# Deconvoluting the Role of Charge in a Supramolecular Catalyst

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S *Supporting Information*

ABSTRACT: We have demonstrated that the microenvironment of a highly anionic supramolecular catalyst can mimic the active sites of enzymes and impart rate accelerations of a million-fold or more. However, these microenvironments can be challenging to study, especially in the context of understanding which specific features of the catalyst are responsible for its high performance. We report here the development of an experimental mechanistic probe consisting of two isostructural catalysts. When examined in parallel transformations, the behavior of these catalysts provides insight relevant to the importance of anionic host charge on reactivity. These two catalysts exhibit similar host-substrate interactions, but feature a significant difference in overall anionic charge (12^- and 8^-). Within these systems, we compare the effect of constrictive binding in a net neutral aza-Cope rearrangement. We then demonstrate how the magnitude of anionic host charge has an exceptional influence on the reaction rates for a Nazarov cyclization, evidenced by an impressive 680-fold change in reaction rate as a consequence of a 33% reduction in catalyst charge.
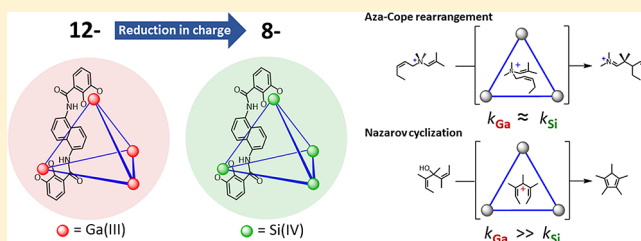
INTRODUCTION

Starting from humble beginnings,[1–4] some supramolecular catalysts now rival enzymes in accelerating rates of catalyzed reactions.[5–18] In contrast to typical homogeneous small molecular catalysts, self-assembled supramolecular catalysts achieve these rate accelerations by emulating the mechanisms of enzymes. Like enzymatic active sites, the microenvironments within these assemblies encapsulate substrate molecules with specificity and utilize noncovalent host–guest interactions to induce significant rate accelerations and impart remarkable selectivities.[19–22] Thus, supramolecular hosts are important to study not only for the design of improved synthetic catalysts but also to advance our understanding of the governing principles that underlie enzymatic catalysis.

The catalytic activity of supramolecular hosts is dictated by multiple parameters, including overall charge, cavity size, and the degree of solvent exclusion.[23,24] However, it is often challenging to deconvolute the consequences of these specific features of supramolecular catalysts on reactivity, and such studies are lacking. We report here a powerful experimental approach that exploits the modularity of a reported metal–ligand supramolecular assembly, enabling the isolation of host charge to investigate its influences on reaction rates.

Supramolecular host Ga-**1** ($K_{12}Ga_4\mathbf{2}_6$) developed by Raymond and co-workers was chosen as a suitable candidate for the development of a catalyst with varied charge. The unusually large anionic host charge (12^-) is due to four trianionic homochiral Ga(III) triscatecholate vertices, which enforce overall T symmetry upon the framework (Figure 1).[25] Host Ga-**1** effectively catalyzes a variety of transformations in
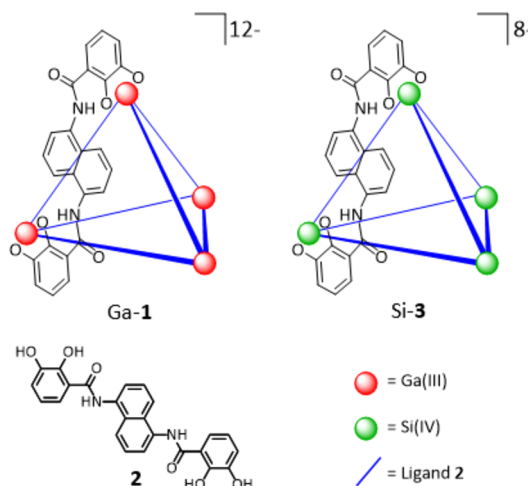

