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Impact of host flexibility on selectivity in a supramolecular-host-catalyzed enantioselective aza-Darzens reaction

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ABSTRACT: A highly enantioselective aza-Darzens reaction (up to 99% ee) catalyzed by an enantiopure supramolecular host has been discovered. To understand the role of host structure on reaction outcome, nine new gallium(III)-based enantiopure supramolecular assemblies were prepared via substitution of the external chiral amide. Despite the distal nature of the substitution in these catalysts, changes in enantioselectivity (61% ee to 90% ee) in the aziridine product were observed. The enantioselectivities were correlated to the flexibility of the supramolecular host scaffold, as measured by the kinetics of exchange of a model cationic guest. This correlation led to the development of a best-in-class catalyst by substituting the gallium(III)-based host with one based on indium(III), which generated the most flexible and selective catalyst.

INTRODUCTION

Protein flexibility plays a key role in enzymatic catalysis, enabling stabilization of transition states via various electrostatic and noncovalent interactions (NCIs).^{1,2} As our understanding of protein dynamics has matured, the “lock and key” model of substrate binding has been refined to include conformational selection and induced fit models, reflecting the flexible nature of enzymes.³ Likewise, the role of flexibility in small molecule catalyst design has received greater appreciation over the last decade. An awareness that increased catalyst flexibility can enable multiple NCIs to stabilize transition states has led to the development of more selective catalysts.^{4,5} Supramolecular hosts are viewed as hybrid scaffolds that mimic enzymes by enabling remarkable rate enhancements and selectivity via NCIs while maintaining the simplicity and promiscuity of small molecule catalysts.⁶⁻¹² However, unlike enzymes and small molecule systems, the role of scaffold flexibility in facilitating NCIs in supramolecular systems is underappreciated, and its effect on reaction rate and selectivity is poorly understood.

In asymmetric catalysis mediated by small molecules, flexibility is now frequently cited as a crucial factor in enhancing selectivity, and efforts have been made to engineer more flexible scaffolds.¹³ Work from our lab has highlighted the importance of scaffold flexibility in facilitating NCIs in asymmetric catalysis.^{14,15} In addition, peptide-based catalysts and hydrogen-bond-donating catalysts highlight the enantioselectivity that can be achieved when flexibility is incorporated into catalyst backbones.¹⁶⁻²⁰ Asymmetric catalysis mediated by supramolecular cages could be an excellent way to scrutinize the effect of cage flexibility on reaction outcome; however, the field of supramolecular asymmetric catalysis remains underdeveloped.^{21,22} Many enantiopure hosts rely on the incorporation of already high-performing small molecule catalysts.²³⁻³² Because of this, the selectivity observed in the majority of these systems is intrinsic to the small molecule catalyst, not to the overall supramolecular scaffolding. There are few enantiopure supramo-

lecular hosts which enable enantioselective catalysis in the absence of an already high-performing small molecule ligand.³³⁻³⁹ In the systems reported herein, enantioinduction is a product of supramolecular chirality, presenting an opportunity to systematically explore the role of flexibility on the reactions occurring in this chiral space.

Probing the effect of host flexibility on reaction selectivity requires a series of structurally related hosts. However, in contrast to the success of strategies to generate libraries of catalytically active enzymes,⁴⁰ little progress has been made in the development of supramolecular host catalyst libraries. Much like enzymes, where a single mutation of an amino acid can lead to a misfolded protein, cage molecules are often difficult to derivatize due to the constraints imposed by self-assembly. Due to these limitations, small changes in host-ligand structure are often prohibitive, leading to complex, intractable mixtures. The constraints of self-assembly have proven prohibitive for the preparation of libraries of self-assembled supramolecular catalysts necessary for the study of systematic structure-activity relationships (SARs) that are prevalent in typical small-molecule catalyst design. Recently, despite the challenges imposed by self-assembly, a large number of metal-coordination-based hosts have been reported, expanding the field of available supramolecular systems to study.^{8,41-45} Strategies such as the assembly of heteroleptic cages and the post-synthetic modification of supramolecular cages have proven promising for the generation of related functional cages,^{46,47} and future work is expected to show some of these systems to be catalytically active. Also, a number of SARs have been reported for a few supramolecular hosts, including studies from our own lab and others that have explored the effect of host charge, host size, and the role of pendant functionalities on catalysis.^{33,49-53} These examples highlight the critical role that the individual components of a host play in catalysis and motivate the need for further in-depth SAR studies with supramolecular hosts.

