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Heterogeneous Supramolecular Catalysis through Immobilization of Anionic M₄L₆ Assemblies on Cationic Polymers

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ABSTRACT: Although most of the currently developed supramolecular catalysts that emulate enzymatic reactivity with unique selectivity and activity through specific host–guest interactions work under homogeneous conditions, enzymes in nature can operate under heterogeneous conditions as membrane-bound enzymes. In order to develop such a heterogeneous system, an immobilized chiral supramolecular cluster Ga₄1₆ (2) was introduced into cross-linked polymers with cationic functionalities. These heterogeneous supramolecular catalysts were used in aza-Prins and aza-Cope reactions and successfully applied to continuous-flow reactions. They showed high durability and maintained high turnovers for long periods of time. In sharp contrast to the majority of examples of heterogenized homogeneous catalysts, the newly developed catalysts showed enhanced activity and robustness compared to those exhibited by the corresponding soluble cluster catalyst. An enantioenriched cluster was also immobilized to enable asymmetric



catalysis, and activity and enantioselectivity of the supported chiral catalyst were maintained during recovery and reuse experiments and under a continuous-flow process. Significantly, the structure of the ammonium cations in the polymers affected stability, reactivity, and enantioselectivity, which is consistent with the hypothesis that the cationic moieties in the polymer support interact with cluster as an exohedral protecting shell, thereby influencing their catalytic performance.

INTRODUCTION

Self-assembled supramolecular hosts provide unique opportunities to emulate the mechanisms leveraged by enzymes for catalysis. Like enzymatic active sites, supramolecular assemblies encapsulate substrate molecules with specificity and utilize noncovalent host-guest interactions to induce significant rate accelerations and impart remarkable selectivities.¹ Most currently developed supramolecular catalysts, in which encapsulation enables catalysis through host-guest noncovalent interactions, work under homogeneous conditions. On the other hand enzymes, such as membrane enzymes stabilized in lipid bilayers, can also operate under heterogeneous conditions in Nature.² In contrast, immobilization of supramolecular catalysts that contain a well-defined cavity as the catalytically active site within a metal-organic cage into heterogeneous reaction environments is exceedingly rare. A number of fundamental questions emerge when considering this possibility, for example: (a) Is the catalytic performance of supramolecular catalysts observed under homogeneous conditions retained under heterogeneous conditions? (b) Can supramolecular assemblies be stabilized in solid phases in order to maintain catalytic performance during recovery and reuse and under continuous-flow conditions? (c) How are reactivities and selectivities influenced by contents and compositions of heterogeneous supports?

Previously, heterogenized supramolecular catalysts, in which catalytically active sites are parts of the components of

supramolecular systems, have been developed and some have been employed in flow systems.³ For example, Schaaf et al. developed a supramolecular hydrogel system, derived from a peptide catalyst and melamine, as a heterogeneous catalyst that was employed in a circulating-flow system (Figure 1A).^{3a} Reek et al. reported a soluble supramolecular catalyst, composed of a dendrimer-anchored palladium complex, which was packed into membrane for continuous-flow catalysis; however, a gradual decrease in catalytic activity was observed (Figure 1B).^{3b} On the other hand, catalysis by heterogenized metalorganic supramolecular cages is largely unexplored and has generally derived from catalytically active metal sites of unsupported cage-type complexes which can be recovered and reused (Figure 1C).^{3c,d} In contrast, heterogeneous catalysts based on metal-organic cage-type supramolecular assemblies in which the catalysis is enabled by noncovalent host-guest interactions in the well-defined cavity of the cage are exceedingly rare (Figure 1D).

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Figure 1. Heterogeneous supramolecular catalysts and flow systems.

The supramolecular tetrahedral cluster composed of biscatecholate ligands (1) and Ga(III), $K_{12}Ga_4 \mathbf{1}_6~(2~in~Figure~2)$



Figure 2. Structure of ligand 1, metal—organic cage 2, monomers, and copolymers.

developed by Raymond and co-workers shows enzyme-like catalytic activities through encapsulation of guest substrate in its well-defined cavity, including specific rate accelerations, substrate specificities, and chemo- and stereoselectivities.^{1e,4} Guest exchange in cluster **2**, which is important for smooth catalytic turnover, proceeds through a nondissociative mechanism in which an aperture in the host structure enlarges to accommodate guest passage.⁵ In addition, **2** is chiral as a result of the three bidentate catecholates coordinating each gallium center and can be enantioresolved by addition of (-)-N'-methylnicotinium iodide (S-nicI).⁶ Enantioenriched **2** acts as a chiral host for asymmetric catalysis, including an enantioselective aza-Cope rearrangement of prochiral enammonium salts.^{4c}

Previously, immobilization of metal—organic cages in polymers relied on covalent bonding in loop-rich gels where supramolecular clusters acted as the polymer cross-linker.⁷ However, this strategy requires that the supramolecular structure be rigidly incorporated in the polymer network, impacting dynamic movement that might be required for catalytic turnover.

On the other hand, inspired by previously described immobilization of transition metal catalysts through electrostatic and noncovalent interactions,⁸ we envisioned that direct incorporation of multianionic cluster **2** into a multicationic polymer through electrostatic interactions might provide an alternative, straightforward approach for rendering supramolecular catalysts heterogeneous (Figure 1D-i). We posited that the highly anionic (12⁻) nature of **2** would prevent its leaching from a cationic polymer by multiple electrostatic interactions, even when cationic guests are used as substrate or additive. Moreover, using this immobilization strategy we envisioned that the catalyst would retain much of the dynamic movement, such as the aperture motion, required for smooth guest exchange and high catalytic turnover through noncovalent interaction (Figure 1D-ii).⁵ In addition, resolved chiral cluster 2 is expected to be immobilized directly into the polymer for enantioselective reactions. In this strategy, the impact of polymer properties, including the structure of cationic moieties in the polymer, on catalytic performance of cluster 2 through potential allosteric modulation is a fundamental question (Figure 1D-ii). There are also questions of whether the resolved cluster would be stable to racemization during immobilization and heterogeneous catalysis, and if it was, would the reaction environments constructed by polymer support affect the reaction mechanism of chiral discrimination?