Figure 1. $[Ga_4\mathbf{2}_6]^{-12}$ tetrahedron Ga-**1** and the $[Si_4\mathbf{2}_6]^{-8}$ tetrahedron Si-**3**. Only one ligand **2** is shown of six for clarity. Blue lines represent **2** and spheres represent metal ions.

polar solvents like water. Two notable examples are the **1**-catalyzed Nazarov cyclization of a dienol substrate as well as aza-Cope rearrangements of cationic enammoniums.[26] Subsequent kinetics and DFT-based investigations have probed the origins of these rate enhancements, proposing several factors such as anionic host charge and constrictive binding.[27,28] Thus,
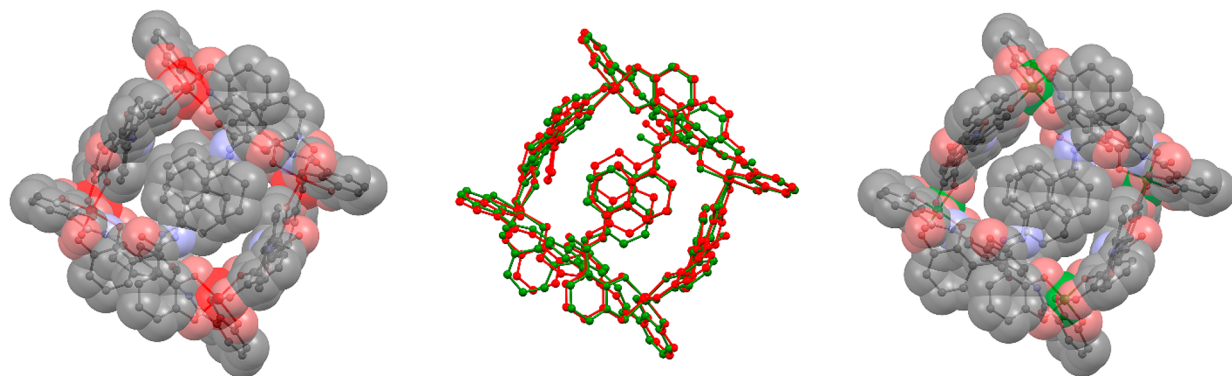
Figure 2. (Left) $[Ga_4\mathbf{2}_6]^{12-}$ Ga-**1**. (Center) Overlay of Si-**3** in green and Ga-**1** in red. (Right) $[Si_4\mathbf{2}_6]^{8-}$ Si-**3**. Counterions, solvents, and guests are removed for clarity.

we envisioned an experimental investigation of the specific role of charge in these reactions by changing the metal vertices in Ga-**1** to reduce the overall host charge while maintaining the chemical structure and geometry of the microenvironment.

RESULTS AND DISCUSSION

To this end, we turned to Si(IV) as an alternative vertex to access an isostructural $M_4\mathbf{2}_6$ host with overall reduced charge (Figure 1). Triscatecholate Si(IV) complexes are well-reported in literature, wherein the hypervalent metalloid coordination environment is pseudooctahedral, similar to that of Ga(III) in host Ga-**1**.[29] To test if an $M_4\mathbf{2}_6$ host with Si(IV) vertices could form, six equivalents of ligand **2** and four equivalents of tetramethyl orthosilicate were heated in DMF in the presence of tetraethylphosphonium bromide, a strongly binding template. The appearance of six aromatic resonances in the ^{1}H NMR spectrum in concomitance with a diagnostic upfield shift in the resonances of one equivalent of the tetraethylphosphonium cation confirmed that the host–guest inclusion complex $PEt_4^+ \subset$ Si-**3** had formed (see Supporting Information). Conditions were then screened for the template-free synthesis of Si-**3**. This is often the most challenging step of accessing new cavity-bearing architectures and has previously prohibited access to related octaanionic, catalytically active hosts.[30] In addition to the lack of the thermodynamic driving force of strong guest binding, multiple iterations of self-assembly and self-correction are required for high conversion to the desired host. Ultimately, long reaction times and elevated temperatures (60 h, 150 °C) were necessary for the clean assembly of template-free Si-**3**, likely due to the low lability of mechanically coupled silicon catecholate bonds.