RESULTS AND DISCUSSION

We hypothesized that supramolecular host **1** could be systematically modified at the external chiral amide, allowing access to a large library of chiral, catalytically active supramolecular hosts (**Figure 1**). This external chiral amide directs the assembly of host **1** to a single diastereomer, regulating the chirality of all four Ga(III) corners to a single enantiomer.³⁷ In addition, host **1** is an enantioselective catalyst, providing up to 69% ee in a Prins cyclization.³⁷ As the external chiral amide in host **1** is distal to the host's active site, substituting the amide would not be expected to directly affect bond-forming steps occurring in the cavity of the cage. However, these external amides might be expected to impose more subtle effects, including affecting scaffold flexibility since the external amides are mechanically coupled to the aperture of the host.

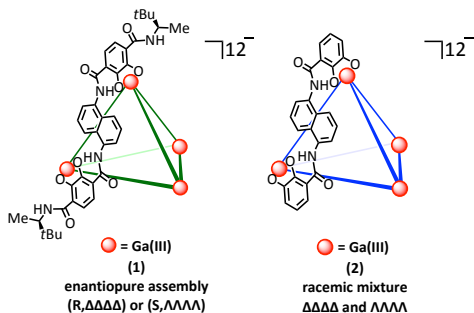


Figure 1. Enantiopure assembly **1** and racemic mixture of assembly **2**

We posited that the previously discovered host-**2**-catalyzed aza-Darzens condensation reaction might be rendered enantioselective using enantiopure host **1** as a catalyst (**Scheme 1**).⁵³ Moreover, the observed enantioselectivity in this transformation could serve as a sensitive measurement of the role that ligand design plays in host catalytic performance. In addition, a number of enantioselective aza-Darzens condensations catalyzed by chiral acids have been reported,⁵⁴⁻⁵⁶ and recently, racemic aza-Darzens reactions have been explored in other host architectures, making this reaction an attractive, well-studied target to gain a deeper understanding of chiral host **1**.⁵⁷ To this end, performing the aza-Darzens reaction with 2 mol% of enantiopure host **1** (*R*, ΔΔΔΔ) as a catalyst in 50% CD₃OD/D₂O (pD 8, 100 mM K₃PO₄) provided excellent yield and enantioselectivity (99% NMR yield, 98% ee) for the *trans*-aziridine **3a** (**Table 1**). Testing multiple concentrations of CD₃OD and D₂O (pD 8, 100 mM K₃PO₄) maintained this high selectivity for **3**; however, running the reaction in pure CD₃OD provided diminished yields and selectivity. The diminished selectivity and reactivity observed in pure CD₃OD is consistent with the reaction requiring hydrophobic binding of the neutral α -diazo ester to the cavity of the host.⁵³ In addition, subjecting the reaction to the opposite enantiomer of host **1** (*S*, ΛΛΛΛ) provided the opposite

enantiomer of aziridine **3a**. The excellent selectivity for **3** is remarkable considering that host **1** contains no traditionally high-performing chiral ligand in its architecture or a defined directing group, suggesting that the host molecule simply acts as a chiral container for the reaction environment.

Scheme 1. Aza-Darzens condensation catalyzed by enantiopure host **1**

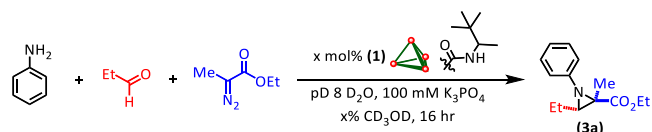


Table 1. Asymmetric aza-Darzens condensation for the synthesis of aziridine **3a**

Solvent	Cat. loading	Yield	ee
3:1 D ₂ O:MeOD	2 mol% 1 (<i>R</i> ,ΔΔΔΔ)	91%	97%
1:1 D ₂ O:MeOD	2 mol% 1 (<i>R</i> ,ΔΔΔΔ)	99%	98%
1:3 D ₂ O:MeOD	2 mol% 1 (<i>R</i> ,ΔΔΔΔ)	99%	98%
MeOD	2 mol% 1 (<i>R</i> ,ΔΔΔΔ)	61%	91%
1:1 D ₂ O:MeOD	1 mol% 1 (<i>R</i> ,ΔΔΔΔ)	99%	96%
1:1 D ₂ O:MeOD	2 mol% 1 (<i>S</i> ,ΛΛΛΛ)	96%	-98%

With a highly enantioselective host-**1**-catalyzed transformation in hand, we turned to the preparation of a series of new chiral ligands with the goal of discerning the effect of ligand architecture on reaction selectivity. The strategy for diversification of host **1** focuses on installing various chiral amides at the apex of the host. To achieve this, a library of chiral bis-catecholate ligands were accessed via sequential amide-bond-formation reactions and boron tribromide deprotection of the catecholate oxygens (see SI). The assembly of the new ligands was attempted under the reported self-assembly conditions for host **1**, requiring hot methanol.³⁷ This procedure led to the formation of complex mixtures, with little to no product supramolecular host visible by ¹H NMR. However, varying the rate of base addition to the hot reaction mixture led to mixtures with some formation of product (see SI). Optimized conditions for host synthesis required slow addition of base by syringe pump while heating the reaction mixture to 72°C in ethanol. After cooling, precipitation with diethyl ether enabled isolation of the hosts by filtration as yellow powders (**Figure 2**). ¹H NMR of these hosts with the addition of a strongly bound guest, tetraethylammonium, exhibited the diagnostic upfield shifts of an encapsulated guest and