In this article, we present a strategy for the immobilization of an anionic supramolecular host that has a cavity as its catalytically active space into cross-linked polymers with cationic functionalities. Moreover, we demonstrate that such heterogenized supramolecular assemblies are amenable to continuous-flow reaction, recovery and reuse experiments and heterogeneous asymmetric transformation with high robustness (Figure 1D-iii).

RESULTS AND DISCUSSION

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Development of Heterogeneous Metal-Organic Cage Catalysts. First, styrenes (3a-c) substituted at the para-position with different quaternary ammonium cations were prepared (Figure 2). Before and after polymerization, the host-guest behavior of these monomers and the resulting linear polymers was investigated by ¹H NMR (see the SI). These experiments showed that N,N,N-trimethyl and triethylsubstituted monomers were both encapsulated by 2 and interacted with the exterior of 2, while the monomer containing the larger N,N,N- tri-n-butyl group mostly interacted with the exterior of 2. In contrast, the cationic residues in linear copolymers 4a-4c, which incorporate 3a or 3b through random radical copolymerization with styrene or N-tert-butylacrylamide as spacer units, were not encapsulated by cluster 2 in solution phase. These observations suggest that, despite encapsulation of the smaller ammonium moieties in the monomers, after polymerization the main chain of polymer prevents the ammonium groups from encapsulation by 2, and they interact primarily with the exterior of 2.

With these results in hand, cross-linked copolymers were prepared by random radical copolymerization of divinyl benzene cross-linkers, quaternary ammonium cation monomers (3a-c) and styrene (5a-b) or N-tert-butylacrylamide (6a-c) as spacer units (Figure 2). Styrene and N-tertbutylacrylamide were chosen as spacer monomers, because the hydrophobicity of the polymer can be modulated by changing these spacer units, thereby allowing for evaluation of the impact associated with this factor on catalytic activity. Different percentages of divinylbenzene (2-8%) were also tested and we found 4% to provide optimal performance due to appropriate stiffness and swelling ability of resulting polymer. The polymers (5 and 6) were swelled using a 1:1(v/v) mixture of methanol and pD = 8 phosphate buffer solution (for representative swelling capacity in solvent systems, see Table 1). After combining the swelled polymers with an aqueous solution of 2, the resulting mixture was stirred

Table 1. Swelling Capacity (SC) of Polymer 6a and Catalyst 8a in Various Solvent Systems

entry	solvent	6a	8a	SC(6a)/SC(8a)
1	H ₂ O	3.6	2.0	1.8
2	H ₂ O-MeOH (1:1)	5.4	3.4	1.6
3	H ₂ O-MeOH (1:10)	11.3	4.3	2.5
4	H ₂ O-MeCN (1:1)	8.8	5.1	1.7
5	MeOH		5.8	
6	MeCN		3.3	
7	toluene		3.9	

for 3 days under inert atmosphere (Scheme 1). The polymerimmobilized cluster catalysts (7a-b and 8a-c) were collected

Scheme 1. Preparation of Immobilized 2 on Cationic Cross-Linked Co-Polymers



by filtration and the filtrate was analyzed by ¹H NMR to quantify the amount of 2 that had not been immobilized by polymer using DMF as an internal standard. At the same time, the amounts of Ga in the solid catalysts were quantified by inductively coupled plasma (ICP) analysis after digesting the catalyst-containing polymer with acid. The maximum loading of 2 in the polymers (saturation level) was found to be almost 0.1 mmol/g and loading levels were controlled at the range of 0.06-0.09 mmol/g for their use as heterogeneous catalysts. Cluster 2 was also deposited on commercially available ionexchange resin, Dowex1x4Cl, that bear methylpyridinium cations; however, the loading level was noticeably lower (0.035 mmol/g). We measured the swelling capacity (SC = $(W_{\rm s} - W_{\rm d})/W_{\rm d}$; $W_{\rm d}$ = weight of dry polymer; $W_{\rm s}$ = weight of polymer after swelling) of polymer 6a and catalyst 8a in several solvent systems (Table 1) and found that the swelling properties of polymers changed with immobilization of cluster 2. Swelling capacity of the material decreased after incorporation of cluster 2 in all solvent systems tested by 1.6-2.5 times (entries 1-4). These observations suggest that incorporation of the multianionic cluster into the polymer restricted the degree of freedom of cationic side chains in polymer, resulting in reduced swelling capacity. Interestingly, swelling capacity of 8a in MeOH was decreased on addition of water (entries 2 and 3 vs 5); on the other hand, the swelling capacity of 8a in MeCN increased on addition of water (entries 4 vs 6). Catalyst 8a also swelled well in a nonpolar solvent, toluene (entry 7).

Aza-Prins Reaction Using Heterogeneous Metal– Organic Cage Catalysts. The catalytic activities of prepared immobilized cluster catalysts (7a-b and 8a-c) were evaluated using the cyclization reaction of amine 9 and formaldehyde. In previous studies, cluster 2 catalyzed the formation of a different product (10) than that generated under Brønsted acidic conditions (10').^{4e} This divergent reactivity provides a clear indication that the reaction occurred in the cavity of clustercontaining polymer, rather than through a nonhost mediated process.

