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Heterogeneous Supramolecular Catalysis through Immobilization of Anionic M_4L_6 Assemblies on Cationic Polymers.

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ABSTRACT: Although most of 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. To develop such a heterogeneous system an immobilized chiral supramolecular cluster Ga_4L_6 (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 improved TOF, TON 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.

Supporting Information Placeholder

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 non-covalent host-guest interactions to induce significant rate accelerations and impart remarkable selectivities.¹ Although most currently developed supramolecular catalysts, in which encapsulation enables catalysis through host-guest non-covalent interactions, work under homogeneous conditions, enzymes can operate under heterogeneous conditions in Nature. For example, many proteins and enzymes exhibit catalytic functions while incorporated and stabilized in lipid bilayers of cellular membranes and organelles through hydrophobic and electrostatic interactions, hydrogen bonding, and specific lipid-protein interactions. Within this heterogeneous environment, enzyme performance is sensitive to a variety of lipid-protein interactions, so-called lipid allostery.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?

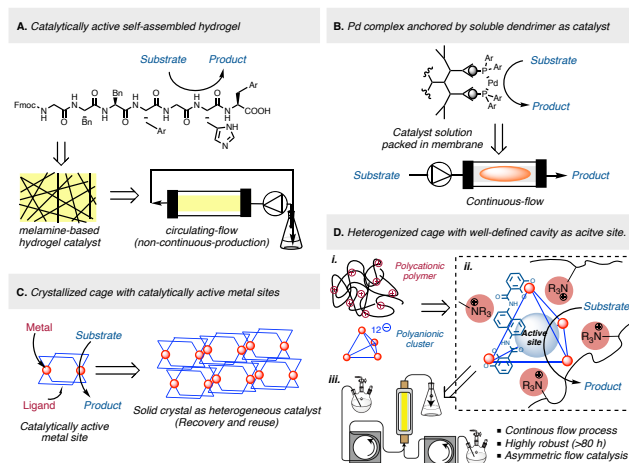


Figure 1. Heterogeneous supramolecular catalysts and flow systems

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 and Jierry *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 1, A).^{3a} Reek and Meijer *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 1, B).^{3b} On the other hand, catalysis by heterogenized metal-organic 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 1, C).^{3c,d} In contrast, heterogeneous catalysts based on metal-organic cage-type supramolecular assemblies in which the catalysis is enabled by non-covalent host-guest interactions in the well-defined cavity of the cage are exceedingly rare (Figure 1, D).

The supramolecular tetrahedral cluster composed of bis-catecholate ligands (**1**) and Ga(III), $K_{12}Ga_4I_6$ (**2** in Figure 2) 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 stereo-selectivities.^{1e, 4} Guest exchange in cluster **2**, which is important for smooth catalytic turn-over, proceeds through a non-dissociative 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}

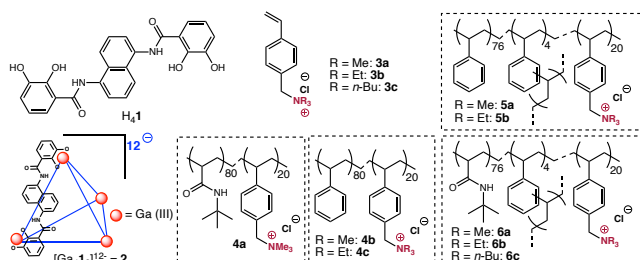


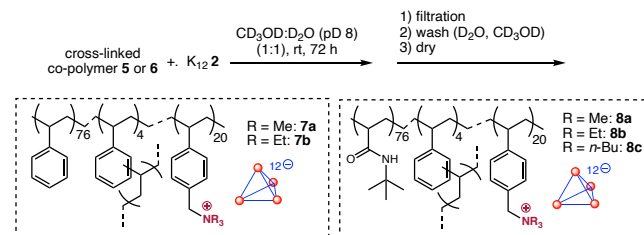
Figure 2. Structure of ligand 1, metal-organic cage 2, monomers and co-polymers

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 non-covalent interactions,⁸ we envisioned that direct incorporation of multi-anionic cluster **2** into a multi-cationic polymer through electrostatic interactions might provide an alternative, straightforward approach for rendering supramolecular catalysts heterogeneous (Figure 1, D-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 non-covalent interaction (Figure 1, D-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 1, D-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 1, D-iii).

