

Substrate-Induced Covalent Assembly of a Chemzyme and Crystallographic Characterization of a Chemzyme–Substrate Complex

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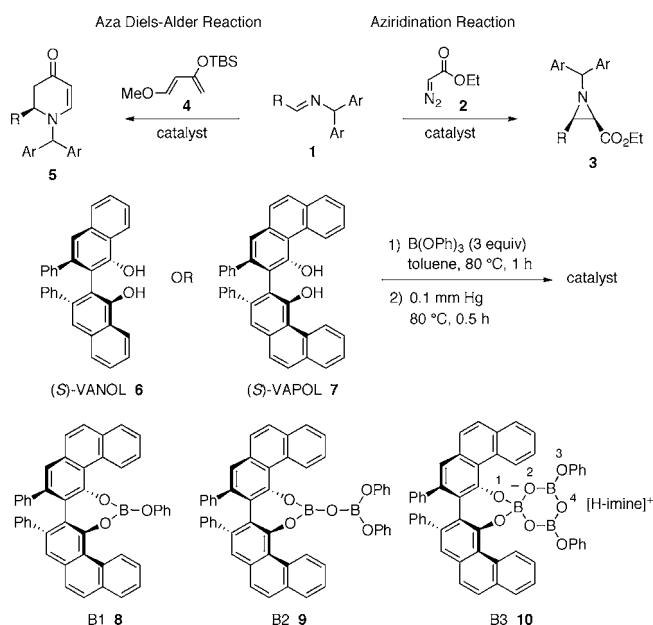
Abstract: A substrate induced covalent assembly of a highly organized chemzyme known to be effective in both catalytic asymmetric aziridination and aza Diels–Alder reactions is described and the information gained from which led to an efficient one-pot aziridination protocol. The crystal structures of two chemzyme–iminium complexes were elucidated by X-ray diffraction analysis that provides critical insights into the binding of the substrates with the chemzyme.

1. Introduction

In the long course of biological evolution, organisms have developed biosynthetic pathways to a diverse array of organic compounds by harnessing enzymes that can catalyze a great number of organic reactions with high selectivities and catalytic efficiencies under mild conditions. In modern organic synthesis, nonenzymatic chiral catalysts are playing an ever increasing role, but their development and rational design is a daunting challenge since the possibilities and strategies for function in nonproteogenic chiral systems are just beginning to be defined. In most cases, both proteinaceous and nonproteinaceous chiral catalysts, or chemzymes,^{1,2} are preformed or generated in situ in advance. We describe here a novel system involving a chemzyme whose covalent assembly is induced by its substrate. In addition, a detailed mapping of the interactions between the chemzyme and its substrate is elucidated by single-crystal X-ray diffraction analysis.

We have previously developed a catalyst that gives high asymmetric inductions for both the aza Diels–Alder³ and aziridination reactions⁴ (Scheme 1). This catalyst is prepared from the vaulted biaryl ligand VANOL **6** or VAPOL **7** by heating with 3 equiv of triphenylborate at 80 °C for 1 h and then removing all volatiles under high vacuum. The resulting catalyst derived from VAPOL is a mixture of the mesoborate **8** (B1) and the pyroborate **9** (B2) as suggested by the ¹H NMR and ¹¹B NMR spectra as well as by mass spectral analysis.⁵ The mixture is significantly in favor of the pyroborate species **9** with ratios varying from 4:1 to 20:1 depending on the exact protocol for catalyst formation.⁵ More recently, we have reported that the mixture of mesoborate **8** and pyroborate **9** is converted

Scheme 1



under the reaction conditions to the boroxinate **10** (B3) and we have provided NMR evidence that **10** is the actual catalyst in these reactions.⁶

2. Substrate-Induced Assembly

The fact that the mixture of mesoborate **8** and pyroborate **9** is converted to the boroxinate **10** under the reaction conditions in both the aza Diels–Alder and aziridination reactions suggests that perhaps this is caused by the imine since it is a substrate common to both reactions. Thus, a series of NMR experiments were designed to address this issue and to determine if the preformation of the pyroborate **9** was even necessary. The identification of these species is facilitated by the fact that

(1) Bjerre, J.; Rousseau, C.; Marinescu, L.; Bols, M. *Appl. Microbiol. Biotechnol.* **2008**, *81*, 1.