First, cluster catalysts immobilized on polystyrene-based polymers (7a and 7b) were evaluated as catalysts for aza-Prins cyclization in methanol—water (10:1) mixed solvent systems (Table 2, entries 1 and 2). Only product 10 derived from the

Table 2. Aza-Prins reaction catalyzed by immobilized metalorganic cage catalysts

Me Me 9	Me _{NH} + HCHO (10	eq.) CD ₃ OD:D ₂ O	Me ,40 h, rt	$\begin{array}{c} Me \\ Me \\ Me \\ Me \\ Me \\ Me \\ Me \end{array} \right)$
entry	catalyst	2 (mol %)	CD ₃ OD:D ₂ O	10 yield (%) ^{<i>a</i>}
1	7a	8	10:1	63
2	7b	8	10:1	63
3	8a	8	10:1	86
4	8a	8	1:1	58
5	8b	8	10:1	77
6	8c	8	10:1	13
7	2 on Dowex	15	1:1	15
8	5a	0	10:1	0
9	6a	0	10:1	0
^{a1} H NN	/IR analysis with	DMF as an i	nternal standard	

cluster (2)-catalyzed reaction was obtained in moderate yields regardless of structure of the ammonium cations in the polymer. Next, cluster catalysts immobilized on acrylamidebased polymers (8a-c) were tested and, once again, product 10 was exclusively formed. The best yield (86%) was obtained with catalyst 8a prepared from trimethylammonium cationcontaining polymer 6a (entry 3). The catalyst 8b prepared from the polymer 6b substituted with triethylammonium cations also gave good yields however, catalyst 8c, prepared from tri-*n*-butylammonium cation-substituted polymer **6c**, gave low yields (entries 5 and 6). When a methanol-water (1:1)mixed solvent system was employed for catalyst 8a, a lower vield was obtained, likely due to inadequate swelling of 8a (SC = 3.4 in methanol-water (1:1) vs SC = 4.3 in methanol-water (10:1), see Table 1) in this solvent system (entry 4). In contrast, the catalyst prepared from commercially available Dowex1 \times 4, which swelled well in methanol–water (1:1), gave only 15% yield with 15 mol % of loading, likely a result of the methylpyridinium cation moiety in the polymer not providing sufficient stabilization of 2 (entry 7). As control experiments, in the absence of cluster, the polymers did not catalyze this reaction (entries 8 and 9). Notably, 10' was not observed in any of the cases tested.

With the highly active heterogeneous cluster 8a as the optimized catalyst, a continuous-flow reactor where 8a was packed in a column was constructed. Continuous-flow systems have various advantages over traditional batch reactors such as higher-ordered control of reactivity and selectivity, productivity, efficiency of space and energy, and integration with other systems. They can be applied to the practical synthesis of fine chemicals, such as active pharmaceutical ingredients and organic materials, enable discovery of new mechanistic insight, and provide different reactivity and selectivity compared with those observed using batch reactors.⁹ When 250 mg of 8a was packed in a column and 0.011 M of 9 and 0.11 M of formaldehyde in methanol–water (3:1) solution, containing

DMF as an internal standard, were passed through the catalyst bed at a flow rate of 0.03 mL/min at 50 °C, a moderate yield of **10** was eluted from the flow system; although the yield was low at room temperature (SI, Figure 1). When the amount of catalyst was increased to 500 mg, product **10** was eluted in >80% and >90% yields at 50 and 65 °C, respectively. Yields of **10** were constant for >16 h under steady state at each temperature and no catalyst deactivation was observed (Figure 3). In addition, the flow system was stable at 50 °C for 50 h and the yield of **10** was maintained at 75–85% for >80 h with a gradual decrease in reactivity (SI, Figure 2).



Figure 3. Schematic image of continuous-flow system (upper). Time course of aza-Prins reaction under flow conditions (lower) at two temperatures.

In order to further assess whether the reaction was occurring in the cavity of the immobilized host, the reaction in the flow reactor was conducted under identical conditions, with the exception that the eluent also contained 24 equiv of tetraethylammonium cation, a strong guest with high affinity to the cavity of $2^{4d,10}$ Under these conditions, the catalytic activity of polymer-containing 2 was completely suppressed and only the starting substrate was eluted with no observable conversion to 10 or 10' (SI, Figure 3). This observation strongly supports the hypothesis that the aza-Prins cyclization proceeded in the cavity of immobilized 2 under continuousflow conditions. Moreover, when the substrate solution was continuously flowed after the experiment with tetraethylammonium cation, the catalytic activity was gradually restored, likely a result of displacement of the tetraethylammonium inhibitor from 2 by the iminium cation intermediate derived from the condensation of 9 and formaldehyde (SI, Figure 3). The absence of leaching of cluster 2, gallium, and ligand 1 during continuous-flow reactions was confirmed by both ¹H NMR and ICP analysis (detection limit of Ga ICP: <0.023% of used 2 in catalyst 8a).

Aza-Cope Reaction Using Heterogeneous Metal– Organic Cage Catalysts. Catalysis of the aza-Cope reaction

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was also examined with the heterogeneously immobilized supramolecular cluster catalysts. Previous studies have shown that this reaction is accelerated by encapsulation of substrate 13, in the space-restrictive host cavity of cluster 2, in a tightly packed conformation that closely resembles the conformation of the chair-like transition state.^{4b,c,11} The investigation was started using 20 mol % of 8a as catalyst in D₂O; however, the reaction proceeded sluggishly to afford rearranged product 14 in 44% yield after 15 h, likely because the ineffective polymer swelling (SC = 2.0; see Table 1) limited substrate access to the catalyst (Table 3, entry 1). When a mixed solvent system of



	RA	(x mol%)		
	NMe₃	8a	, Å	
Θ_{OTs}	solvent, 50 °	C, t (h)	14	15
13			14	
entry	solvent	2 (mol %)	<i>t</i> (h)	14 yield (%) ^e
1	D ₂ O	20	15	44
2	D ₂ O:CD ₃ OD (1:3)	20	3	72
3 ^{<i>a</i>}	D ₂ O:CD ₃ OD (1:3)	20	3	51
4	D ₂ O:d-Tol (1:1)	20	3	>99
5	D ₂ O:d-Tol (1:1)	10	3	74
6	D ₂ O:d-Tol (1:1)	5	3	43
7 ^a	D ₂ O:d-Tol (1:1)	5	3	31
8 ^b	D ₂ O:d-Tol (1:1)	5	3	41
9	D ₂ O:d-Tol (1:10)	5	3	37
10	D ₂ O:d-Tol (4:1)	5	3	26
11	d-Tol	5	6	<5
12	D ₂ O: CDCl ₃ (1:1)	5	3	42
13	CDCl ₃	5	3	6
14	D ₂ O: CD ₃ CN (1:1)	5	3	42
15	D ₂ O: CD ₃ CN (1:1)	10	3	74
16 ^a	D ₂ O: CD ₃ CN (1:1)	10	3	43
17	D ₂ O: d-THF (1:1)	5	3	47
18	D ₂ O:d-Tol (1:1)	0	3	11
19 ^c	D ₂ O:d-Tol (1:1)	0	3	9
20 ^d	D ₂ O: CD ₃ CN (1:1)	0	3	6