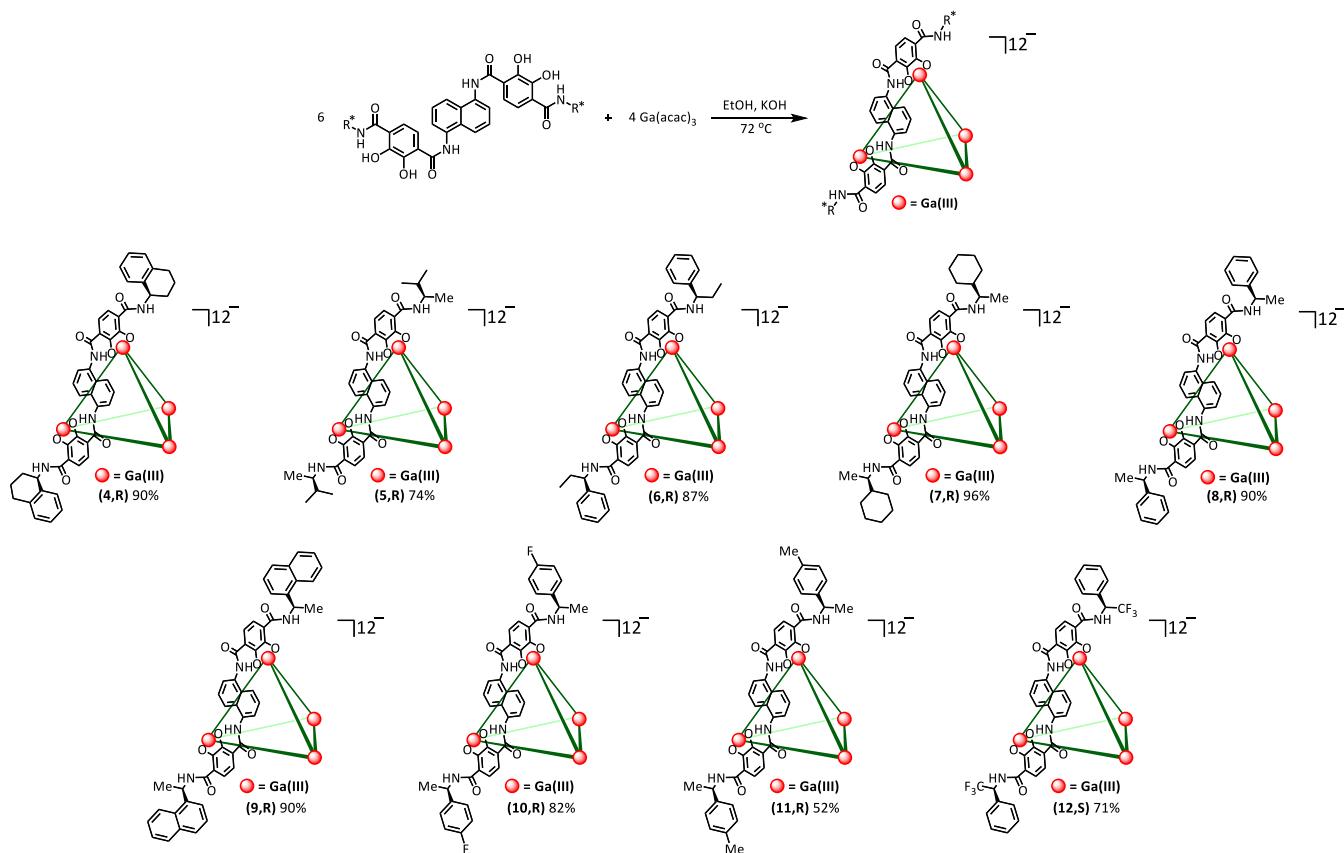


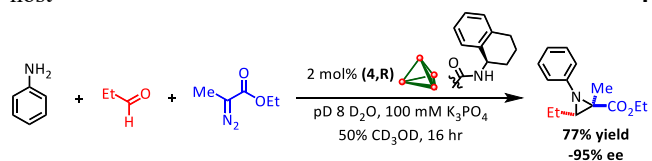
Figure 2. Nine new Ga(III)-containing enantiopure hosts prepared from structurally related biscatechololate ligands

ESI HRMS confirmed the formation of Ga_4L_6 species for all supramolecular hosts. ^1H NMR shows the formation of a single high symmetry host species, consistent with the formation of a single diastereomer of host ($R, \Delta\Delta\Delta\Delta$). In addition, binding experiments using a chiral ammonium guest as a chiral shift reagent show the guest to be a single encapsulated species, providing further evidence that these nine new hosts assemble as a single diastereomer. Circular dichroism (CD) spectrophotometry of these hosts are consistent with the CD spectra of reported host **1** (See SI).

