JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Enabling New Modes of Reactivity via Constrictive Binding in a Supramolecular-Assembly-Catalyzed Aza-Prins Cyclization

David M. Kaphan, F. Dean Toste,* Robert G. Bergman,* and Kenneth N. Raymond*

Chemical Sciences Division, Lawrence Berkeley National Laboratory and Department of Chemistry, University of California, Berkeley, California 94720, United States

Supporting Information

ABSTRACT: Supramolecular assembly **1** catalyzes a bimolecular aza-Prins cyclization featuring an unexpected transannular 1,5-hydride transfer. This reaction pathway, which is promoted by constrictive binding within the supramolecular cavity of **1**, is kinetically disfavored in the absence of **1**, as evidenced by the orthogonal reactivity observed in bulk solution. Mechanistic investigation through kinetic analysis and isotopic labeling studies indicates that the rate-limiting step of the transformation is the encapsulation of a transient iminium ion and supports the proposed 1,5-hydride transfer mechanism. This represents a rare example of such an extreme divergence of product selectivity observed within a catalytic metal–ligand supramolecular enzyme mimic.

Enzymes have evolved over the course of millions of years to facilitate biochemical transformations though selective transition-state stabilization. In some cases, such as the skeletal rearrangements in the formation of many complex natural products, the enzymatic binding pocket is able to control the reactivity of high-energy intermediates through a series of cooperative noncovalent interactions and substrate preorganization in order to selectively form molecules that would be difficult to access in bulk solution.[1] The cavity of a supramolecular capsule bears a strong resemblance to many hydrophobic enzymatic active sites.[1g,h] The properties of such capsules can be investigated to shed light on the nature of analogous enzymatic catalysis as well as to develop highly selective and specific synthetic catalysts.[2]

In emulation of its biological inspiration, the strategy of catalysis within a supramolecular cluster cavity relies upon controlled microenvironments and noncovalent interactions to promote specific reactivity. Many supramolecular architectures have shown high levels of catalytic activity. In particular, specially designed molecular capsules have been shown to accelerate reactions such as Diels–Alder cyclizations, condensations, and sigmatropic rearrangements, among other transformations.[3,4] Despite these accomplishments, complete divergence of reactivity by selective stabilization of reaction pathways too high in energy to be observed in bulk solution is rare in catalytic supramolecular systems.[5]

The Raymond group has developed a metal–ligand capsule of M_4L_6 stoichiometry (**1**).[6] Previous studies have illustrated the unique chemical microenvironment within the cluster. For example, amines and phosphines exhibit an effective pK_a shift of up to 4 units upon encapsulation.[7] Moreover, constrictive binding[8] within the cluster cavity lowers the entropic barrier to reactions with constrained transition-state conformations and enthalpically disfavors less compact transition-state conformations. These synergistic effects have been shown to promote a variety of acid-catalyzed, as well as pericyclic, transformations. Notably, the cluster catalyzes a Nazarov-like cyclization with up to 10^6 fold rate acceleration as well as the Prins cyclization of citronellal and related derivates.[4,9] Cluster **1** is also capable of stabilizing a number of high-energy species within its cavity (e.g., quantitative iminium ion formation can be observed within the cluster in aqueous media).[10]

We envisaged that the cluster's propensity to effect cyclizative reactivity and stabilize transient carbocations, combined with its ability to promote iminium ion formation, could facilitate an aza-Prins reaction, whereupon an amino group tethered to a nucleophilic double bond would undergo condensation with an aldehyde or ketone, followed by cyclization and elimination or hydration of the resulting carbocation. Unexpectedly, treatment of amine **2** with formaldehyde in the presence of **1** at ambient temperature afforded substituted piperidine **3** as the main product, wherein demethylation at nitrogen and reduction of the putative carbenium generated by the cyclization of **2** had occurred (Scheme 1). This stands in stark juxtaposition to the aza-Prins cyclization of **2** in bulk solution, which required heating to reflux in neat formic acid and afforded alcohol **4** as the product.