^{*a*}Soluble K₁₂2 was used as catalyst under homogeneous conditions. ^{*b*}With 0.2 M NMe₄⁺. ^{*c*}In presence of polymer 6a. ^{*d*}In presence of polymer 6c. ^{*e*1}H NMR analysis with *o*-xylene as an internal standard and iminium intermediate 15 was not observed in reaction solution.

water-methanol (1:3) was employed, a better yield was obtained after a shorter reaction time of 3 h (entry 2). The reaction also proceeded smoothly to give quantitative yield in a biphasic water-toluene mixed solvent system. The effective-ness of this system likely results from effective catalyst swelling in toluene (SC = 3.9) and the amphiphilic nature of the polymer enabling the water-soluble substrate to penetrate into the catalyst swelled with both toluene and water (entry 4). When the catalyst loading was decreased to 10 and 5 mol %, the reaction proceeded smoothly to afford product 13 in 74 and 43% yields, respectively (entries 5 and 6).

A solvent mixture of toluene and water was important for the reaction rate, with a 1:1 ratio of these solvents proving optimal (entries 6 and 9 vs 10). Catalysis also occurred in other mixed solvent systems of water and chloroform, acetonitrile, or tetrahydrofuran (entries 12, 14, and 17); however, the reaction proceeded sluggishly in the absence of

water (entries 11 and 13). Water is important for catalysis by cluster 2 even after immobilization in heterogeneous catalyst 8a. Several reasons for the importance of water have been posited, including the general impact of water on the entropically driven encapsulation of hydrophobic substrates and the specific requirement of stoichiometric water for the hydrolysis of iminium intermediate 15. Moreover, in this heterogeneous system, in the absence of water, the strong ionic interaction between the ammonium cation site in the polymer and anionic cluster 2 may prevent the dynamic movement of 2 that is important for encapsulation of 13 through aperture motion. Under these conditions, the noncatalyzed background reaction gave 11% of the product 14 (entry 18). Further control experiments showed that polymers with different hydrophobicity, 6a or 6c, did not catalyze the reaction in the absence of cluster and gave yields that were consistent with the background reaction (entries 19 and 20). Taken together, these experiments provide strong support for the conclusion that the immobilized supramolecular catalyst is responsible for the majority of the product formed.

The reactivity of immobilized catalyst 8a and original soluble cluster 2 were compared in various solvent systems. Interestingly, immobilized catalyst 8a showed higher yields than those observed with original soluble cluster 2 in all solvent systems (entry 2 vs 3, 6 vs 7, and 15 vs 16). The comparison of reaction profiles of homogeneous and heterogeneous systems under the same reaction conditions showed faster reaction rate under heterogeneous conditions than homogeneous conditions (SI, Figure 9 for detail of reaction profiles of entries 15 and 16). The rate limiting step of the aza-Cope rearrangement catalyzed by 2 was previously reported to be dissociation of externally bound iminium cation 15, and this step was accelerated by the addition of an ammonium cation.¹¹ Ammonium cations in the polymer of catalyst 8a may play a similar role in aiding the dissociation of outside bound 15 from 2, resulting in increased catalyst efficiency and reaction acceleration. In accord with this hypothesis, the addition of the trimethylammonium cation to the catalyst 8a did not significantly impact the reaction outcome (entries 6 vs 8).

Next, recovery and reuse experiments were conducted using 15 mol % catalyst 8a in toluene and water for 3 h (SI, Table 1). After completion of the reaction, the solid catalyst 8a was easily separated from the solution containing product 14 by simple filtration. The collected catalyst was dried under vacuum and used in the next run. The electron-rich gallium catecholate structure of homogeneous catalyst 2 is prone to oxidation; therefore, degassed solvents and inert atmosphere are required for most catalytic reactions.^{1e,4b-e} In order to examine the potential stabilizing effect of the polymer support, nondegassed solvents were used and filtration was conducted under air. Remarkably, no loss of catalytic activity was observed over 18 runs, and >95% yields were maintained even under conditions in which no precautions were taken to avoid oxygen. The absence of leaching of cluster 2, ligand 1, and gallium metal were confirmed by ¹H NMR and ICP analysis (the detection limit of Ga ICP was <0.17% of used 2 in catalyst 8a) for recovery and reuse experiments. In addition, hot filtration tests were conducted to confirm that catalysis took place in the solid phase. The aza-Cope reaction was run for 0.5 h at 50 °C, at which point the catalyst was removed by filtration. Continued heating of the filtrate, now lacking solid catalyst, produced only minimal amounts of product. A similar

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experiment, in which the catalyst was removed by filtration after heating for 1 h at 50 $^{\circ}$ C, also showed minimal conversion with continued heating of the filtrate. The catalytic reactions clearly terminated at the point of the filtration and any additional product 14 generated after filtration corresponded to the estimated amount generated from the uncatalyzed background reaction (SI, Scheme 1 and Figure 8).

The aza-Cope reaction was also conducted under continuous-flow conditions. In this experiment, separately pumped solutions of 3 mM 13 in water and the internal standard (*o*xylene in acetonitrile) were combined just before the inlet of the catalyst-containing column. The combined solution was passed through the column packed with 80 mg of 8a (0.0055 mmol of 2) and 300 mg of Celite heated at 50 °C. Catalyst 8a dramatically swelled with toluene or acetonitrile; therefore, dilution of catalyst 8a in a column was required to maintain smooth flow of the eluent. Under these conditions, substrate 13 was fully converted to product 14 with a short residence time (~15 min) of the substrate-containing solution in the column (Figure 4). The catalytic reaction under continuous-



Figure 4. Schematic image of the continuous-flow system (upper). Time course of the aza-Cope reaction under flow conditions (lower) for a long period. The yield was determined by GC analysis with an internal standard.

flow conditions was highly stable, with full conversion maintained for over 60 h. In addition, ICP analysis of all of the combined collected fractions detected no Ga leaching (the detection limit of Ga ICP was <0.073% of used 2 in catalyst 8a). The uncatalyzed background reaction using a Celite-packed column under identical reaction conditions gave only 3% conversion to 14 (SI, Figure 6), further supporting the conclusion that the vast majority of the product formed using 8a, in the continuous-flow system, was generated from the host-catalyzed reaction. The total turnover numbers (TON) of 8a in both the recovery—reuse and continuous-flow experiments were calculated as >100.