(2) Corey, E. J.; Chen, C. P.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5547.

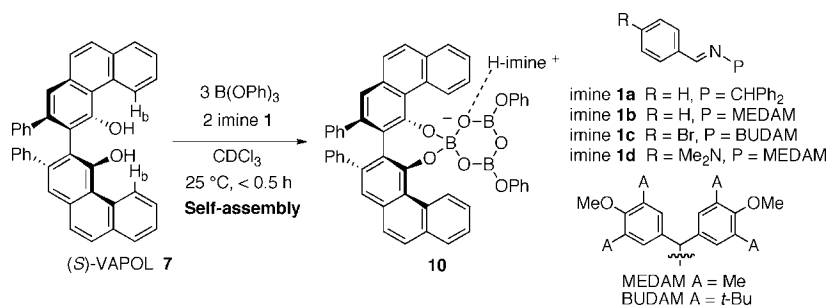
(3) Newman, C. A.; Antilla, J. C.; Chen, P.; Predeus, A.; Fielding, L.; Wulff, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 7216.

(4) For a review, see: Zhang, Y.; Lu, Z.; Wulff, W. D. *Synlett*, **2009**, 2715.

(5) Zhang, Y.; Desai, A.; Lu, Z.; Hu, G.; Ding, Z.; Wulff, W. D. *Chem.–Eur. J.* **2008**, *14*, 3785.

(6) Hu, G.; Huang, L.; Huang, R. H.; Wulff, W. D. *J. Am. Chem. Soc.* **2009**, *131*, 15615.

Scheme 2



the bay protons (H_b) of VAPOL and its derivatives are quite distinct (Scheme 2), and for VAPOL, this doublet is at $\delta = 9.77$ ppm (CDCl_3). Specifically, the question to be asked is whether an imine can cause the formation of the boroxinate **10** directly from VAPOL and commercially available B(OPh)_3 that is always partially hydrolyzed at room temperature (Scheme 2). As a control, (*S*)-VAPOL and 3 equiv of B(OPh)_3 were dissolved in CDCl_3 , and after 10 min, the ^1H NMR revealed very little reaction (Figure 1, entry 1). A small amount (3%) of the pyroborate **9** is observed as the doublet at $\delta = 9.22$ ppm and this does not change after 24 h. However, if a 1:3 mixture of VAPOL and B(OPh)_3 is treated with 2 equiv of imine **1b** at room temperature, a red solution is immediately formed, and in the time that it takes to perform ^1H NMR and ^{11}B NMR analysis, the boroxinate complex **10b** is formed in 76% yield as indicated by the doublet at $\delta = 10.31$ ppm (Figure 1, entry 2). The remainder is the free VAPOL ligand and a small amount of benzaldehyde from imine hydrolysis and the presence of the mesoborate **8** and pyroborate **9** can not be detected (Figure 1, entry 2). In contrast, the addition of the aziridine **3b** to a mixture of (*S*)-VAPOL and B(OPh)_3 does not induce the formation of a boroxinate species to any significant extent (Figure 1, entry

3), an observation consistent with the facile turnover observed for the reaction.⁵ The boroxinate **10** can be easily distinguished from the other boron species by ^{11}B NMR. Most three coordinate aryl borate compounds have very broad absorptions at 16–18 ppm in the ^{11}B NMR, and thus, it is difficult to distinguish one borate species from another. However, the increased spherical symmetry of a four coordinate boron leads to sharp lines in the spectrum and the negative charge of the borate causes an upfield shift. The boroxinate **10b** has a sharp absorption at 5.51 ppm (Figure 2, entry 2).