Scheme 1. Preparation of immobilized **2** on cationic cross-linked co-polymers



RESULTS AND DISCUSSION

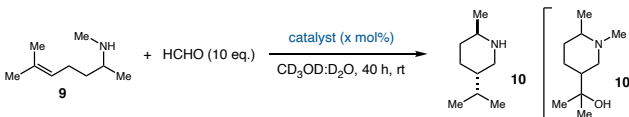
Development of heterogeneous metal-organic cage catalysts:

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 SI). These experiments showed that *N,N,N*-trimethyl and triethyl-substituted 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 co-polymers **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 co-polymers were prepared by random radical copolymerization of divinyl benzene crosslinkers, quaternary ammonium cation monomers (**3a-c**) and styrene (**5a-b**) or *N-tert*-butylacrylamide (**6a-c**) as spacer units (Figure 2). Styrene and *N-tert*-butylacrylamide 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. After combining the swelled polymers with an aqueous solution of **2**, the resulting mixture was stirred for 3 days under inert atmosphere (Scheme 1). The polymer-immobilized cluster catalysts (**7a-b** and **8a-c**) were collected 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 ion-exchange resin, Dowex®1x4Cl, that bear methylpyridinium cations; however, the loading level was noticeably lower (0.035 mmol/g).

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'**).^{4c} This divergent reactivity provides a clear indication that the reaction occurred in the cavity of cluster-containing polymer, rather than through a non-host mediated process.

Table 1. Aza-Prins reaction catalyzed by immobilized metal-organic cage catalysts



entry	catalyst	2 (mol%)	CD ₃ OD : D ₂ O	10 yield (%) ^a
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

^a ¹H NMR analysis with DMF as an internal standard.

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 1, entries 1 and 2). Only product **10** derived from the cluster (**2**)-catalyzed reaction was obtained in moderate yields regardless of structure of the ammonium cations in the polymer. Next, cluster catalysts immobilized on acrylamide-based 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 cation-containing 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 yield was obtained, likely due to inadequate swelling of **8a** in this solvent system (entry 4). In contrast, the catalyst prepared from commercially available Dowex®1x4, 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 °C 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 >80 h and the yield of **10** was maintained at 75-85% (SI_Figure 2).

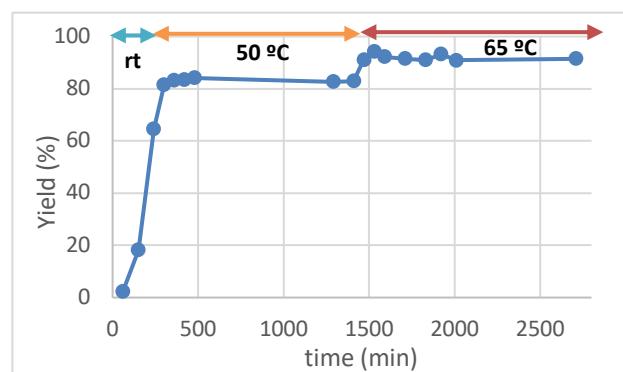
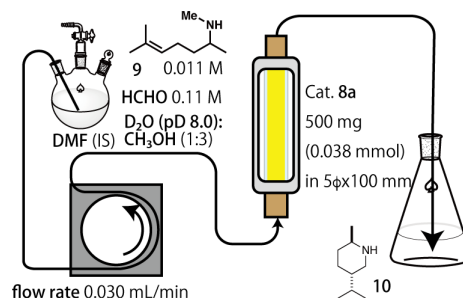


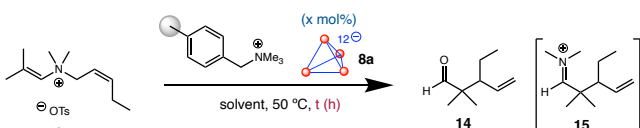
Figure 3. Schematic image of continuous flow system (upper). Time course of aza-Prins reaction under flow conditions (lower) at two temperatures.