Electrospray mass spectrometry (ESI-MS) confirmed the $Si_4\mathbf{2}_6$ stoichiometry and octaanionic charge of Si-**3**, primarily detected with various countercations in the 3^- and 4^- charge states (see Supporting Information). Further support for the proposed structure of Si-**3** was obtained by single crystal X-ray diffraction analysis. Crystals suitable for X-ray diffraction were grown by vapor diffusion of benzene into a solution of $NEt_4^+ \subset$ Si-**3** in DMSO and measured with synchrotron radiation. Despite minor perturbations in ligand conformation, both Si-**3** and Ga-**1** are ideal tetrahedra and the Si(IV) and Ga(III) coordination environments are remarkably well-preserved (see Supporting Information).[31] More importantly, these data confirm the architecture of Si-**3** and demonstrate the isostructural relationship between Si-**3** and Ga-**1** (Figure 2).

With isostructural catalysts Si-**3** and Ga-**1** in hand, we sought to compare their catalytic activities in order to probe the effects of host charge. Because Si-**3** is designed to mirror all the features of catalyst Ga-**1** except for the overall anionic character, their catalytic profiles should be identical unless the reaction mechanism is sensitive to a change in substrate charge. Two mechanistically distinct reactions were selected to profile the catalytic abilities of Si-**3** and Ga-**1**: the aza-Cope rearrangement and the Nazarov cyclization. In the aza-Cope rearrangement of enammonium substrates accelerated by host Ga-**1**, the cationic substrate charge is maintained throughout the reaction, thus resulting in no change in overall charge. In contrast, the Nazarov cyclization involves protonation of a neutral substrate, leading to an increase in cationic charge within the microenvironment. Investigating the Ga-**1**- and Si-**3**-catalyzed reactions in parallel should thus enable us to determine the extent to which their rate accelerations depend on anionic host charge.

The aza-Cope rearrangement features a [3,3] sigmatropic shift of allyl- or propargyl-enammonium substrates to generate γ,δ-unsaturated iminium species via a cationic cyclic transition state (Figure 3).[32] Under reaction conditions with catalyst Ga-**1**, an enammonium substrate such as **4** is initially encapsulated prior to the rate-limiting sigmatropic shift. We postulated earlier that rate acceleration from Ga-**1** derives from a reduction of the entropic barrier of cyclization due to constrictive binding within the host. Specifically, the proposed chairlike conformation of the encapsulated substrate resembles the sigmatropic rearrangement transition state more closely than the preferred extended conformations the substrate adopts in bulk solution. Note that the resulting iminium product **5** is also strongly encapsulated but hydrolyzes upon rapidly reversible egress to the corresponding γ,δ-unsaturated aldehyde **6**. This precludes product inhibition and enables catalyst turnover.[33] Because iminium hydrolysis was previously shown to proceed outside the host cavity, the reaction proceeds with a true retention of cationic charge inside Ga-**1**.