The traditional method for catalyst formation involves heating (*S*)-VAPOL with 3 equiv of B(OPh)_3 at 80 °C to generate the pyroborate **9** now known to be the precatalyst. When this procedure is monitored by NMR, the pyroborate **9** is formed in 53% yield along with a 6% yield of the mesoborate **8** which has a doublet at $\delta = 9.55$ ppm and 20% of unreacted VAPOL (Figure 1, entry 4). Treatment of this mixture with 2 equiv of the imine **1b** at room temperature within a few minutes results in the conversion of the colorless solution of **8** and **9** to a red solution of boroxinate **10b** in 81% yield with most of the free VAPOL ligand consumed as indicated by its spectra (Figures 1 and 2, entries 5). When this solution is treated with 2.4 equiv

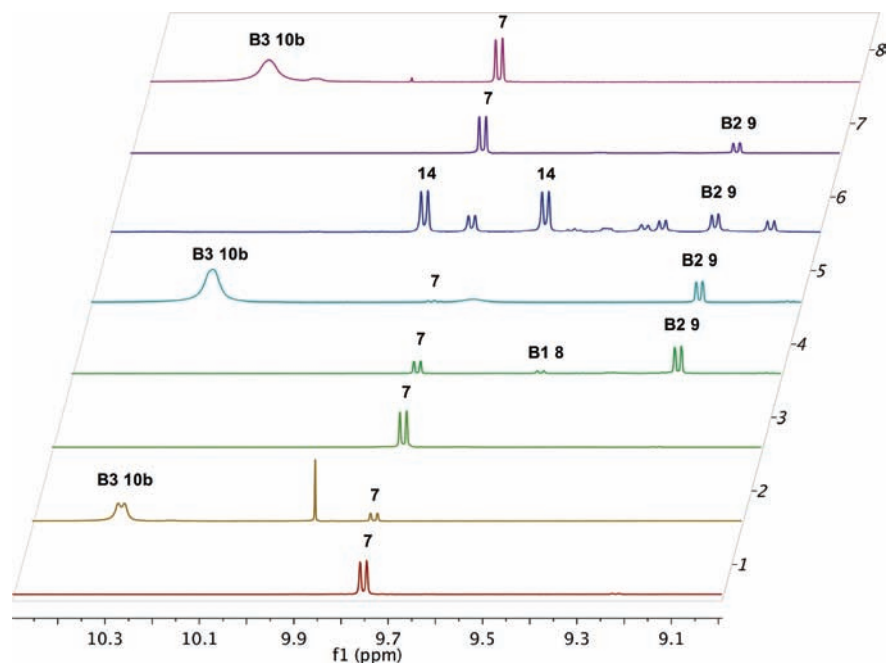


Figure 1. ^1H NMR spectra of the reaction mixture (Scheme 2) in CDCl_3 with Ph_3CH as internal standard. Entry 1: (*S*)-VAPOL plus 3 equiv B(OPh)_3 at 25 °C for 10 min. Entry 2: (*S*)-VAPOL plus 3 equiv B(OPh)_3 and 2 equiv imine **1b** at 25 °C for 10 min. Entry 3: (*S*)-VAPOL plus 3 equiv B(OPh)_3 and 2 equiv aziridine **3b** at 25 °C for 10 min. Entry 4: (*S*)-VAPOL plus 3 equiv B(OPh)_3 were heated at 80 °C in toluene for 1 h followed by removal of volatiles under vacuum for 0.5 h. Entry 5: 2 equiv of imine **1b** added to the solution in entry 4 for 10 min at 25 °C. Entry 6: 2.4 equiv of ethyl diazoacetate added to the NMR tube containing the solution in entry 5 and kept for 9 days at 25 °C. Entry 7: (*S*)-VAPOL plus 1 equiv triphenoxyboroxine **13** at 25 °C for 10 min. Entry 8: 2 equiv imine **1b** added to solution in entry 7 for 10 min at 25 °C.