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 equivalents 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 continuous-flow conditions. Moreover, when 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 was also examined with the heterogeneous immobilized supramolecular cluster catalysts. Previous studies have shown that this reaction is accelerated by encapsulation of substrate **13**, in a tightly packed conformation that closely resembles the conformation of the chair-like transition state.^{4b,4c,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 limited substrate access to the catalyst. (Table 2, entry 1). When a mixed solvent system of 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 (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).

Table 2. Aza-Cope reaction catalyzed by immobilized metal-organic cage catalyst **8a**



entry	Solvent	2 (mol %)	t (h)	14 yield (%) ^e
1	D ₂ O	20	15	44
2	D ₂ O:CD ₃ OD (1:3)	20	3	72
3 ^a	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 K₁₂**2** 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 ¹H NMR analysis with *o*-xylene as an internal standard and iminium intermediate **15** was not observed in reaction solution.

A solvent mixture of toluene and water was important for reaction rate, with a 1:1 ratio of these solvents proving optimal (entries 6, 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 non-catalyzed 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 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; 15 vs. 16; see SI_Figure 9 for detail of reaction profiles of entries 15 and 16). The calculated turnover frequency (TOF /h) of the heterogeneous catalyst **8a** (4.0/h) was also higher than that measured using homogenous catalyst **2** (2.0 /h). 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, addition of trimethylammonium cation to the catalyst **8a** did not significantly impact the reaction outcome (entries 6 vs. 8).

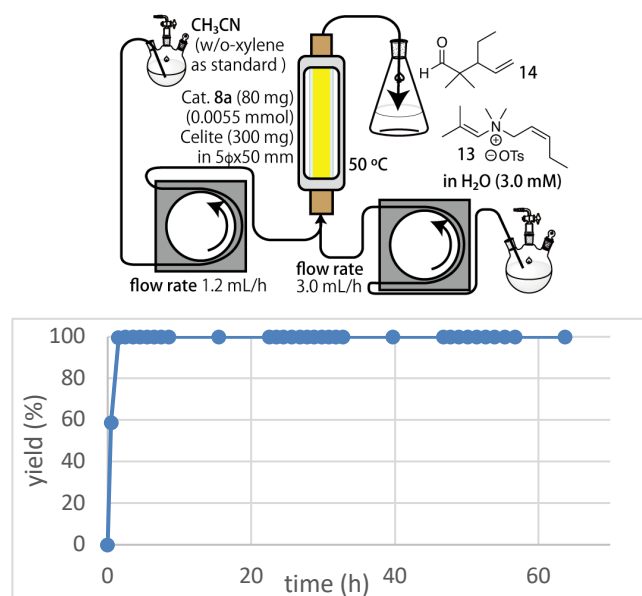


Figure 4. Schematic image of continuous flow system (upper). Time course of aza-Cope reaction under flow conditions (lower) for long period. Yield was determined by GC analysis with an internal standard.

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 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, non-degassed 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 (Detection limit of Ga ICP: <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 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 experiment, in which the catalyst was removed by filtration after heating for 1 h at 50 °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 SI_Figure 8).

The aza-Cope reaction was also conducted under continuous-flow conditions. In this experiment, separately pumped solutions of 3 mM of **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-flow conditions was highly stable, with full conversion maintained for over 60 h. In addition, ICP analysis of all the combined collected fractions detected no Ga leaching (detection limit of Ga ICP: <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. In sharp contrast to the previously reported maximum TON of **2** under homogeneous conditions (<10),^{4b} the total turnover numbers (TON) of **8a** in both the recovery-reuse and continuous-flow experiments were calculated as >100.