Reversible Inhibition-Reactivation Behavior of Catalyst 8a in the aza-Cope Reaction under Continuous-Flow Conditions. Tetraethylammonium cation (Et_4N^+) is a

strongly bound guest (log $K_a = \sim 4.5$ in water) for Ga cluster $2;^5$ therefore, like an inhibitor or antagonist in an enzyme catalyzed reaction, Et_4N^+ inhibits catalysis of reactions by Ga cluster 2 under homogeneous conditions.^{4d,10} As a result, clusters that are assembled with Et_4N^+ as a template, must be "emptied" of this inhibitor prior to their use as catalysts under homogeneous conditions. Therefore, in order to assess whether the immobilization could circumvent this requirement and allow for reversible inhibition-reactivation behavior, reactions of the immobilized metal—organic cage catalysts in the presence of various ammonium cations were examined in continuous-flow processes.

First, under conditions with no added ammonium salt, quantitative conversion was observed for the aza-Cope reaction in the toluene-H₂O solvent system at 60 °C under continuous-flow conditions with a molar hourly space velocity of 0.35 h^{-1} of 13 (mole flow rate of 13 (mol· h^{-1}) per mole of catalyst 2 in column) (SI, Figure 4). In order to ascertain the effect of inhibition and reactivation well, the reaction was conducted at a molar hourly space velocity of 1.64 of 13, such that 50% conversion was observed at steady state. An aqueous solution of 3 mM 13 and 30 mM tetra-n-butylammonium chloride (n-Bu₄NCl) was combined with a toluene solution of an internal standard (o-xylene) just before the inlet of the column, and the resulting two-layer solution passed through the column packed with 80 mg of 8a (0.0055 mmol of 2) and 300 mg of Celite heated at 60 °C. Almost 50% conversion was observed under steady state (~1.5 h after pumping was initiated; Figure 5). As previous observed, *n*-Bu₄N⁺ is too large to be encapsulated by 2; however, it interacts with 2 as an external guest through electrostatic interaction and cation- π interaction with the naphthalene moieties of the ligand.¹¹ On the basis of these observations, it is expected that there will be



Figure 5. Schematic image of the continuous flow system (top). Time course of aza-Cope reaction under flow conditions (bottom) by switching ammonium additives. The yield was determined by GC analysis with an internal standard.

external interactions between immobilized **2** and both ammonium cation moieties of polymer and the added *n*-Bu₄N⁺. Under these circumstances, the cavity of Ga cluster remains "empty" and able to catalyze the aza-Cope reaction (Figure 6A).



Figure 6. Schematic image of the states of the immobilized Ga cluster with different externally added ammonium cations during the time course of the continuous-flow reaction.

In contrast, when the continuous-flow reaction was charged with to 3 mM 13 and 30 mM Et₄NCl in water, the catalytic reactivity dramatically decreased and ultimately reached 12% conversion of 13 at steady state (Figure 5, ~5 h). Here, it is important to note that the background reaction proceeded in 7% conversion with a Celite-packed column instead of the 8a packed column under continuous-flow conditions (SI, Figure 7); therefore, it is likely that only a very small portion of the observed conversion in the presence of the strong inhibitor Et₄N⁺ is likely to have resulted from a host-catalyzed process.

The inhibition-reactivation process is graphically depicted in Figure 6. First, n-Bu₄N⁺ interacted with the immobilized Ga cluster only outside allowing for catalytic conversion from 13 to 14 (Figure 6A). After 3.5 h, addition of Et_4N^+ to the eluent resulted in rapid replacement of n-Bu₄N⁺ and establishment of an equilibrium between tetraethylammonium-filled and empty host. Given the high binding constant of Et_4N^+ , at these concentrations, the cavity of immobilized Ga cluster at the steady state was almost entirely occupied by Et₄N⁺ ; therefore, little-to-no catalytic activity was observed (Figure 6B). After 7 h, the substrate solution was switched to 3 mM 13 and 30 mM n-Bu₄NCl in water. At this point, the conversion of 13 increased slowly, until it reached the level observed prior to the introduction of Et_4N^+ (Figure 5, 7–10 h). While it is expected that Et_4N^+ associated with the exterior of the anionic Ga cluster was readily replaced by n-Bu₄N⁺, the strongly encapsulated Et₄N⁺ remained bound and was only displaced as a result of the equilibrium between internal encapsulated state and exterior bounding state (Figure 6C). As a result, during the additional 3 h under continuous-flow conditions, the remaining Et_4N^+ was washed away with excess $n-Bu_4N^+$ and the catalytic activity was gradually restored (Figure 6A).

The importance of externally added ammonium cation during the catalytic activity recovery process was further highlighted by experiments using tetramethylammonium cation (Me₄N⁺) or without ammonium cation (SI, Figure 5). Me₄N⁺ is small and can be encapsulated by Ga cluster 2 but with a lower binding affinity than Et₄N⁺; however, it can strongly interact with the exterior of 2.⁴ The reversible

inhibition-reactivation experiment using Me_4N^+ instead of *n*-Bu₄N⁺ showed a similar inhibition-reactivation profile by switching ammonium cations between Et_4N^+ and Me_4N^+ . On the other hand, in the absence of additional ammonium cation, recovery of the catalytic activity after stopping the flow of Et_4N^+ was significantly slower; however, the fact that the activity returned to some extent indicated that substrate **13** itself could displace the strong "antagonist", Et_4N^+ under flow conditions (SI, Figure 5).