The new library of hosts was subjected to the aza-Darzens conditions with the goal of benchmarking reaction selectivity to determine the effect of the external chiral amides on host-cavity-mediated catalysis. Unexpectedly, the aza-Darzens reaction catalyzed by host **4**, which bears the chiral amide derived from (R)-1-aminotetraline, provided aziridine **3a** in high selectivity (-95% ee) but with absolute stereochemistry opposite to that formed in the host-**1** ($R, \Delta\Delta\Delta\Delta$)-catalyzed process (**Scheme 2**). NMR experiments investigating the chemical shift of encapsulated R - α -methylbenzylammonium and S - α -methylbenzylammonium salts revealed that the cavity of host **4** has the opposite sense of chirality to host **1** ($R, \Delta\Delta\Delta\Delta$) (See SI). We infer from these observations that host **4** assembles as the ($R, \Lambda\Lambda\Lambda\Lambda$) diastereomer, therefore generating an enantiopure cavity of opposite supramolecular chirality to host **1** ($R, \Delta\Delta\Delta\Delta$). The ^1H NMR spectrum of host **4** revealed a highly fluxional species with broadened signals for the aromatic walls of the host at room temperature. Despite the fluxional nature of the

assembly, the peak of the bound guest remained sharp, consistent with a highly defined binding pocket, while the external amides' conformation remains more poorly defined. (See SI)

Scheme 2. Asymmetric aza-Darzens condensation catalyzed by host **4**



Hosts **5-9** derived from (R) chiral amines provided the same major enantiomer of product as host **1** ($R, \Delta\Delta\Delta\Delta$) with similarly excellent selectivity and yield for aziridine **3a** (>98% yield, >98% ee). However, an interesting effect was observed when 4-methoxyaniline was used as a coupling partner instead of aniline (**Figure 3**). This substrate provided divergent reactivity across the catalyst series for the 4-methoxyaniline-derived aziridine (**3d**) with host **1** affording 90% ee for aziridine **3d** while host **9** gave the lowest selectivity (61% ee). We hypothesize that this differential selectivity is due to the increased size and linear nature of 4-methoxyaniline, rendering it more difficult to encapsulate within the host. Indeed, when 4-methylaniline and 4-chloroaniline were subjected to the reaction, disparate selectivity for aziridines **3e** and **3f** was observed across the catalyst series. A similar trend in selectivity for aziridine **3c** of weaker magnitude was observed when the smaller 4-fluoroaniline was used in the reaction. In contrast, when 3-methylaniline was employed as a coupling partner, similar high enantioselectivity was observed for aziridine **3b** across the catalyst series.

This observation is consistent with 3-methylaniline occupying a more compact configuration compared to 4-methylaniline, making it more readily accommodated across the series of catalysts. As a result, the largest 4-substituted substrates lead to the

greatest differences in observed selectivity across the catalyst series.