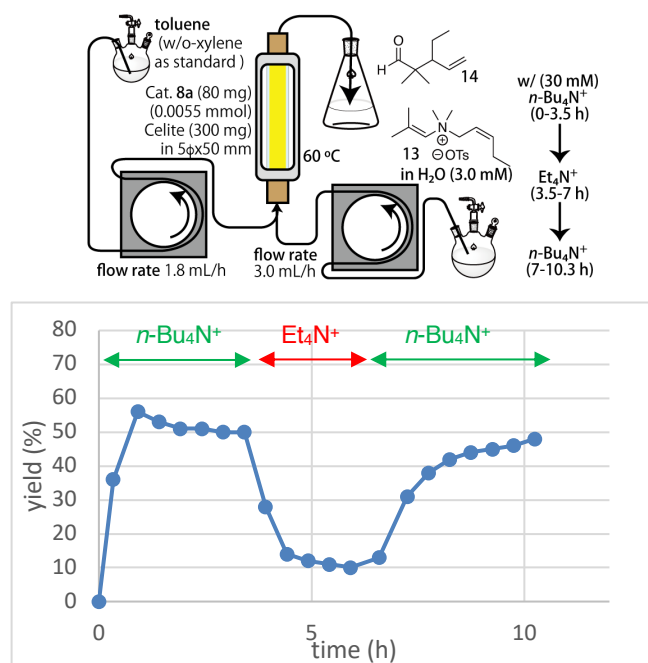


Figure 5. Schematic image of continuous flow system (upper). Time course of aza-Cope reaction under flow conditions (lower) by switching ammonium additives. Yield was determined by GC analysis with an internal standard.

Reversible inhibition-reactivation behavior of catalyst **8a in the aza-Cope reaction under continuous-flow conditions:** Tetraethylammonium cation (Et₄N⁺) is a strongly-bound guest (logK_a = ~4.5 in water) for Ga cluster **2**; ⁵ therefore, like an inhibitor or antagonist in an enzyme catalyzed reaction, Et₄N⁺ inhibits catalysis of reactions by Ga cluster **2** under homogeneous conditions.^{4d,10} As a result, clusters that are assembled with Et₄N⁺ 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 a continuous-flow processes.

First, under conditions with no added ammonium salt, quantitative conversion was observed for the aza-Cope reaction in toluene-H₂O solvent system at 60 °C under continuous-flow conditions with a molar hourly space velocity of 0.35 mol(**13**)h⁻¹ (per mole of catalyst **2** in column), to give (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 mol(**13**)h⁻¹, such that 50% conversion was observed at steady state. An aqueous solution of 3 mM of **13** and 30 mM of 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 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).

In contrast, when the continuous-flow reaction was charged with to 3 mM of **13** and 30 mM of 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.

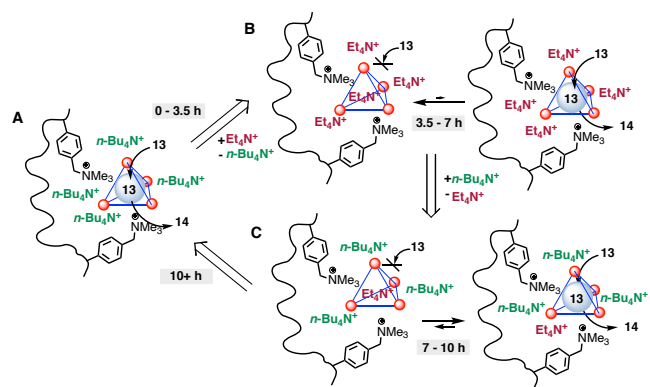


Figure 6. Schematic image of states of immobilized Ga cluster with different externally added ammonium cations during the time course of the continuous-flow reaction.

The inhibition-reactivation process is graphically depicted in Figure 6. First, *n*-Bu₄N⁺ interacted with 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 $n\text{-Bu}_4\text{N}^+$ 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 Et_4N^+ ; therefore, little-to-no catalytic activity was observed (Figure 6B). After 7 h, the substrate solution was switched to 3 mM of **13** and 30 mM of $n\text{-Bu}_4\text{NCl}$ 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 $n\text{-Bu}_4\text{N}^+$, the strongly encapsulated Et_4N^+ 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 $n\text{-Bu}_4\text{N}^+$ 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 (Me_4N^+) or without ammonium cation (SI_Figure 5). Me_4N^+ is small and can be encapsulated by Ga cluster **2**, but with a lower binding affinity than Et_4N^+ ; however, it can strongly interact with the exterior of **2**.⁴ The reversible inhibition-reativation experiment using Me_4N^+ instead of $n\text{-Bu}_4\text{N}^+$ showed a similar inhibition-reativation 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’.