These experiments suggest that inhibition of catalytic activity of **8a** by a strong "antagonist" is reversible and that the catalytic activity can be restored by externally added ammonium cations that interact with cluster **2** as exohedral guests. Under these circumstances, even strong guests (such as Et_4N^+) can be displaced from the cavity of **2** to generate the catalytic "empty" cavity under continuous-flow and solid phase catalysis. Moreover, these observations suggest that, unlike the homogeneous variants, clusters associated with guests can be used directly as catalysts under flow-conditions without the requirement of being made "empty".

Effect of Ammonium Cations in Polymers and Solution on the Asymmetric aza-Cope Reaction Using Heterogeneous Enantiomerically Enriched Metal-Organic Cage Catalysts. In particular, we were interested in whether this property of the heterogenized cluster could facilitate the application of these hosts to asymmetric catalysis. More specifically, Ga cluster 2 is chiral as a result of the three bidentate catecholates coordinating each gallium center. It can be enantioresolved by addition of (-)-N'-methylnicotinium iodide (S-nic⁺ I⁻) into two isomers: $\Lambda\Lambda\Lambda\Lambda$ -K₆(S-nic)₅[(Snic) $\subset 2$ and $\Delta\Delta\Delta\Delta$ -KH₃(S-nic)₇[(S-nic) $\subset 2$] (17).⁶ S-nic⁺ is a relatively strong guest of cluster 2, and removal of S-nic⁺ by ion exchange chromatography was required to prepare an "empty" cluster, $\Delta\Delta\Delta\Delta$ -(NMe₄)₁₁ [(NMe₄) \subset **2**] (16), prior to its use as a homogeneous catalyst.^{4c} Moreover, attempts to use supramolecular assembly 17 as a catalyst without removal of Snic⁺, resulted in both lower yields and enantioselectivities in asymmetric aza-Cope reaction, likely a result of the inhibitory effect of S-nic⁺ allowing for an increased proportion of nonselective background reaction (Table 4, 1 vs 3 and 2 vs 4).

On the basis of the reversible inhibition-reactivation experiments (Figure 5), we hypothesized that the immobilization of 17 on the polymer support would allow for its direct use in asymmetric catalysis and circumvent the requirement for the resource-consuming ion exchange process to form an "empty" cluster. Moreover, we envisioned that the enantiomerically enriched state of 2 would show increased stability on the polymer support and, therefore, provide a practical platform for the preparation of catalytically active heterogeneous chiral catalysts. In the event, resolved cluster $\Delta\Delta\Delta\Delta$ -KH₃(S-nic)₇[(S-nic) \subset 2] (17) was directly used for immobilization, and 6–7 equiv of S-nic⁺ was recovered during the immobilization suggested that the S-nic⁺ "inhibitors" were successfully removed during the immobilization process.

When resolved cluster $\Delta\Delta\Delta\Delta$ -2 immobilized on polymer 6a was used as the heterogeneous catalyst (12a), the product was formed with 60% ee and quantitative yield with 15 mol % catalyst loading (entry 5). This enantioselectivity is comparable to the previously reported best results under homogeneous conditions using soluble "empty" cluster 16 as catalyst.⁵ When the resolved cluster immobilized on polystyrene-based polymer 5a was used as the catalyst (11a), a

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Table 4. Asymmetric aza-Cope Reaction Catalyzed by Immobilized Enantiomerically Enriched Metal-Organic Cages

Me	Me Me	catalyst (15 mol%)		Me
Me	● ● ● ● ● ● ● ● ● ● ● ● ● ● ● ● ● ● ●	CH ₃ CN (1:1), 50 °C, 3 h	H	Me 14
entry	catalyst (X in polymer)	additive (0.1 M)	yield (%) ^a	ee (%)
1	17 (homogeneous)		29	42
2 ^b	17 (homogeneous)		26	30
3	16 (homogeneous)		79	50
4 ^{<i>b</i>}	16 (homogeneous)		66	43
5	12a (Me ₃ N)		>99	60
6	11a (Me ₃ N)		99	55
7	11b (Et ₃ N)		>99	48
8	12c (<i>n</i> -Bu ₃ N)		>99	28
9	12a (Me ₃ N)	Et_4N^+	13	12
10	11a (Me ₃ N)	n-propyl ₄ N ⁺	42	38
11	11a (Me ₃ N)	n-pentyl ₄ N ⁺	>99	41
12	12c (<i>n</i> -Bu ₃ N)	Me_4N^+	47	23
13	20 (QN)		>99	50
14	22 (QN)		>99	9
15	21 (CNI)		>99	62
16	23 (CNI)		>99	-20 ^c
17	polymer 19		14	0
an .			• • • •	. 1

"Determined by GC analysis with *o*-xylene as an internal standard after extraction by toluene. ^{*b*}In H_2O . ^{*c*}Opposite enantiomer was major.

Scheme 2. Immobilization of Enantiomerically Enriched Metal-Organic Cage Catalysts on Polymers Containing Chiral Ammonium Cations



slightly lower ee (55%) was obtained although the yield was quantitative (entry 6).

The effect of the molecular structure of ammonium cations in the polymer supports (-⁺NEt₃ for **5b** and -⁺N(*n*-Bu)₃ for **6c**) on the catalytic activity and enantiomeric induction was examined. The aza-Cope reaction catalyzed by $\Delta\Delta\Delta\Delta$ -2, supported on polymers which varied only in their ammonium group, showed a clear difference in enantioselectivity. Enantioselectivity decreased as the size of ammonium cation

increased (entries 7 and 8). When exogeneous tetraethylammonium cation was added to the reaction catalyzed by 12a, the yield (13%) and enantioselectivity (12% ee) significantly decreased (entry 9), likely as a result of catalyst inhibition due to the strong binding of tetraethylamonium with cluster 2 and an increased portion of product formation through uncatalyzed background reaction. When the tetra-n-propylammonium cation, which is weakly encapsulated by cluster 2, was added to the reaction catalyzed by 11a, partial suppression catalytic activity resulted in a 42% yield and 38% ee (entry 10 vs 5). Similarly, catalysis of the aza-Cope rearrangement by 11a in the presence of tetra-n-pentylammonium cation, which is sterically inhibited from encapsulation in the cavity of cluster 2, to the reaction mixture, resulted in a decrease in enantioselectivity to 41% ee while maintaining quantitative yield (entry 11). When the tetramethylammonium cation was externally added to heterogeneous catalyst 12c containing the tri-n-butylammonium cation-substituted polymer, both yield and enantioselectivity decreased compared to the case without added ammonium cation (entry 12 vs 8).