One consideration when comparing the kinetics of the Si-**3**- or Ga-**1**-catalyzed aza-Cope rearrangement is the difference in binding strength of the cationic substrate due to a variation in anionic charge of the catalysts. While it is likely that the association constant of **4** is smaller with octaanionic catalyst Si-**3**, compared to that of its dodecanionic counterpart Ga-**1**, experiments with a model substrate show that this difference is negligible under our reaction conditions (see Supporting Information).[34,35] Indeed, treatment of **4** with catalytic
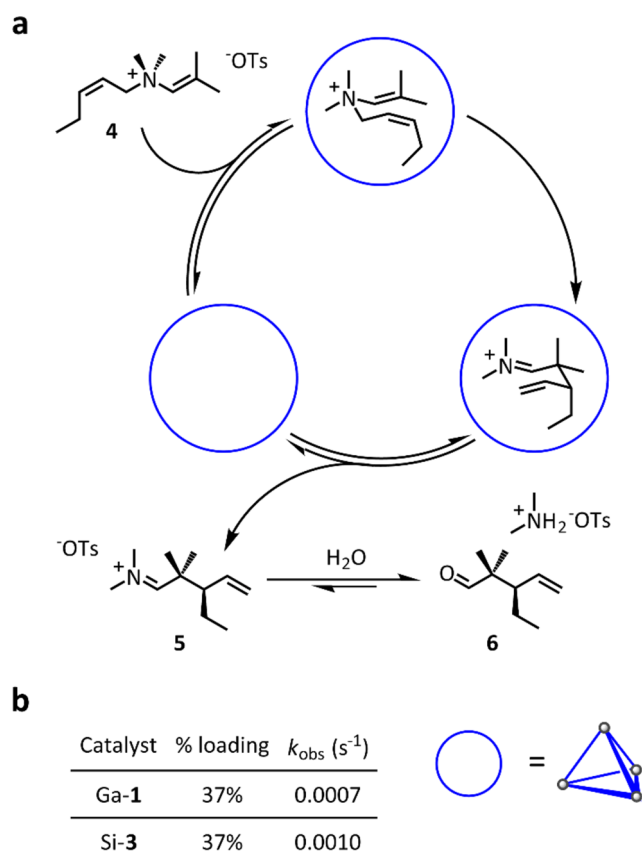
Figure 3. (A) Proposed mechanism for Si-**3**- or Ga-**1**-catalyzed aza-Cope rearrangement. (B) Rate constants (k_{obs}) for the catalyzed aza-Cope rearrangement.

amounts of Si-**3** in DMSO-d_6 immediately generated the quantitatively encapsulated host-substrate complex **4** ⊂ Si-**3**, evidenced by upfield resonances in the ^{1}H NMR spectrum corresponding to one equivalent of **4**. The subsequent reaction was tracked, and it was noted that the concentration of **4** ⊂ Si-**3** is maintained at early reaction times via catalyst turnover and further encapsulation of free **4**. This has been previously observed with Ga-**1**, where it was also shown that the aza-Cope rearrangement proceeds with first-order dependence on the host-substrate complex [enammonium ⊂ Ga-**1**].[36] We thus concluded that any differences in the association constant of **4** with Si-**3** or Ga-**1** have no effect at early reaction times in which the catalyst cavities are fully occupied. Therefore, the Ga-**1**- and Si-**3**-catalyzed aza-Cope rearrangements of **4** can both be analyzed by the method of initial rates.

The catalytic aza-Cope rearrangement of **4** was monitored at 37% catalyst loading with Si-**3** and Ga-**1**.[37] The reactions proceeded at similar rates, with rate constants (k_{obs}) of 1.0×10^{-2} and 6.5×10^{-3} s^{-1} for Si-**3** and Ga-**1**, respectively. The excellent agreement in rates for the Si-**3**- and Ga-**1**-catalyzed rearrangement suggests that the two microenvironments exert a near-identical influence on **4**, despite the 33% difference in overall host charge.[38] Furthermore, these data uphold the conclusions of our crystallographic analysis that the hosts are isostructural analogues. Consequently, these data confirm our previous analysis that the rate acceleration is purely a consequence of constrictive host-substrate interactions in which host charge plays a negligible role.