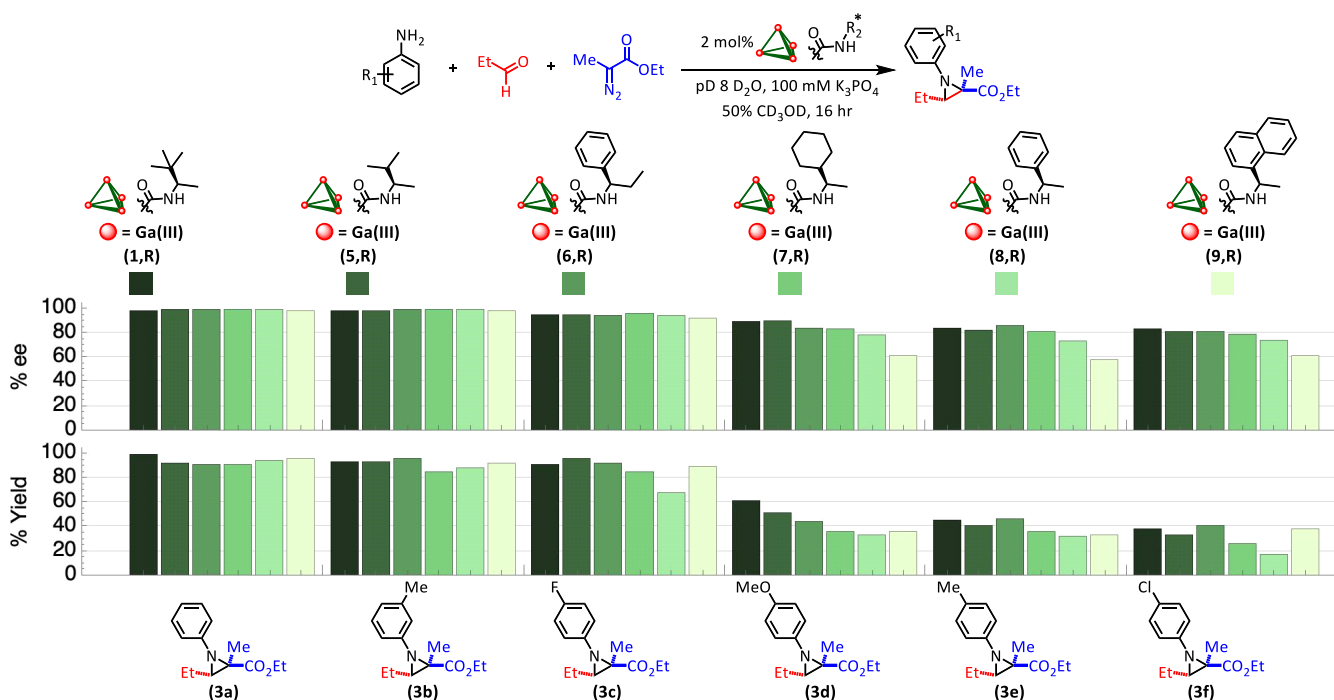


Figure 3. Divergent selectivity in enantiopure-host-catalyzed aza-Darzens reaction

Since the larger substrates provide the lowest yields, they could potentially experience a greater degree of background reactivity, leading to diminished selectivity and disparate selectivity across the host series. To determine if the diminished selectivity was a function of the background uncatalyzed process outpacing the more selective host-catalyzed process, the reaction was examined with an increased catalyst loading of host **9**, the least selective catalyst (**Figure 4a**). Under these conditions an increase in NMR yield was observed; however, selectivity remained modest. Conducting the same experiment with the stoichiometric addition of a competing strongly bound unreactive guest, tetraethylammonium, revealed poor reactivity, suggesting that the difference in observed selectivity between hosts **1** and **9** cannot be explained by a background process alone. Interestingly, NMR studies of bound cationic salts showed that the cavities of hosts **1** and **7** represent different chemical environments as evidenced by the different chemical shifts observed for bound internal guest, despite nearly identical binding constants (**Figure 4b**). This result suggests that these hosts present different chemical environments, detectable by 1H NMR, to the encapsulated guests.

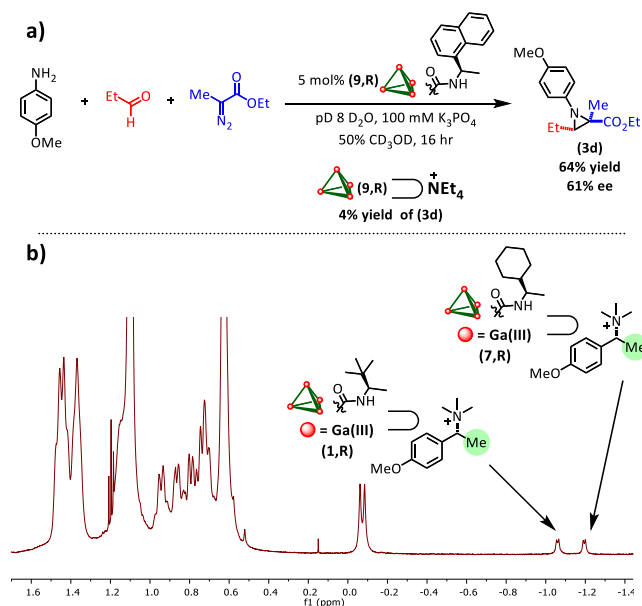


Figure 4. a) Increased catalyst loading for host-9-catalyzed aza-Darzens reaction provides similar enantioselectivity as 2 mol% catalyst loading of host **9**. Host **9** blocked by a strongly bound guest NEt_4Cl background provides little to no reactivity. b) A 1:1 binding competition experiment between hosts **1** and host **7** for a cationic guest. Encapsulated guest signals are in the negative region of the NMR and show differing chemical signals for each host.