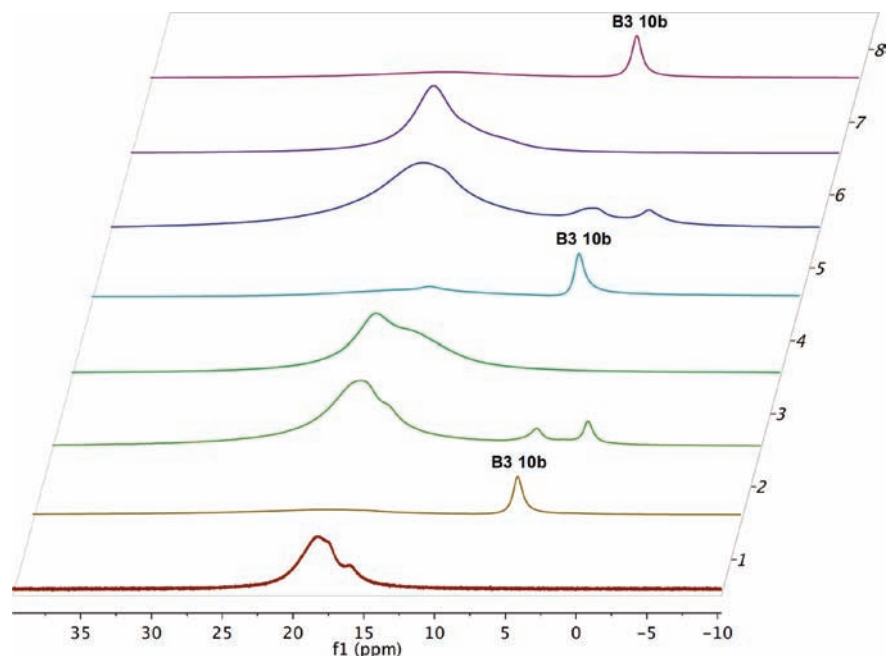
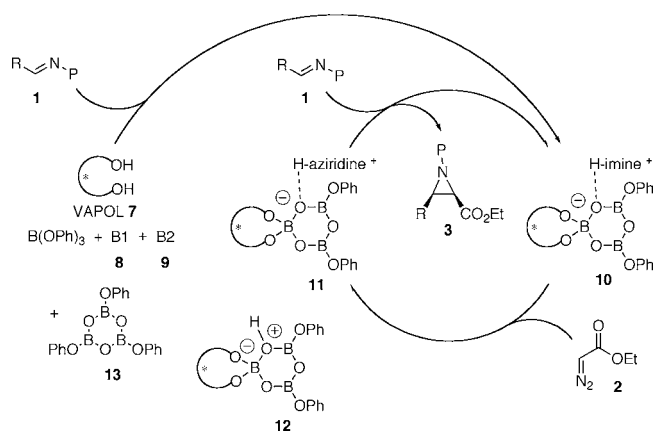


Figure 2. ^{11}B NMR spectra corresponding to the ^1H NMR spectra in Figure 1.

Scheme 3



of ethyl diazoacetate **2**, a complex mixture of compounds containing VAPOL is produced and most of the boroxinate has been consumed at the end of the reaction (Figure 1, entry 6). The two large doublets ($\delta = 9.83$ and 9.58 ppm) have been identified as the monoalkylation product of VAPOL **14** by ethyl diazoacetate (Figure 1).⁵

The formation of the three B–O–B linkages in the boroxine ring in the boroxinate catalyst **10** requires 3 equiv of water and the source of this most certainly results from partial hydrolysis of $\text{B}(\text{OPh})_3$.⁸ All commercial samples of $\text{B}(\text{OPh})_3$ that we have encountered are effective in the aziridination reaction and all contain varying amounts of partially hydrolyzed boron compounds with triphenoxyboroxine **13** (Scheme 3) identified as the major one based on NMR analysis of one particular sample. No further hydrolysis is required to give the boroxinate–imine complex **10** except only an exchange reaction of a phenol unit

in boroxine **13** with the VAPOL ligand. To test the efficacy of triphenoxyboroxine **13** as a source for catalyst formation, an independent sample of triphenoxyboroxine **13** was prepared⁹ and treated with an equimolar amount of VAPOL. The ^1H and ^{11}B NMR spectra do not reveal the presence of a boroxinate species but rather the presence of largely unreacted VAPOL (Figures 1 and 2, entries 7). However, addition of 2 equiv of imine **1b** to this mixture results in the immediate formation of a red color and the appearance of boroxinate **10b** in 55% yield (Figures 1 and 2, entries 8). This clearly demonstrates that triphenoxyboroxine **13** can serve as an alternative source of the boroxinate catalyst without the need to ensure that some water or water surrogate is present.