We proceeded to investigate the effect of altering host charge for our second model system, the Ga-**1**- and Si-**3**-catalyzed

Nazarov cyclization. In bulk solution, the Nazarov cyclization of dienols such as **7** requires strong Lewis or Brønsted acids which promote ionization of the C−O bond to generate the key carbocationic intermediate, followed by cationic 4π-electrocyclic ring closure.[39] In the presence of catalytic Ga-**1**, however, the Nazarov cyclization of **7** proceeds efficiently under basic aqueous conditions with no other additives. The proposed Ga-**1**-catalyzed mechanism invokes reversible binding of **7** driven by the hydrophobic effect, followed by reversible protonation and ionization to release water (Figure 4). It is noteworthy that encapsulated **7** is protonated efficiently despite the basic pH of the exterior medium. The resulting dienyl carbocation **8** then undergoes irreversible 4π-electrocyclization followed by proton loss to generate isomers of the cyclopentadiene product **9**.[40] Because **9** and substrate **7** are competitive guests, product inhibition was precluded by trapping **9** as the corresponding Diels−Alder adduct, which is too bulky for encapsulation (see Supporting Information).[26,27]

The overall course of the reaction for the Ga-**1**-catalyzed Nazarov cyclization could be monitored over several hours at room temperature. In contrast, our preliminary observations of the analogous Si-**3**-catalyzed reaction under identical conditions did not show significant progress, even after 12 hours. This disparity in reaction rate motivated a quantitative rate comparison of Si-**3** and Ga-**1** as catalysts. Heating the reaction with catalyst Si-**3** to 72 °C was sufficient to measure the reaction rate (k_{obs}) on a practicable experimental time scale. The Ga-**1**-catalyzed reaction, however, proceeds very rapidly and suffers from catalyst decomposition at elevated temperatures, precluding reliable rate constant extraction. An Eyring analysis of the Ga-**1**-catalyzed reaction was thus used to extrapolate the corresponding rate constant to 72 °C (see Supporting Information).[27] As predicted, the two reactions proceed with a significant difference in rate, with $k_{obs} = 2.2 \times 10^{-4}$ s^{-1} for Si-**3** and 1.5×10^{-1} s^{-1} for Ga-**1**. This corresponds to a 680-fold difference in rate acceleration for dodecaanionic Ga-**1** relative to the octaanionic host Si-**3**.