While enantioselectivities were only slightly affected by the hydrophobicity of polymer supports (entries 5 vs 6), the results described above suggest that the reaction outcome depends on the structure of ammonium cations in polymer supports that externally interact with the immobilized cluster. In previous studies, varying the concentration of externally added ammonium cations did not change the reaction rate of this rearrangement step in the racemic reaction.¹¹ On the other hand, the structure of ammonium cations in the polymer or in solution affected the enantioselectivity in these asymmetric reactions. Decreased enantioselectivities in entries 9, 10, and 12 can be mainly attributed to the increased proportion of background reaction, because of competition of substrate encapsulation by externally added ammonium cations. On the other hand, the decreased selectivities in the presence of ammonium cations with longer alkyl chains in polymer supports or externally added cations in entries 7, 8, and 11 are less likely to be the result of proportional increases in background reaction but to be the effect of externally interacting ammonium cations with the immobilized cluster, because the reaction proceeded smoothly to afford quantitative conversion in each case. Almost no difference in background reaction with different copolymers (6a and 6c) was also confirmed (Table 3, entries 19 and 20).

Given these observations, the "matched-mismatched" interactions between chiral ammonium cation moieties in polymers and chiral Ga cluster 2 were investigated. Polymer 18 and 19 containing chiral ammonium cations derived from quinidine and cinchonidine were prepared. Both resolved cluster 17 and racemic cluster $K_{12} {\bf 2}$ were immobilized on ${\bf 18}$ and 19 to prepare catalyst 20 (from 18 and 17), 21 (from 19 and 17), 22 (from 18 and K₁₂2), and 23 (from 19 and K₁₂2; Scheme 2). The catalysts prepared from racemic K_{12} with polymer 18 and 19 (22 and 23) both gave the desired products quantitatively with some enantioselectivity, but the stereochemistry of the major enantiomer was opposite (Table 4, entries 14 and 16). There are two explanations for the observed enantioselectivity in these reactions: (1) polymer 18 thermodyanmically favors binding of $\Delta\Delta\Delta\Delta$ -2, while $\Lambda\Lambda\Lambda\Lambda$ -**2** is favored by polymer **19**, or (2) $\Delta\Delta\Delta\Delta$ -**2** is kinetically more reactive in polymer 18 irrespective of the relative concentration of the cage enantiomers in the polymer (and the opposite would be true of polymer 19).

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These results clearly demonstrate that the polymer cation can influence the outcome of the cage-catalyzed reaction. In order to gain further insight into this influence, catalysts derived from polymers 18 and 19 and enantioenriched cage $\Delta\Delta\Delta\Delta$ -2 were prepared and examined in the aza-Cope reaction. Both catalysts gave high conversions; however, the heterogeneous catalysts prepared from $\Delta\Delta\Delta\Delta$ -2 and polymer 19 (catalyst 21) gave noticeably higher enantioselectivity (62% ee, entry 15) than that prepared from polymer 18 (catalyst 20, 50% ee, entry 13). Interestingly, what was expected to be the "mismatched catalyst" 21 provided the highest enantioselectivity to date. No significant acceleration of background reactions and no enantioselective catalysis just in the presence of the polymer was confirmed by the control experiment (entry 17).

Based on the above obtained results, variation of enantioselectivity likely results from the different microreaction environment constructed by the different polymer supports. NMR, X-ray crystallography, and calorimetry studies have shown that ammonium cations interact with $M_4 1_6$ as exohedral guests and through cation- π interactions between six exohedral NEt₄⁺ cations and the naphthyl rings of each ligand in $M_4 1_6$ assembly. In addition, these exterior binding ammonium cations control the host stability and flexibility, inducing changes to the dynamics guest passage by deformation of the host structure.^{4a,5} It is likely that the ammonium cations in the polymers are behaving in a similar manner, forming an exterior cationic shell for the immobilized anionic hosts and influencing its dynamics and thereby the selectivity (Figure 1D-ii).

Recovery and reuse experiments of chiral heterogeneous catalyst **12a** were conducted using the asymmetric aza-Cope reaction. The recovered catalysts, which were reisolated by simple filtration without additional precautions, displayed consistent yields and enantioselectivities for seven recycling runs (Table 5). These results confirm the stability of the chiral

Table 5. Recovery and Reuse of Catalyst 12a in theAsymmetric aza-Cope Reaction



structure of **2** in the polymer support even in the presence of oxygen. On the basis of these results, the asymmetric aza-Cope reaction was conducted under continuous-flow conditions (Figure 7). The catalytic reaction was highly stable under the continuous-flow conditions. Full conversion and a similar level of enantioselectivity, consistent with that obtained under the batch conditions (55-60% ee), were maintained for over 8 h. In addition, no Ga leaching was detected from combined collected fractions by ICP analysis (the detection limit of Ga ICP was <0.073% of used **2** in catalyst **8a**).