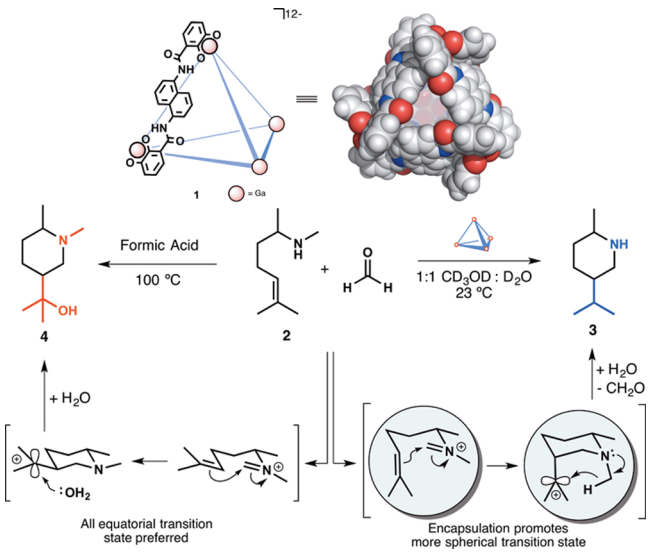
To understand this unusual result, we first prepared an isotopically enriched analogue of the starting material (**2**-d_3) in an effort to elucidate the origin of the hydrogen of the isopropyl methine in **3**. **2**-d_3 was subjected to the cluster-catalyzed aza-Prins cyclization conditions, followed by treatment with *p*-nitrobenzenesulfonyl chloride, in order to facilitate purification. The resulting sulfonamide, **5**-d_1, exhibited complete deuterium incorporation at the isopropyl methine (Scheme 2). Conversely, reaction of unlabeled amine **2** under otherwise identical conditions furnished nosylated product **5**, which did not incorporate any deuterium at the isopropyl methine. (Deuterium exchange with the solvent mixture does not explain the formation of **5**-d_1.)

Another observation that shed light on the mechanism of the divergent reactivity of **2** came from the exposure of the *N*-benzyl analogue of the starting material (**2i**) to cluster cyclization conditions. Importantly, the identical dealkylated

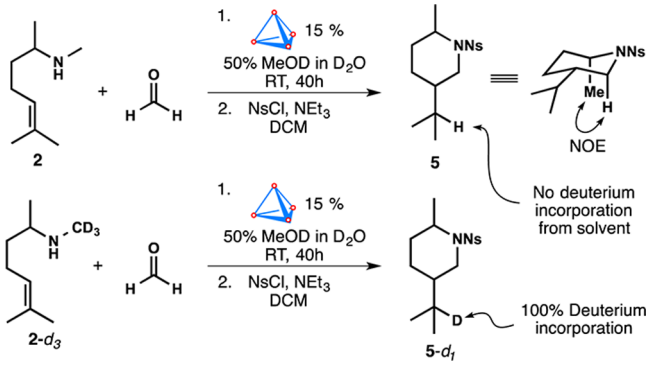
Received: February 4, 2015
Published: July 15, 2015

DOI: 10.1021/jacs.5b01261
J. Am. Chem. Soc. 2015, 137, 9202–9205

Scheme 1. Divergent Selectivity of Cluster-Catalyzed Aza-Prins Cyclization



Scheme 2. Deuterium Labeling Study

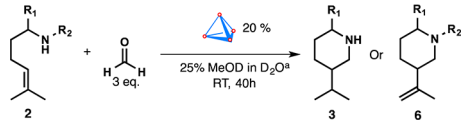


amine product (**3**) was observed in conjunction with the appearance of benzaldehyde, suggesting the intermediacy of an iminium species resulting from hydride abstraction alpha to nitrogen, which undergoes hydrolysis.

The observation of quantitative deuterium incorporation from the cyclization of amine **2**-d_3, in addition to the appearance of benzaldehyde in the cyclization of **2i**, is consistent with a mechanism involving an aza-Prins cyclization with subsequent transannular 1,5-hydride transfer from the *N*-methyl group to the nascent tertiary carbocation (Scheme 1). We hypothesize that this divergent reactivity is the result of the constrictive binding of the cluster cavity which favors more compact transition states. This constrictive binding results in a preference for the more compact axial orientation of the double bond in the transition state of the cyclization. Consequently, after cyclization, the carbocation in the intermediate is preorganized in close proximity to the *N*-methyl C−H bonds, facilitating a 1,5-through-space hydride transfer. Hydrolysis of the resulting iminium ion in bulk solution affords **3**.[11] The relative configuration of product **5**, with the methyl group in the axial position as determined by 1,3-diaxial NOE interactions, supports this hypothesis (Figure S1). This diastereomer likely reflects a transition-state conformation that places the methyl group in an equatorial position and the double bond in an axial position followed by a ring flip of the product to place the more sterically demanding isopropyl group in the equatorial position. In the absence of the unique cavity environment (i.e., in bulk solution), the enthalpically favored equatorial olefin orientation in the transition state should predominate. Because the carbocation resulting from cyclization in bulk solution lacks the proximity to the *N*-methyl group and solvent seclusion necessary for hydride transfer to occur, it is rapidly sequestered by water to form alcohol **4**. This emergent mechanistic pathway is notable because of the fact that it is too high in energy to be observed in the absence of the constrictive microenvironment of the cluster's interior binding pocket.