This dramatic change in rate acceleration is particularly striking in light of the near-identical reaction rates of the Ga-**1**- and Si-**3**-catalyzed aza-Cope rearrangement. As showcased in the aza-Cope rearrangement, the isostructural relationship between hosts Ga-**1** and Si-**3** exerts effective control over the degree of constrictive binding during the irreversible electrocyclization step. Thus, the decrease in catalytic efficacy of Si-**3** for the Nazarov cyclization can be interpreted as the identification of the effect of reducing anionic charge. Previous DFT-studies have proposed that the significance of the anionic host charge stems from stabilization not only of the initial protonation step but also of the subsequent carbocationic intermediates and transition state.[27] The experimentally observed 680-fold reduction in rate not only demonstrates that the anionic charge stabilizes cations but also puts into perspective the magnitude of this effect: an attenuation in charge from 12$^-$ to 8$^-$ was sufficient to shift the rate constant (k_{obs}) substantially. This experimental rate comparison thus serves as an important proof of concept, which aids us in understanding the extent to which host charge influences reactivity. Follow-up studies to quantify the relative thermodynamic stabilization invoked by incremental increases in anionic host charge are currently underway. Emphasis is placed on identifying the extent to which each step of the Nazarov cyclization, specifically the protonation and the electrocyclization, depends on the strongly anionic host charge.
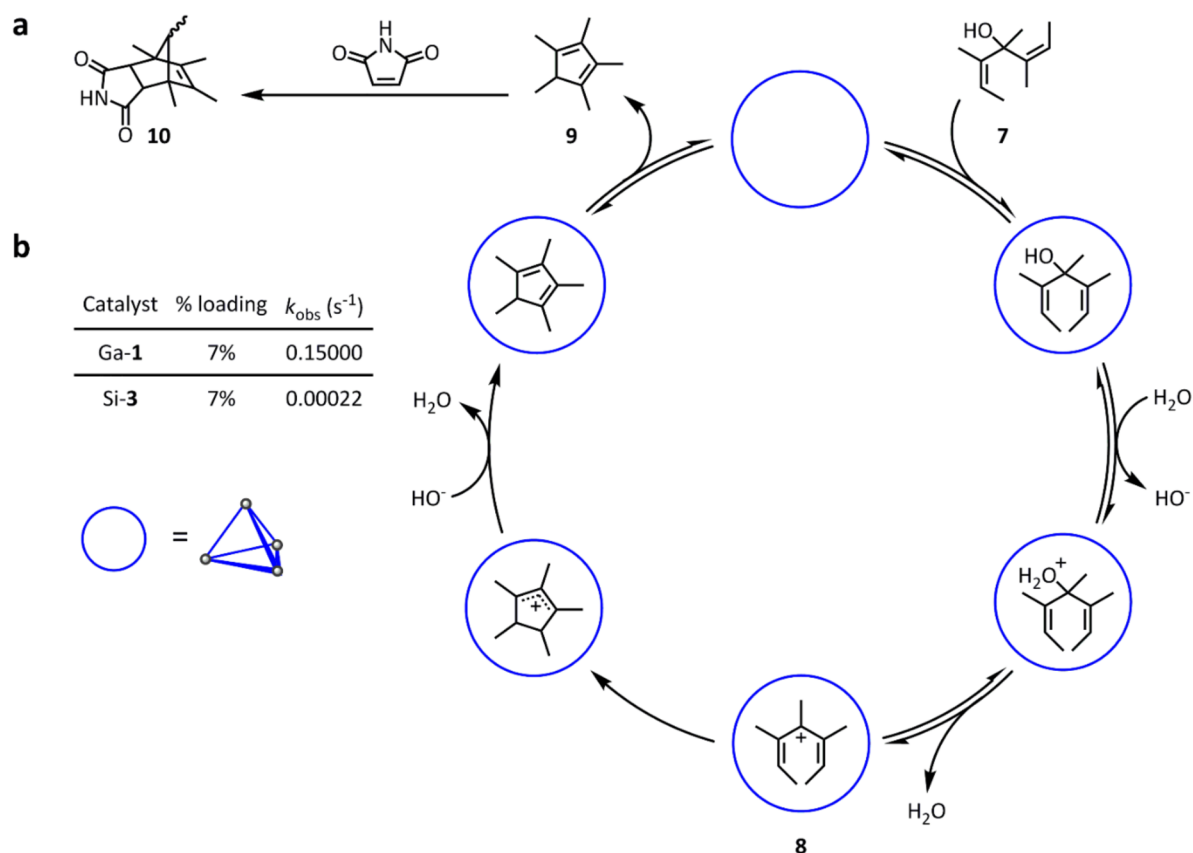
Figure 4. (A) Proposed mechanism for Si-**3**- or Ga-**1**-catalyzed Nazarov rearrangement. (B) Rate constants (k_{obs}) for the catalyzed Nazarov rearrangement.

In conclusion, the development of octaanionic catalyst Si-**3** as an isostructural analog of dodecaanionic catalyst Ga-**1** has enabled a unique experimental investigation that allows us to connect supramolecular structural features with specific mechanisms of reactivity. A Ga-**1**- and Si-**3**-catalyzed aza-Cope rearrangement in which the substrate experiences no change in charge proceeded at comparable rates, demonstrating the dominant effect of constrictive binding over host charge on the observed rate acceleration. The catalytic abilities of hosts Ga-**1** and Si-**3** were then compared in a mechanistically distinct Nazarov cyclization, in which the neutral substrate undergoes an increase in charge to access cationic transition states. The significant consequences (680-fold difference in rate constants, k_{obs}) of reducing host charge from 12^- in Ga-**1** to 8^- in Si-**3** stand as an experimental validation of the significant stabilizing effect of the anionic host charge in reactions that feature a buildup of cationic charge. Though charge and electrostatic effects have been highlighted in catalysis,[41−43] this is the first example in which these effects have been experimentally defined in a synthetic microenvironment system.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications Web site at DOI: The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b01701.