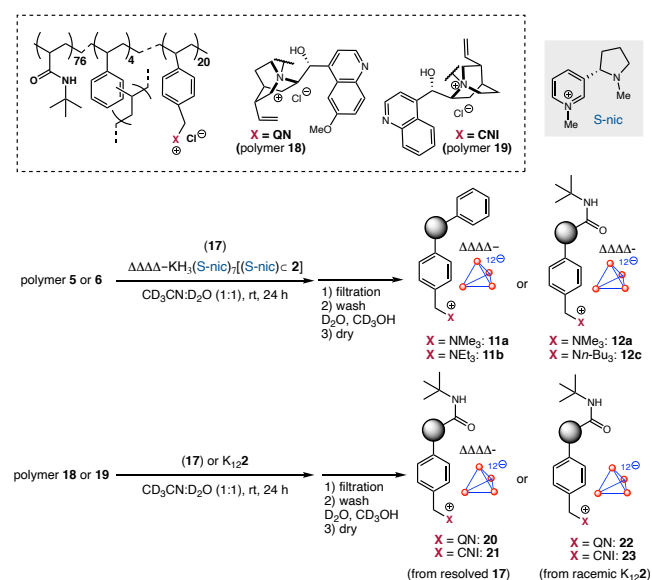
Effect of ammonium cations in polymers and solution on the asymmetric aza-Cope reaction using heterogeneous enantioselectively enriched metal-organic cage catalysts: In particular, we were interested in whether this property of the heterogenized cluster could facilitate the application of these hosts 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 ($\text{S-nic}^+ \text{I}^-$) into two isomers: $\Delta\Delta\Delta\Delta\text{-K}_6(\text{S-nic})_3[(\text{S-nic})\text{C} \text{ 2}]$ and $\Delta\Delta\Delta\Delta\text{-KH}_3(\text{S-nic})_7[(\text{S-nic})\text{C} \text{ 2}]$ (**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, $\Delta\Delta\Delta\Delta\text{-(NMe}_4)_3[(\text{NMe}_4)\text{C} \text{ 2}]$ (**16**) prior to its use as a homogeneous catalyst.^{4c} Moreover, attempts to use supramolecular assembly **17** as a catalyst without removal of S-nic^+ , 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 non-selective background reaction (Table 3, 1 vs. 3; 2 vs. 4).

On the basis of the reversible inhibition-reativation 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 $\Delta\Delta\Delta\Delta\text{-KH}_3(\text{S-nic})_7[(\text{S-nic})\text{C} \text{ 2}]$ (**17**) was directly used for immobilization, and 6-7 equivalents of S-nic^+ were recovered during the immobilization of $\Delta\Delta\Delta\Delta\text{-2}$ on copolymers **5** and **6** (Scheme 2). This observation suggested that the S-nic^+ ‘inhibitors’ were successfully removed during the immobilization process.

When resolved cluster $\Delta\Delta\Delta\Delta\text{-2}$ 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 catalyst (**11a**), a slightly lower ee (55%) was obtained although yield was quantitative (entry 6).

Scheme 2. Immobilization of enantiomerically enriched metal-organic cage catalysts on polymers containing chiral ammonium cations

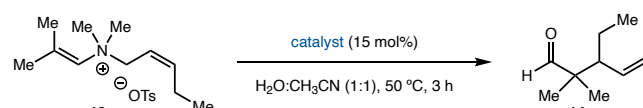


The effect of the molecular structure of ammonium cations in the polymer supports ($^-\text{NEt}_3$ for **5b** and $^-\text{N}(n\text{-Bu})_3$ for **6c**) on the catalytic activity and enantiomeric induction was examined. The aza-Cope reaction catalyzed by $\Delta\Delta\Delta\Delta\text{-2}$, supported 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 exogenous 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 tetraethylammonium 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 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 tetramethylammonium cation was

externally added to heterogeneous catalyst **12c** containing 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 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 2, entries 19 and 20).