The difference in selectivity and cavity chemical environment across the host series is significant, as the hosts only vary at the

apex position which is distal to the active site. We hypothesized that the observed differences in enantioselectivity originate from how readily the host accommodates the enantiodetermining transition state and that these differences might be reflected by host flexibility. Since movement of the aperture of the host is mechanically coupled to the external amides, any differences in interactions between the external chiral amides are expected to translate to the aperture and the active site of the host. This effect is expected to be exaggerated for larger guests which require increased aperture deformation to both allow for encapsulation and to accommodate the bond-forming event. Indeed, it is only for the largest 4-substituted substrates that differences in host selectivity are observed, suggesting that host flexibility may play a key role in reaction selectivity.

To address this hypothesis, the kinetics of binding of a number of model cationic salts were measured using selective inversion recovery NMR (SIR NMR) as a probe to benchmark host flexibility in the transition state. Similar exchange kinetics across the host series are observed when smaller cationic guests were used, consistent with the similar selectivity that we observed for smaller substrates (see SI). This result prompted us to synthesize cationic salt **13**, which could be a suitable model for the substrates in the aza-Darzens condensation. Salt **13** contains a chiral center and a large 4-substitution on its aromatic ring, mimicking the substrates which demonstrate the largest differences in selectivity across the catalyst series. This salt was readily encapsulated in the supramolecular hosts and displayed differing chemical shifts between the chiral hosts in the encapsulated region of the ^1H NMR (see SI). Using SIR NMR, the rate of exchange of model salt **13** with the supramolecular host (10:1 guest:host ratio) was measured. A difference in exchange rate was observed across the catalyst series, and this difference correlated to the observed selectivity in the aza-Darzens condensation when 4-methoxyaniline was used as a coupling partner (Figure 5). The trend shows that the hosts that exchanged guest **13** the fastest were those which provided the highest degree of selectivity in the aza-Darzens reaction.

Using the rate of exchange as an indirect measurement of host flexibility in the transition state, we concluded that the most flexible hosts provide the highest degree of selectivity. Unfortunately, host **9** was not soluble under the exchange conditions. Using pure CD_3OD to enable solvation of the host/salt exchange system, the least selective host **9** exchanged at a slower rate than our most selective host **1** (see SI), consistent with the measurements in $\text{CD}_3\text{OD}/\text{D}_2\text{O}$ (pD 8, 100 mM K_3PO_4) mixtures. To validate the correlation of flexibility and selectivity and to gain a better understanding of substituent effects on host structure, hosts **10-12** (Figure 2) bearing aromatic substitution were subjected to the aza-Darzens condensation with 4-methoxyaniline as the coupling partner, and the exchange rates of hosts **10-12** with the model salt **13** were measured. Hosts **10** and **11** fit the correlation of selectivity to host exchange rate; however, despite being a competent catalyst for the synthesis of aziridine **3d** (76% ee, 53% yield), host **12** is insoluble under the SIR NMR conditions, precluding the exchange rate measurement.

To further study host flexibility, ion mobility-mass spectrometry experiments were performed. The arrival-time distributions of all empty clusters show only one narrow, single peak, indicating the presence of one well-defined, distinct gas-phase conformation for all hosts. Interestingly, arrival-time distributions of clusters with encapsulated achiral PET_4^+ guest

clearly indicate the presence of two distinct gas-phase conformation for all hosts. These findings provide further evidence for the flexible nature of these supramolecular catalysts which increases with the introduction of a suitable guest into the system (SI).⁵⁸⁻⁶⁰

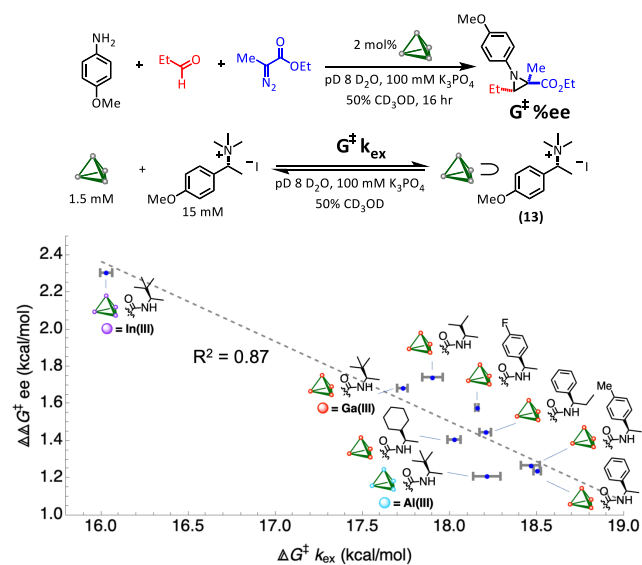


Figure 5. Correlation of reaction enantioselectivity to host flexibility as measured by SIR NMR exchange kinetics of model salt **13**