Having proposed a mechanism for the formation of **3** consistent with the experimental observations, we varied the substitution at nitrogen in order to gain further insight (Table 1). Parent *N*-methyl substrate **2a** underwent full conversion

Table 1. Effect of N Substitution on Reactivity



Entry	R_1	R_2	Product	% Conversion[b]
1 (**2a**)	Me	Me	**3**	100
2 (**2b**)	H	Me	**3**	100
3 (**2c**)	Me	Et	**3**	53
4 (**2d**)	Me	*n*-Pr	**3**	43
5 (**2e**)	Me	*n*-Bu	**3**	9
6 (**2f**)	Me	*i*-Pr	*n/a*	0[c]
7 (**2g**)	Me	Cy	*n/a*	0[c]
8 (**2h**)	H	*i*-Pr	**3**	25
9 (**2i**)	Me	Bn	**3**	51[c]
10 (**2j**)	Me		*n/a*	0
11 (**2k**)	Me		**6**	100

[a]pD 8.0, [PO_4^{3-}] = 100 mM. [b]Calculated by ratio of extracted product to starting material by ^{1}H NMR spectroscopy. [c]Conversion at 60 °C.

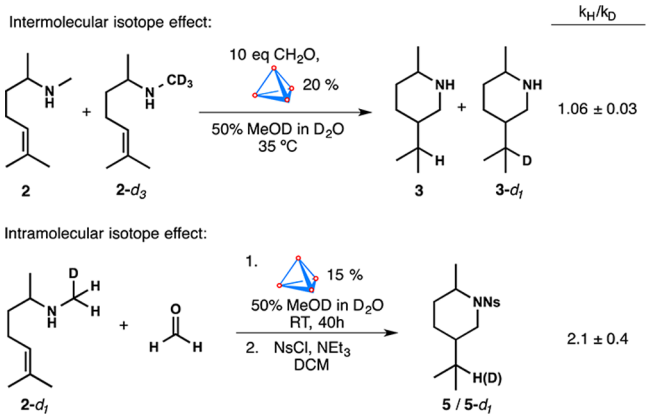
with 3 equiv of formaldehyde and 20 mol % cluster in a 25% MeOD in D_2O solvent mixture at room temperature in 40 h. Increasing the chain length of *N*-alkyl substitution led to a sharp decrease in conversion: *N*-ethyl, -propyl, and -butyl substrates proceeded to 53, 43, and 9% conversion, respectively. These data are consistent with size exclusion imposed by the congested interior of the cluster. Branching alpha to the amine inhibits reactivity completely, even at elevated temperatures (Table 1, entries 6 and 7); however, removal of the methyl group on the carbon backbone partially restored reactivity for the *N*-isopropyl substrate (Table 1, entry 8). One possible explanation for this phenomenon is that doubly α-branched substrates are simply too bulky to undergo the condensation with formaldehyde to form the initial iminium ion which precludes further reaction. *N*-benzylamine **2i** (Table 1, entry 9) showed only trace reactivity, but by warming the reaction mixture to 60 °C, 51% conversion was achieved after 40 h. However, 2-methoxybenzylamine **2j** (Table 1, entry 10) did not react, even at elevated temperatures. This observation is again consistent with substrate specificity through size exclusion from the cluster cavity. Unexpectedly, *N*-trifluoroethyl substitution (Table 1, entry 11) led to complete consumption of the starting material, but no hydride transfer was observed. Instead, elimination product **6** was observed exclusively.[12] This is most likely due to decreased

DOI: 10.1021/jacs.5b01261
J. Am. Chem. Soc. 2015, 137, 9202−9205

hydricity alpha to the nitrogen because of the inductive electron withdrawal of the $-CF_3$ group.