Table 3. Asymmetric aza-Cope reaction catalyzed by immobilized enantiomerically enriched metal-organic cages



entry	catalyst (X in polymer)	Additive (0.1 M)	yield (%) ^a	ee (%) ^a
1	17 (homogeneous)	-	29	42
2 ^b	17 (homogeneous)	-	26	30
3	16 (homogeneous)	-	79	50
4 ^b	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 ₄ N ⁺	13	12
10	11a (Me ₃ N)	<i>n</i> -Propyl ₄ N ⁺	42	38
11	11a (Me ₃ N)	<i>n</i> -Pentyl ₄ N ⁺	>99	41
12	12c (<i>n</i> -Bu ₃ N)	Me ₄ N ⁺	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

^a Determined by GC analysis with *o*-xylene as an internal standard after extraction by toluene. ^b In H₂O. ^c Opposite enantiomer was major.

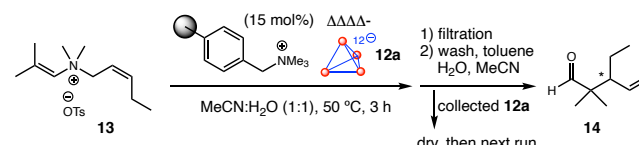
Given these observations, the ‘matched-mismatched’ interactions between chiral ammonium cation moieties in polymers and chiral Ga cluster **2** were investigated. Polymer **18** and **19** containing chiral ammonium cations derived from quinidine and cinchonidine were prepared. Both resolved cluster **17** and racemic cluster K₁₂**2** were immobilized on **18** and **19** to prepare catalyst **20** (from

18 and **17**), **21** (from **19** and **17**), **22** (from **18** and K₁₂**2**) and **23** (from **19** and K₁₂**2**) (Scheme 2). The catalysts prepared from racemic K₁₂**2** 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 3, entries 14 and 16). There are two explanation for the observed enantioselectivity in these reactions: (1) polymer **18** thermodynamically 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 more 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**).

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 control experiment (Entry 17).

Based on the above obtained results, variation of enantioselectivity likely results from the different micro-reaction environment constructed by the different polymer supports. NMR, X-ray crystallography and calorimetry studies have shown that ammonium cations interact with M₄I₆ as exohedral guests and through cation- π interactions between six exohedral NEt₄⁺ cations and the naphthyl rings of each ligand in M₄I₆ 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 1, D-ii).

Table 4. Recovery and reuse of catalyst 12a in asymmetric aza-Cope reaction



run	1	2	3	4	5	6	7
yield (%) ^a	>99	>99	>99	>99	>99	>99	>99
ee (%) ^a	60	61	59	58	59	64	61

^a Yield was determined by GC analysis with an internal standard.

Recovery and reuse experiments of chiral heterogeneous catalyst **12a** were conducted using the asymmetric aza-Cope reaction. The recovered catalysts, which were re-isolated by simple filtration without additional precautions, displayed consistent yields and enantioselectivities for seven recycling runs (Table 4). These results confirm the stability of the chiral 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 similar level of enantioselectivity, consistent with that obtained under the batch conditions (55-60% ee), was maintained for over 8 h. In addition, no Ga leaching was detected from combined

collected fractions by ICP analysis (Detection limit of Ga ICP: <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 slightly basic solution was optimal for maintaining enantiopurity under homogeneous conditions.⁶ In contrast, resolved **2** 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 3 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 multi-cationic polymers (Figure 1 D-ii).