Single crystals of host **9** suitable for x-ray diffraction measurements were grown from DMSO/benzene solvent systems in the presence of eight equivalents of tetraethylammonium chloride. The crystal structure of **9** revealed a unique packing motif, in that one potassium ion is bound, partly, by the carbonyl oxygens of two different host molecules, generating a polymeric chain in the solid state. The crystal structure of **9** confirmed the structure being a highly symmetric tetrahedron with each corner adopting Δ chirality enforced by the external (R)-naphthyl amides (Figure 6). The cavity size of host **9** is similar to the cavity size of host **1**, with host **9** having an average Ga-Ga distance of 12.7 Å and host **1** having an average Ga-Ga distance of 12.6 Å.³⁷ An overlay of the crystal structures of host **1** and host **9** revealed similar cavity structure and size (see SI). The similarity in cavity size and shape between host **1**, the most selective and flexible host, and host **9**, the least selective host, provides further evidence that *the observed differences in the host are more than a ground state effect, as the external chiral amides affect overall host flexibility in the transition state for guest encapsulation.*

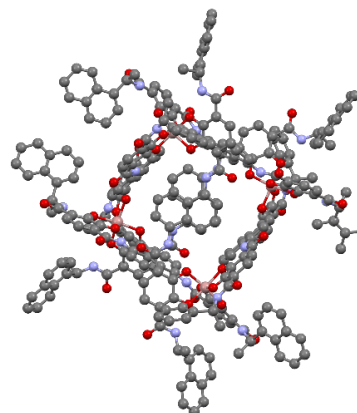
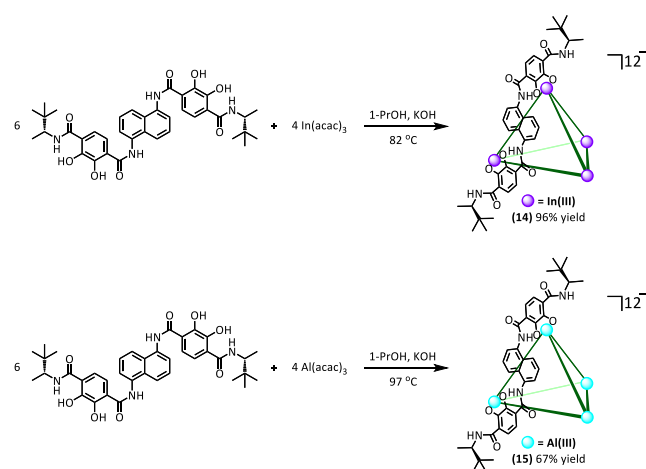


Figure 6. Single crystal XRD structure of host **9** (R, $\Delta\Delta\Delta\Delta$).

SIR NMR experiments revealed that the most flexible ligand scaffolds provided the highest selectivity in the aza-Darzens condensation, and XRD analysis of host **9** suggested that the observed effect is not due to differing cavity size or shape. Since little change in cavity structure was observed in the crystal structure of the least selective host, host **9**, we hypothesize that host flexibility could be altered by other means besides ligand substitution. A host synthesized from other group 13 atoms, aluminum or indium, instead of gallium should show little to no difference in cavity structure or size; but this change could potentially have effects on host flexibility. Since aperture dilation is mechanically coupled to the corners of the host, host deformation should proceed to some degree *via* distortion of the octahedral metal corners to a pseudo-octahedral orientation about gallium. As the indium-oxygen bonds in the triscatecholate should be longer than the gallium-oxygen bonds, we envisioned that hosts based on indium might more readily accommodate distortions at the metal corners in the transition state and also show lower energy barriers for guest encapsulation. Conversely, a host synthesized from aluminum should destabilize distortions of the triscatecholate, which in turn should decrease the flexibility of the host and raise the kinetic barrier for guest encapsulation. With this strategy in mind, we prepared indium-based host **14** and aluminum-based host **15**.