A series of competition experiments were then conducted to determine the deuterium kinetic isotope effect associated with the 1,5-hydride shift (Scheme 3). First, the intermolecular isotope effect was assessed using a single-vessel rate comparison of amine **2** and its trideuteromethyl labeled analogue **2**-d_3. In this experiment, the intermolecular kinetic isotope effect was found to be 1.06 ± 0.03. The intramolecular isotope effect was then measured by preparing monodeuteromethylamine **2**-d_1 and subjecting it to the standard cluster-catalyzed cyclization conditions. The intramolecular isotope effect was found to be 2.1 ± 0.4. The absence of an intermolecular isotope effect, while an intramolecular isotope effect was observed, indicates that the hydride transfer event occurs after the rate-limiting step of the catalytic cycle.

Scheme 3. Deuterium Kinetic Isotope Experiments



Further kinetic analysis of the reaction was conducted with trifluoroethylamine **2k** as the substrate, given its convenient ^{19}F-NMR handle. Although **2k** undergoes an eliminative pathway to form product **6**, it should follow a kinetic profile similar to that of **2a** because of the kinetic invisibility of the 1,5-hydride transfer in the transformation of **2a** to **3** (vide supra). When **2k** was exposed to formaldehyde in either the presence or absence of the cluster, a new peak was observed in the ^{19}F-NMR spectrum in addition to that of **2k**, which was assigned as hemiaminal **X**, the adduct of the amine and formaldehyde (Supporting Information). The consumption of starting material [**2k** + **X**] displayed pseudo-first-order kinetic behavior with 10 or greater equiv of formaldehyde.[13] Despite the tendency for tertiary amines to have a higher affinity for cluster **1**,[14] the product (**6**) was not strongly encapsulated; therefore, no product inhibition was observed. However, because of heterogeneity at the late stages of the reaction, the technique of initial rates was implemented.

The order of the reaction in cluster **1**, substrate **2k**, and formaldehyde was examined. The reaction was found to be first-order in **2k**; however, the low solubility of the substrate precluded probing of the high-concentration regime. The dependence of the rate on formaldehyde concentration[15] was also found to be first-order over a range of 0.15−0.6 M (10−40 equiv, Figure S6). Intriguingly, variation of the concentration of the supramolecular catalyst did not result in a linear first-order rate dependence. Instead, a roughly first-order regime was observed at low cluster concentrations, which transitioned into a zero-order region at higher cluster concentrations (Figure 1).

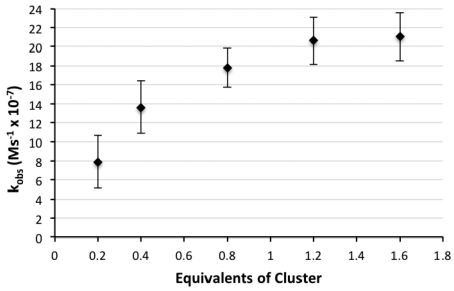
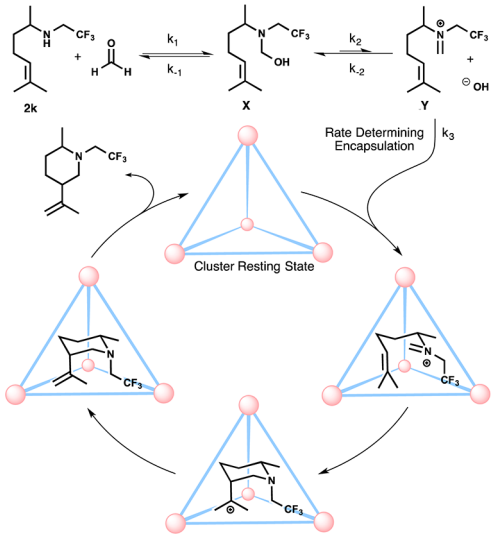


Figure 1. Dependence of initial rate on cluster equivalents.