General synthetic procedures, procedures for kinetics experiments, representative spectra and kinetics data, ESI-MS data, crystallographic analysis of Si-**3**, characterization of new compounds, and ^{1}H NMR spectra (PDF) Crystallographic analysis (CIF)

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Notes
The authors declare no competing financial interest.

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■ REFERENCES

(1) Lehn, J. M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27* (1), 89−112.

(2) Lehn, J.-M.; Sirlin, C. *J. Chem. Soc., Chem. Commun.* **1978**, *21*, 949−951.

(3) Cram, D. J.; Tanner, M. E.; Thomas, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30* (8), 1024−1027.

(4) Chao, Y.; Cram, D. J. *J. Am. Chem. Soc.* **1976**, *98* (4), 1015−1017.

(5) Yoshizawa, M.; Klosterman, J. K.; Fujita, M. *Angew. Chem., Int. Ed.* **2009**, *48* (19), 3418−3438.

(6) Brown, C. J.; Toste, F. D.; Bergman, R. G.; Raymond, K. N. *Chem. Rev.* **2015**, *115* (9), 3012−3035.

(7) Koblenz, T. S.; Wassenaar, J.; Reek, J. N. H. *Chem. Soc. Rev.* **2008**, *37* (2), 247.

(8) Kaphan, D. M.; Levin, M. D.; Bergman, R. G.; Raymond, K. N.; Toste, F. D. *Science* **2015**, *350* (6265), 1235−1238.

(9) Berryman, O. B.; Sather, A. C.; Lledó, A.; Rebek, J. *Angew. Chem., Int. Ed.* **2011**, *50* (40), 9400−9403.

(10) Neelakandan, P. P.; Jiménez, A.; Thoburn, J. D.; Nitschke, J. R. *Angew. Chem.* **2015**, *127* (48), 14586−14590.

(11) Lee, S. J.; Cho, S.-H.; Mulfort, K. L.; Tiede, D. M.; Hupp, J. T.; Nguyen, S. T. *J. Am. Chem. Soc.* **2008**, *130* (50), 16828−16829.

(12) Catti, L.; Tiefenbacher, K. *Chem. Commun.* **2015**, *51* (5), 892−894.

(13) Zhang, Q.; Tiefenbacher, K. *Nat. Chem.* **2015**, *7* (3), 197−202.

(14) Wiester, M. J.; Ulmann, P. A.; Mirkin, C. A. *Angew. Chem., Int. Ed.* **2011**, *50* (1), 114−137.

(15) Meng, W.; League, A. B.; Ronson, T. K.; Clegg, J. K.; Isley, W. C.; Semrouni, D.; Gagliardi, L.; Cramer, C. J.; Nitschke, J. R. *J. Am. Chem. Soc.* **2014**, *136* (10), 3972−3980.

(16) Vriezema, D. M.; Comellas Aragonès, M.; Elemans, J. A. A. W.; Cornelissen, J. J. L. M.; Rowan, A. E.; Nolte, R. J. M. *Chem. Rev.* **2005**, *105* (4), 1445−1490.

(17) Yoshizawa, M.; Tamura, M.; Fujita, M. *Science* **2006**, *312* (5771), 251−254.

(18) Cullen, W.; Misuraca, M. C.; Hunter, C. A.; Williams, N. H.; Ward, M. D. *Nat. Chem.* **2016**, *8* (3), 231−236.

(19) Hart-Cooper, W. M.; Clary, K. N.; Toste, F. D.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2012**, *134* (43), 17873−17876.

(20) Lützen, A. *Angew. Chem., Int. Ed.* **2005**, *44* (7), 1000−1002.

(21) Yoshizawa, M.; Miyagi, S.; Kawano, M.; Ishiguro, K.; Fujita, M. *J. Am. Chem. Soc.* **2004**, *126* (30), 9172−9173.