Scheme 3. Synthesis of In(III)- and Al(III)-derived hosts

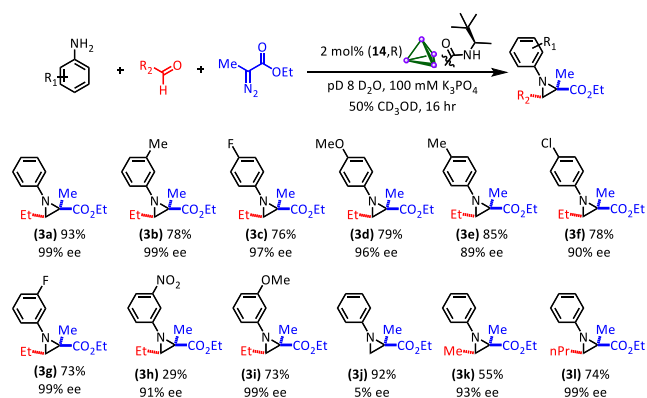


The indium- and aluminum-based hosts **14** and **15** readily assembled under modified conditions, employing In(acac)₃ and Al(acac)₃ rather than Ga(acac)₃, using 1-propanol as solvent to facilitate higher reaction temperatures, and increasing the temperature of the reaction to 82 °C and 97 °C, respectively (**Scheme 3**). Precipitation with ether provides hosts **14** and **15** in excellent yield, and ESI HRMS confirms the composition of these new hosts. Despite hosts **1**, **14**, and **15** being composed of identical ligands, differences in cavity chemical environment can be observed by comparing the chemical shift of encapsulated guests (see SI). In addition, the indium-based host **14** exchanged model guest **13** considerably faster than its gallium-based counterpart, confirming the hypothesis that indium would lower the barrier for guest exchange (**Figure 5**). When subjected to the aza-Darzens condensation reaction with 4-methoxyaniline as the coupling partner, the aziridine product was formed with 96% ee and in 93% yield, making host **14** the most selective in the catalyst series. Likewise, host **15** with aluminum-based corners exchanged model guest **13** at a slower rate than host **1**, despite being composed of identical ligands, suggesting that aluminum generates a more rigid architecture (**Figure 5**). When host **15** was employed as a catalyst for the aza-

Darzens reaction, it proved to be less selective than the gallium- and indium-based hosts, providing the aziridine in 77% ee and 47% yield.

The best-in-class catalyst, indium derived host **14**, was used to investigate the scope of the asymmetric transformation (**Scheme 4**). The racemic host-2-catalyzed aza-Darzens condensation requires that all components of the reaction must be small enough to encapsulate within the host for the reaction to proceed effectively.⁵³ Investigating the scope of host-**14**-mediated asymmetric transformation revealed that substrate size again played a key role in the host-catalyzed reaction. High selectivity was maintained for 3-substituted anilines, as well as aldehydes of different lengths. Similarly, 4-substituted anilines are also tolerated in the reaction, with the smaller 4-fluoro-substituted aniline providing the highest yields and selectivity. One notable outlier was the use of formaldehyde as a coupling partner, which provided good reactivity but diminished enantioselectivity.

Scheme 4. Scope of aza-Darzens reaction catalyzed by In(III)-derived host **14**



CONCLUSION

Enantiopure host **1** is a competent catalyst for an asymmetric aza-Darzens condensation, providing enantioselectivity up to 98% ee and excellent yields. This high degree of selectivity is remarkable considering host **1** contains no high-performing chiral ligand or catalyst, with enantioinduction being the result of supramolecular chirality. The aza-Darzens condensation was used as a tool to probe the effect of host architecture on reaction enantioselectivity, and nine new gallium-based supramolecular hosts were synthesized. Studying these new hosts revealed that reactions involving larger substrates lead to disparate reactivity, suggesting that these hosts have differing flexibilities to accommodate the transition state. Indeed, the observed selectivity in the aza-Darzens condensation was correlated to the exchange rate of a model cationic salt, revealing that the most flexible hosts are the most selective for the condensation reaction. The observation that flexibility correlates to selectivity and that the crystal structure of host **9** shows little difference in cavity volume prompted the synthesis of hosts containing other group 13 metals, indium-based host **14** and aluminum-based host **15**. Aluminum-based host **14** was less flexible and selective than gallium-based host **1**, while indium-based host **15** was the most flexible and selective catalyst in this class. This study highlights the importance of host dynamic behavior on reaction outcome, suggesting that these container molecules cannot be viewed as just simple containers in which reactions can occur. Rather, supramolecular hosts, much like enzymes, rely on complex mo-

tions to enable favorable NCIs to catalyze the reactions they facilitate. We hope that this study will spur increased interest on the potential of supramolecular asymmetric catalysis, as these enantiopure supramolecular hosts represent an unusual and underexplored chiral space for asymmetric catalysis.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website. General procedures, synthesis and characterization of compounds, general procedures, representative spectra, ESI-MS and ion mobility-MS data, crystallographic analysis of Ge-9, and ¹H NMR spectra and HPLC traces (PDF). Crystallographic data for host 9 (CIF). CCDC 2164000 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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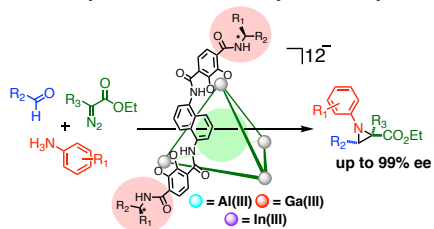
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TOC Graphic

Host Flexibility and Enantioselectivity Directed by Host Design



▪ 11 new host molecules

▪ Flexibility correlates to selectivity

▪ Differential host selectivity