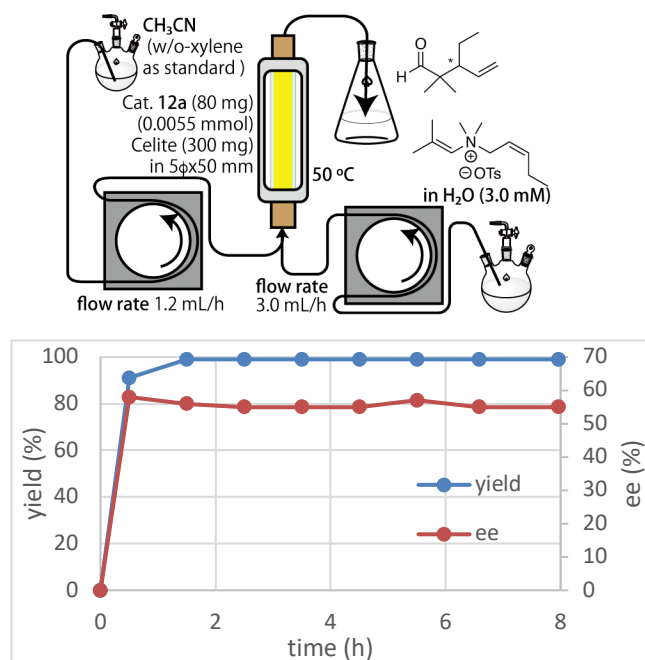


Figure 7. Schematic image of continuous flow system (upper). Time course of asymmetric aza-Cope reaction under flow conditions (lower). Yield and ee were determined by GC analysis with an internal standard.

The racemization of M₄I₆ 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 Ga-catecholate center in the confined space of polymer support. Moreover, 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 1, D). 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 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 8, a-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 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 Ga cluster was observed (Figure 8, g vs. h). While some chloride anion remained after immobilization, almost no potassium, the original counteranion to the Ga cluster, was observed (Figure 6, h). These results indicated that the polymer support was not saturated by Ga cluster in this catalyst, and the original potassium counteranions of 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 increasing 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 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 8, i). 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 oxygen concentration increased slightly probably due to incorporated tosylate, although the Ga cluster did not leach due to its highly charged property (12⁻) (Figure 8, i). In addition, replacement of chloride by 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 multi-anionic cluster **2** and the multi-cationic ammonium-containing 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 non-covalent 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 solution phase, in terms of reaction speed, total turnover number (TON), and turnover frequency (TOF). 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,

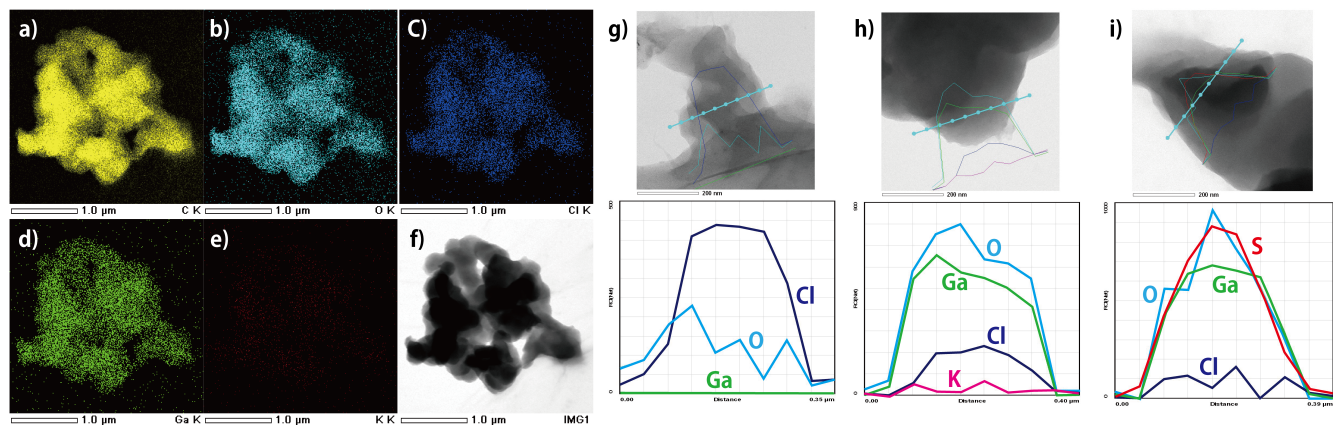


Figure 8. STEM and EDS analysis of immobilized metal-organic cage catalysts. EDS-mapping of 8a: Mapping of C (a), O (b), Cl (c), Ga (d), K (e), STEM image (f); EDS-line analysis of polymer 6a (g), EDS-line analysis of catalyst 8a (h), EDS-line analysis of recovered 8a after using in aza-Cope reactions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

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-reativation process using a strong guest as ‘antagonist’ under continuous-flow catalysis, and the unexpected roles of 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 1, D- ii).¹³

ASSOCIATED CONTENT

Supporting Information

General synthetic procedures, ESI-MS data, and characterization of new compounds are available in the Supporting Information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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