A previous study found that racemization of resolved 2 easily proceeded in neutral to acidic reaction media; therefore, a slightly basic solution was optimal for maintaining enantiopurity under homogeneous conditions.⁶ In contrast, resolved 2



Figure 7. Schematic image of the continuous-flow system (upper). Time course of asymmetric aza-Cope reaction under flow conditions (lower). Yield and ee were determined by GC analysis with an internal standard.

in heterogeneous catalyst 12a was stable against racemization and decomposition, independent of the pH of the solvent (>pH 7) in a temperature range of at least rt-50 °C. Moreover, no decreases in yields and enantioselectivities were observed during recovery and reuse and in continuous-flow systems (Table 5 and Figure 7), which is consistent with a lack of racemization of immobilized resolved cluster during the catalytic reaction and the recovery and reuse process. In addition, heterogeneous catalyst 12a has much more tolerance against oxygen during these processes than does the corresponding soluble 2. These experimental results suggest that anionic supramolecular clusters 2 are stabilized, compared to their behavior in homogeneous solution phase, in the environment created by the multicationic polymers (Figure 1D-ii). pubs.acs.org/JACS

The racemization of M₄1₆ has been proposed to proceed through partial dissociation of a catecholate ligand from the Ga center upon protonation. The partial dissociation of the catecholate ligand from the Ga center also enhances oxidation of dissociated electron-rich catechol moieties, which results in decomposition of the cluster structure. Moreover, previous studies showed that this dissociation process in solution was suppressed by addition of a large excess ammonium cation as external guest to stabilize the tetrahedral structure.⁶ Accordingly, the results of the recovery and reuse and continuous-flow experiments are consistent with the hypothesis that the ammonium cations in the polymer efficiently interact with 2 to stabilize tetrahedral structure and coordination mode of Gacatecholate center in the confined space of polymer support. Moreoever, these interactions protect 2 from both racemization and oxidation leading to increased catalyst robustness during catalytic reactions even in the absence of additional ammonium cations or the pH control that is typically required under homogeneous catalysis (Figure 1D). While the importance of the polymer support on chiral catalysts immobilized through covalent or coordinative interactions has been previously noted,¹² to the best of our knowledge these results provide the first examples of the impact of the support on the reactivity and stability of the immobilized chiral supramolecular cage catalysts.

Structural Analysis of the Heterogeneous Metal– Organic Cage Catalysts. Catalyst 8a was analyzed by scanning transmission electron microscopy (STEM) and energy-dispersive X-ray spectroscopy (EDS) line/mapping analysis (Figure 8). Ga cluster 2 is dispersed over the polymer support as judged by EDS-mapping analysis (Figure 8a–f). These studies, which show that the concentration of Ga is proportional to the thickness of the polymer (polymer thickness corresponds to the concentration of carbon in EDS-line analysis; see the SI), suggest that Ga exists not only on the surface but also penetrates into the polymer (Figure 8, h). Therefore, the reaction environment is not confined to the surface of the solid catalyst but is also present within the polymer.

A significant decrease in chloride anion concentration after immobilization of the Ga cluster was observed (Figure 8, g vs h). While some chloride anion remained after immobilization, almost no potassium, the original countercation to the Ga



Figure 8. STEM and EDS analysis of immobilized metal—organic cage catalysts. EDS-mapping of 8a: Mapping of C (a), O (b), Cl (c), Ga (d), and K (e); STEM image (f); EDS-line analysis of polymer 6a (g); EDS-line analysis of catalyst 8a (h); and EDS-line analysis of recovered 8a after using in aza-Cope reactions for 3 times (i).

cluster, was observed (Figure 6h). These results indicated that the polymer support was not saturated by Ga cluster in this catalyst, and the original potassium countercations of the Ga cluster were fully replaced by the ammonium moieties in the polymer. The observed oxygens correspond to mainly catecholate ligand 1, although the polymer contains some oxygen in its structure. The observed significant increase of the amount of oxygen also indicates the immobilization of Ga clusters 2 that contain oxygen-rich catecholate ligand 1 (Figure 8, g vs h). Analysis of the catalyst recovered after application in the aza-Cope reaction showed that Ga and the oxygen concentration did not decrease. These results are consistent with the observed high stability of Ga cluster 2 in the polymer (Figure 8, h vs i).

A significant increase in the concentration of sulfur, proportional to the thickness of the polymer, was observed in the catalyst after its use in the aza-Cope reaction (Figure 8i). This observation suggests that the majority of the remaining chloride anion was replaced with tosylate anion that is derived from substrate 13 after the aza-Cope reaction and the oxygen concentration increased slightly probably due to incorporated tosylate, although the Ga cluster did not leach due to its highly charged property (12^- ; Figure 8i). In addition, replacement of chloride by the tosylate anion supports the hypothesis that substrates penetrate and react inside the polymer during the aza-Cope reaction.

CONCLUSION

In summary, we have developed the polymer-supported tetrahedral supramolecular cluster 2 as a heterogeneous catalyst. The strategy of immobilization is a straightforward approach that employs electrostatic interaction between the multianionic cluster 2 and the multicationic ammoniumcontaining polymers, leading to preparation procedures that are quite facile. The developed heterogeneous catalysts functioned well in both batch systems and continuous-flow systems. To the best of our knowledge, this is the first example of a heterogeneous metal-organic cage catalyst, in which a catalytic process proceeds through noncovalent encapsulation in the cavity of the host and the catalyst successfully functioned when incorporated into continuous-flow systems. Newly developed heterogeneous metal-organic cage catalyst 8a showed better catalytic performance than the original cluster catalyst 2 in the solution phase, in terms of reaction speed. In addition, the heterogeneous catalysts were robust enough to maintain high catalytic activity and enantioselectivity under continuous-flow conditions and recovery and reuse without precautions for air contamination that has often resulted decomposition of the original homogeneous catalyst 2. Moreover, mechanistic insight that was not easily accessible using soluble catalyst 2 was discovered through the use of heterogeneous and continuous-flow conditions. Examples are a reversible inhibition-reactivation process using a strong guest as "antagonist" under continuous-flow catalysis and the unexpected roles of ammonium cations in the polymer. The structure of the ammonium cations in the polymers affected reactivity and enantioselectivity, likely because the cationic moieties of the polymer support interact with cluster 2 as an exohedral protecting shell and influence their catalytic performance. Therefore, the polymer supports not only work to stabilize the clusters but also provide allosteric modulation that affect the outcome of their catalysis (Figure 1D-ii).¹³

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c09556.

General synthetic procedures, ESI-MS data, and characterization of new compounds (PDF)

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Notes

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