One explanation that is consistent with the observed saturation behavior is that high-energy, steady-state intermediate iminium ion **Y** is formed in bulk solution and undergoes a rate-determining encapsulation event with the cluster. The saturation behavior of cluster concentration corresponds to a transition in the rate limiting step of the reaction. At low cluster concentration, encapsulation of iminium ion **Y** (k_3) is rate-limiting, whereas at higher cluster concentrations, the formation of **Y** (k_2) becomes rate-limiting, and the cluster is no longer involved in the rate limiting step (for a discussion of other mechanistic possibilities, see Supporting Information pages S15-S16).[16,17]

From the information obtained in the above experiments, a catalytic cycle can be proposed for the cluster-catalyzed aza-Prins cyclization (Scheme 4). Trifluoroethylamine **2k** is in rapid pre-equilibrium with the formaldehyde hemiaminal. The hemiaminal leads to the iminium ion as a high-energy, steady-state intermediate that is not directly detectable. The iminium ion is then intercepted in a rate-limiting encapsulation event with the empty cluster (which is the cluster resting state, as observed by ^{1}H NMR spectroscopy). The encapsulated iminium ion then undergoes rapid cyclization, and the nascent carbocation in this cyclized intermediate is quenched by elimination (or hydride transfer in the case of substrates **2a**−**j**). Finally, the product of the reaction is expelled from the cluster cavity, thus regenerating the empty-cluster resting state.

Scheme 4. Proposed Catalytic Cycle for the Supramolecular-Cluster-Catalyzed Aza-Prins Cyclization



DOI: 10.1021/jacs.5b01261
J. Am. Chem. Soc. 2015, 137, 9202−9205

Steady-state analysis of this catalytic pathway leads to the rate law shown in eq 1. This rate law accounts for the first-order behavior in amine and formaldehyde as well as the observed saturation behavior in cluster concentration. This mechanistic conclusion is quite significant because supramolecular catalysts typically form Michaelis-type complexes, with the transformation of the substrate−catalyst complex constituting the rate-determining step.[2]

$$\frac{\partial[\mathrm{P}]}{\partial t} = \frac{K_1 k_2 k_3[2k][\mathrm{CH_2O}][1]}{k_{-2} + k_3[1]} \quad (1)$$

The ability to completely control, redirect, and effect chemical reactivity under mild conditions similar to those of enzymatic catalysis has been a persistent goal of synthetic chemistry since its inception. Constrictive binding through confinement within a molecular cage is one strategy that can be taken advantage of to this effect. We have described a supramolecular-cluster-catalyzed aza-Prins cyclization featuring a 1,5-through-space hydride transfer. The nature of this transformation was probed by isotopic labeling studies and kinetic analysis, and the effect of nitrogen substitution was assessed. This pathway is uniquely available within the constrictive environment of a supramolecular nanovessel and is too high in energy to be observed in bulk solution for this class of substrates. The emergent reactivity of 1,5-hydride transfer in the aza-Prins cyclization represents the most pronounced deviation in reactivity within a supramolecular catalyst to date.

■ ASSOCIATED CONTENT

Supporting Information

Text, tables, and figures giving synthesis methods as well as NMR data including additional spectra and kinetic plots. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b01261.

■ AUTHOR INFORMATION

Corresponding Authors

*fdtoste@berkeley.edu
*rbergman@berkeley.edu
*raymond@socrates.berkeley.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the Director, Office of Science, Office of Basic Energy Sciences and the Division of Chemical Sciences, Geosciences, and Biosciences of the U.S. Department of Energy at LBNL (DE-AC02-05CH11231) and a National Science Foundation Graduate Research Fellowship (grant no. DGE 1106400) to DMK. We thank Mark Levin, Andrew Neel, Dr. Johnathan Brantley, and Dr. Matthew Winston for helpful discussion.

■ REFERENCES

(1) (a) Klose, R. J.; Zhang, Y. *Nat. Rev. Mol. Cell Biol.* **2007**, *8*, 307. (b) Cunningham, F. X.; Gantt, E. *Proc. Natl. Acad. Sci. U. S. A.* **2001**, *98*, 2905. (c) Olguin, L. F.; Askew, S. E.; O'Donoghue, A. C.; Hollfelder, F. *J. Am. Chem. Soc.* **2008**, *130*, 16547. (d) Jordan, F.; Li, H.; Brown, A. *Biochemistry* **1999**, *38*, 6369. (e) Köksal, M.; Hu, H.; Coates, R. M.; Peters, R. J.; Christianson, D. W. *Nat. Chem. Biol.* **2011**, *7*, 431. (f) Christianson, D. W. *Chem. Rev.* **2006**, *106*, 3412. (g) Faraldos, J. A.; Antonczak, A. K.; Gonzalez, V.; Fullerton, R.; Tippmann, E. M.; Allemann, R. K. *J. Am. Chem. Soc.* **2011**, *133*, 13906. (h) Degenhardt, J.; Köllner, T. G.; Gershenzon, J. *Phytochemistry* **2009**, *70*, 1621.

