stereoretentive Substitution Reactions of (S)-3 Catalyzed by Nanovessel Hosts 1, ΛΛΛΛ-2, and ΔΔΔΔ-2

Entry	Catalyst	Time (h)	Yield (%)	Ratio of 4:6[a]	er of 4[b] (S) : (R)	er of 6[b] (S) : (R)
1	ΛΛΛΛ–**2**	24	95	72:28	85:15	78:22
2	ΔΔΔΔ–**2**	24	90	70:30	88:12	73:27
3	(±)-**1** (30 mol%)	16	99	78:22	90:10	75:25
4[c]	(±)-**1** (10 mol%)	96	93	67:33	64:36	53:47
5[c]	ΔΔΔΔ–**2**	96	78	68:32	74:26	42:58
6	$(PEt_4)_{12}Δ_4$**2**	24	21	50:50	23:77	24:76
7	none	24	25	50:50	24:76	27:73

[a]Product ratios were determined by ^{1}H NMR spectrometry with an error limit estimated to be 5%. [b]Enantiomeric ratios were determined by GC fitted with a chiral column with an error limit estimated to be 5%. [c]Reaction at 25 °C.
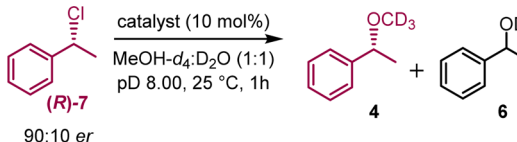
We next studied this stereoretentive substitution reaction in a cosolvent system of a 1:1 mixture of CD_3OD/D_2O buffered at pD 8 in order to neutralize any potential acid and ensure that the desired reactions take place inside the cavities of the host complexes. Although nanovessels **1** and **2** have been shown to exclude water from their cavities due to the hydrophobic effect, hydrolysis of **3** inside the cavity of the host catalysts to give **6** can occur. Indeed, reaction of (S)-**3** with either ΔΔΔΔ-**2** or ΛΛΛΛ-**2** as the catalyst at 50 °C gave a mixture of the desired ether product **4**, with improved selectivity for the retention product (S)-**4** (Table 1, entries 1 and 2), and the corresponding alcohol **6**. When host **1** (30 mol%) was used as the catalyst, substitution of (S)-**3** also proceeded to give **4** with a high level of retention (90%). Longer reaction times were required for substitution reactions of **3** at room temperature in the presence of either racemic or enantiopure host complexes (entries 4 and 5).

Similarly, reactions of enantiopure (R)-**3** in the presence of nanovessels **1** and **2** also gave the desired ether product **4** with moderate to high levels of stereochemical retention (Table 2). Control reactions of (S)-**3** in the presence of PEt_4-blocked **2** gave low yields of **4** with inversion of stereochemistry (entry 6).

Table 2. Stereoretentive Substitution Reactions of (R)-3 Catalyzed by Nanovessel Hosts 1, ΛΛΛΛ-2, and ΔΔΔΔ-2

Entry	Catalyst	Time (h)	Yield (%)	Ratio of 4:6[a]	er of 4 (R) : (S)	er of 6 (R) : (S)
1	ΛΛΛΛ-2	24	95	75:25	83:17	67:33
2	ΔΔΔΔ-2	24	92	70:30	87:12	72:28
3	ΛΛΛΛ-2 (10 mol%)	16	99	80:20	92:8	74:26
4	(±)-1 (30 mol%)	24	94	81:19	92:8	88:12
5[c]	5	1	99	95:5	15:85	--
6	none	24	22	47:53	20:80	18:82

[a]Ratios were determined by ^{1}H NMR spectrometry with an error limit estimated to be 5%. [b]Enantiomeric ratios were determined by GC fitted with a chiral column with an error limit estimated to be 5%. [c]Reaction performed at 25 °C in 100% MeOH-d_4.

Scheme 3. Solvolytic Substitution Reaction of Benzyl Chloride 7 Catalyzed by Enantiopure ΛΛΛΛ-2

99% conv., 4:6 (2.5:1), 14% ee of 4
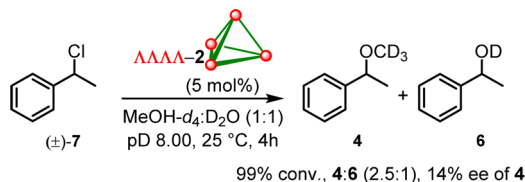
We next examined the substitution of benzyl chloride substrate 7 catalyzed by supramolecular host complexes. Reaction of racemic 7 in the presence of ΛΛΛΛ-2 gave the desired ether product 4 with 14% ee (Scheme 3), similar to the results obtained with racemic 3 (Scheme 1). Repeating the reaction with the other enantiomer of the catalyst, ΔΔΔΔ-2, gave 4 with the same enantiomeric excess but in the opposite direction. More importantly, the substitution of enantioenriched 7 (80% ee) catalyzed by either ΛΛΛΛ-2 or ΔΔΔΔ-2 proceeded to give 4 in high yields and with high levels of stereochemical retention (Table 3), and reaction without any assembly gave the ether product 4 with stereochemical inversion.