(22) Kirby, A. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35* (7), 706−724.

(23) Hart-Cooper, W. M.; Zhao, C.; Triano, R. M.; Yaghoubi, P.; Ozores, H. L.; Burford, K. N.; Toste, F. D.; Bergman, R. G.; Raymond, K. N. *Chem. Sci.* **2015**, *6* (2), 1383−1393.

(24) Azov, V. A. *Tetrahedron Lett.* **2016**, *57* (49), 5416−5425.

(25) Caulder, D. L.; Raymond, K. N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36* (13−14), 1440−1442.

(26) Hastings, C. J.; Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2010**, *132* (20), 6938−6940.

(27) Hastings, C. J.; Bergman, R. G.; Raymond, K. N. *Chem. - Eur. J.* **2014**, *20* (14), 3966−3973.

(28) Frushicheva, M. P.; Mukherjee, S.; Warshel, A. *J. Phys. Chem. B* **2012**, *116* (45), 13353−13360.

(29) Baramov, T.; Keijzer, K.; Irran, E.; Mösker, E.; Baik, M.-H.; Süssmuth, R. *Chem. - Eur. J.* **2013**, *19* (32), 10536−10542.

(30) Davis, A. V.; Raymond, K. N. *J. Am. Chem. Soc.* **2005**, *127* (21), 7912−7919.

(31) Pluth, M. D.; Johnson, D. W.; Szigethy, G.; Davis, A. V.; Teat, S. J.; Oliver, A. G.; Bergman, R. G.; Raymond, K. N. *Inorg. Chem.* **2009**, *48* (1), 111−120.

(32) Horowitz, R. M.; Geissman, T. A. *J. Am. Chem. Soc.* **1950**, *72* (4), 1518−1522.

(33) Fiedler, D.; Bergman, R. G.; Raymond, K. N. *Angew. Chem.* **2004**, *116* (48), 6916−6919.

(34) Because **4** reacts, its K_a cannot be directly measured. The associations of tetraethylammonium to Si-**3** and Ga-**1** were used to approximate **4**'s binding strengths. This approximation is reasonable because both guests are similarly sized ammoniums.

(35) In addition to binding experiments, rates of tetraethylammonium guest self-exchange were measured for both Ga-**1** and Si-**3** using selective inversion recovery NMR. Although the rates are different, they are both more than 3 orders of magnitude faster than the aza-Cope rearrangement rates.

(36) Hastings, C. J.; Fiedler, D.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2008**, *130* (33), 10977−10983.

(37) These data were collected in 99% DMSO-d_6, but the rearrangement has been confirmed to proceed with similar rates for both catalysts in 1:1 DMSO-d_6/D$_2$O (see the Supporting Information).

(38) This conclusion was further supported with aza-Cope rearrangements promoted by the Ge(IV) host. See the Supporting Information.

(39) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61* (32), 7577−7606.

(40) Hastings, C. J.; Backlund, M. P.; Bergman, R. G.; Raymond, K. N. *Angew. Chem.* **2011**, *123* (45), 10758−10761.

(41) Fang, Y.; Xiao, Z.; Li, J.; Lollar, C.; Liu, L.; Lian, X.; Yuan, S.; Banerjee, S.; Zhang, P.; Zhou, H.-C. *Angew. Chem., Int. Ed.* **2018**, *57*, 5283−5287.

(42) For examples in enzyme catalysis (a) Warshel, A.; Sharma, P. Z.; Kato, M.; Xiang, Y.; Liu, H.; Olsson, M. H. M. *Chem. Rev.* **2006**, *106*, 3210−3235. In heterogeneous catalysis: (b) Schlangen, M.; Schwarz, H. *Catal. Lett.* **2012**, *142*, 1265−1278.

(43) For an example of electric field anion-π catalysis see: Akamatsu, M.; Sakai, N.; Matile, S. *J. Am. Chem. Soc.* **2017**, *139*, 6558−6561.