(2) For reviews, see (a) Avram, L.; Cohen, Y.; Rebek, J., Jr. *Chem. Commun.* **2011**, *47*, 5368. (b) Purse, B. W.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 10777. (c) Yoshizawa, M.; Klosterman, J. K.; Fujita, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 3418. (d) Breiner, B.; Clegg, J. K.; Nitschke, J. R. *Chem. Sci.* **2011**, *2*, 51. (e) Weister, M. J.; Ulmann, P. A.; Mirkin, C. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 114.

(3) (a) Kang, J.; Rebek, J. *Nature* **1997**, *385*, 50. (b) Nishioka, Y.; Yamaguchi, T.; Kawano, M.; Fujita, M. *J. Am. Chem. Soc.* **2008**, *130*, 8160. (c) Yoshizawa, M.; Kusukawa, T.; Fujita, M.; Sakamoto, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **2001**, *123*, 10454. (d) Fiedler, D.; Bergman, R. G.; Raymond, K. N. *Angew. Chem.* **2004**, *116*, 6916. (e) Zhang, Q.; Tiefenbacher, K. *J. Am. Chem. Soc.* **2013**, *135*, 16213.

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

(5) (a) Yoshizawa, M.; Tamura, M.; Fujita, M. *Science* **2006**, *312*, 251. (b) Hou, J.-L.; Ajami, D.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2008**, *130*, 7810−7811. (c) Furusawa, T.; Kawano, M.; Fujita, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 5717−5719. (d) Kaanumalle, L. S.; Gibb, C. L. D.; Gibb, B. C.; Ramamurthy, V. *J. Am. Chem. Soc.* **2004**, *126*, 14366−14367. (e) Nishioka, Y.; Yamaguchi, T.; Yoshizawa, M.; Fujita, M. *J. Am. Chem. Soc.* **2007**, *129*, 7000−7001. (f) Zhang, Q.; Tiefenbacher, K. *Nat. Chem.* **2015**, *7*, 197.

(6) Caulder, D. L.; Powers, R. E.; Parac, T. N.; Raymond, K. N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1840.

(7) Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 11459.

(8) Cram originally coined the term "constrictive binding" to describe the contortions of a host in response to steric repulsions during guest ingress or egress though a host aperture. Here, we expand this definition to include the conformational changes imposed on the guest in order to occupy the cavity of the host. For Cram's definition, see Cram, D. J.; Tanner, M. E.; Knobler, C. B. *J. Am. Chem. Soc.* **1991**, *113*, 7717.

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

(10) Dong, V. M.; Fiedler, D.; Carl, B.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 14464.

(11) For an example of a similar hydride transfer promoted by a rigid carbon framework instead of the constrictive binding of a supramolecular cluster microenvironment, see Heathcock, C. H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 665.

(12) Compound **6** was isolated as a mixture of two diastereomers in an 8:1 ratio (Supporting Information). Only one diastereomer of amine **3** was observed.

(13) The ratio of **2k** and **X** remains constant over the course of the reaction, suggesting that the two species are in rapid equilibrium (Supporting Information).

(14) Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 11459−11467.

(15) Concentrations of formaldehyde reflect the total amount of formaldehyde added; however, the majority of the reagent likely resides as a complex mixture of adducts undergoing rapid interconversion with one another.

(16) Although the hemiaminal formaldehyde adduct was observed to be in equilibrium with the starting material, this species can not be the steady-state intermediate responsible for the saturation behavior because under the saturation regime the ratio of the amine and hemiaminal was not perturbed.

(17) It is also possible to derive a rate equation consistent with the experimental observations that involves rate-determining cyclization at low cluster concentration if both the free and encapsulated iminium ions are treated as steady-state intermediates. However, rate-determining encapsulation is more intuitively based on previous studies of this system and similar systems.

DOI: 10.1021/jacs.5b01261
J. Am. Chem. Soc. 2015, 137, 9202−9205