We also wanted to demonstrate the encapsulation of benzylammonium 8, which has a size similar to that of the reactive substrates 3 and 7, in the presence of host complex 1 (Scheme 4). As observed by ^{1}H NMR spectroscopy, ammonium salt 8 was readily encapsulated by 1 to give host–guest complex 9 as a 1:1 mixture of two diastereomers.[20] While no further reaction was observed when 9 was heated at 50−80 °C for 4 days, the encapsulation of 8 suggests that such substrates, along with 3 and 7, are suitable guest molecules for the cavities of 1 and 2 in terms of their size and volume.

Though the detailed mechanism of this nanovessel-catalyzed substitution reaction with retention of stereochemistry for simple benzylic molecules remains under investigation, the results obtained thus far provide some insights into the origin of such unique reactivity. The same level of enantioselectivity observed from reactions with racemic 3 and 7 catalyzed by ΔΔΔΔ-2 suggests that a common intermediate was accessed during the course of the reaction. We propose a benzylic carbocation to be

Table 3. Stereoretentive Substitution Reactions of Enantioenriched 7 Catalyzed by Host ΛΛΛΛ-2 or ΔΔΔΔ-2

90:10 er

Entry	Catalyst	Yield (%)	Ratio of 4:6[a]	er of 4[b] (R) : (S)	% retention from 7 to 4	er of 6[b] (R) : (S)
1	ΔΔΔΔ-2	94	75:25	82:18	91	71:29
2	ΛΛΛΛ-2	96	72:28	84:16	93	76:24
3	none	84	55:45	32:68	35	36:64
4[c]	ΛΛΛΛ-2	99	75:25	72:28	92	76:24

[a]Product ratios were determined by ^{1}H NMR spectrometry with an error limit estimated to be 5%. [b]Enantiomeric ratios were determined by GC fitted with a chiral column with an error limit estimated to be 5%. [c]Reaction at 25 °C.

Scheme 4. Encapsulation of (R)-8 by Racemic Complex 1
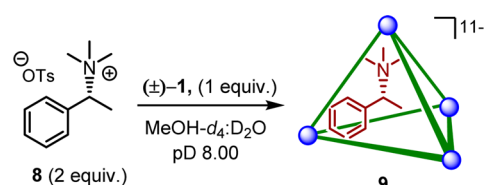
this intermediate. Since the cavity of $K_{12}Ga_4L_6$ hosts has been shown to increase the basicity of encapsulated guests, the protonation of the trichloroacetimidate functional group of 3 and its subsequent ionization to give the corresponding carbocation should be considered favorable. Furthermore, complex PMe_3AuCl has been shown to undergo encapsulation and chloride loss without any silver source in the presence of host 1 to give host−guest complex [$PMe_3Au^+⊂1$] (where ⊂ denotes encapsulation).[19] The strong driving force for the formation of [$PMe_3Au^+⊂1$] from PMe_3AuCl could be operative for the analogous encapsulation and ionization of neutral 7 in the presence of host complex 2. Lastly, the reaction of the isomeric benzylic trichloroacetamide 10 in the presence of 10 mol% of host 1 gave no substitution after heating at 80 °C for 3 days.[20] This rules out a preliminary 1,3-rearrangement of the leaving group with inversion, followed by displacement with a second inversion. In any case this mechanism is not available to the corresponding chloride substrate.

More importantly, the substitution reactions of enantiopure 3 and enantioenriched 7 catalyzed by 1 and 2 proceed with stereochemical retention regardless of the absolute configuration or enantiopurity of the host complexes. This suggests that the intermediate maintains a strong stereointegrity inside the cavity of the host complexes. Furthermore, the low enantioselectivities obtained with reactions of racemic 3 or 7 catalyzed by enantiopure catalysts 2 suggest that the inherent stereochemistry of the reaction overrides any effect of the cavity chirality during catalysis. We propose that, during the course of reaction inside the host catalyst, the electron density of the naphthalene walls stabilizes the developing positive charge at the benzylic carbon in the transition state through cation−π interaction (Figure 2),[21] resulting in one face of the intermediate being blocked from nucleophilic attack. The complexed cation can be thought of as being limited from planarizing inside the sterically constrictive cavities of 1 and 2, and is trapped by a nucleophile faster than the
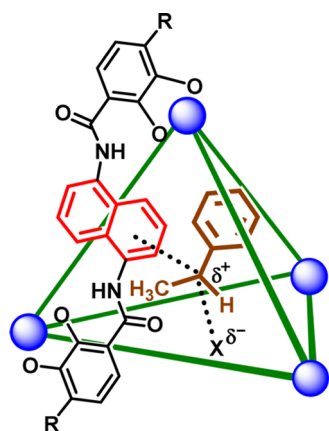
Figure 2. Proposed intermediate showing a transient carbocation interacting with only one of the six naphthalene walls through cation−π interactions (X = leaving group).

cation can rotate, thus giving product with overall retention of stereochemistry.

In conclusion, solvolytic displacement reactions that normally undergo inversion of stereochemistry in bulk hydroxylic solvent have their stereochemistry reversed when the substitution takes place within the cavity of $K_{12}Ga_4L_6$ nanovessels. To interpret these results, we propose not only that the cavity of the host assembly can stabilize the developing positively charged intermediate in the transition state through cation−π interaction, but also that the naphthalene walls of the complex block the back side of the carbocation and thereby control the stereochemical outcome of its substitution to give products with high levels of overall retention. To our knowledge, this observation is unprecedented in the field of catalysis by supramolecular host complexes.

■ ASSOCIATED CONTENT

ⓈSupporting Information

Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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