The results from the experiments outlined in Figures 1 and 2 indicate that the boroxinate catalyst **10** can be assembled by the imine **1** from VAPOL and a number of borate sources including $\text{B}(\text{OPh})_3$, the mesoborate **8**, the pyroborate **9**, and the boroxine **13**. The generation of the catalyst and the subsequent catalytic cycle are proposed in Scheme 3. In the initiation step, the presence of partially hydrolyzed borate species or of water is required (except for boroxine **13**) to generate the three B–O–B linkages in the boroxinate species **10**. Once the boroxinate catalyst **10** is assembled, then presumably the next step involves the reaction with ethyl diazoacetate **2** to give boroxinate–aziridine complex **11**. Turnover then would require the loss of aziridine and then incorporation of another molecule of the imine **1** to regenerate the boroxinate–imine complex **10**. While we have not been able to obtain any direct evidence for the presence of the protonated boroxinate species **12**, it is not clear if the overall conversion of the boroxinate–aziridine complex **11** to the boroxinate–imine complex **10** involves loss of aziridine to give the Brønsted acid **12** which then protonates the imine to give **10**, or if there is an associative reaction between **11** and the imine **1** which directly leads to the aziridine **3** and the boroxinate–imine complex **10**. The fact that this reaction turns over is consistent with the fact that aziridine is

(7) (a) Zhang, Y.; Lu, Z.; Desai, A.; Wulff, W. D. *Org. Lett.* **2008**, *10*, 5429. (b) Mukherjee, M.; Gupta, A. K.; Lu, Z.; Zhang, Y.; Wulff, W. D. *J. Org. Chem.* **2010**, *75*, 5643.

(8) As a control, purified $\text{B}(\text{OPh})_3$ gives after 24 h only a trace of boroxinate species **10a** utilizing 1 equiv of imine **1a** (see supporting information, section G).

(9) Cole, T. E.; Quintanilla, R.; Rodewald, S. *Synth. React. Inorg. Met.–Org. Chem.* **1990**, *20*, 55.

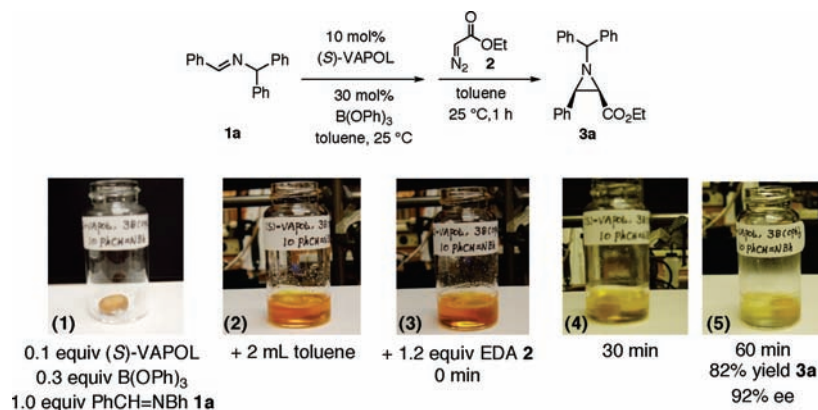
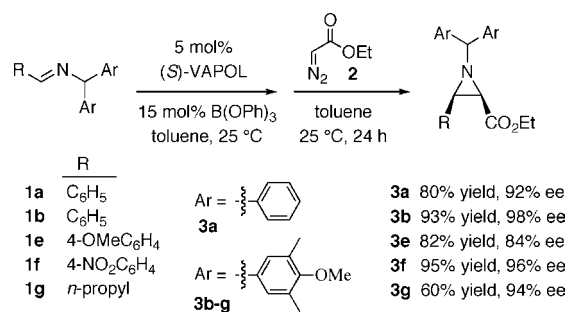


Figure 3. Illustration of boroxinate catalyst formation (red solution) in an open vial directly from VAPOL, B(OPh)₃ and imine and subsequent aziridination with EDA.

significantly slower in inducing boroxinate formation than the imine (Figure 1, entries 2 and 3).

The fact that the substrate-induced covalent assembly of the boroxinate **10** requires 3 equiv of water suggests that the reaction may not be sensitive to normal atmospheric conditions. Indeed, catalyst assembly can be performed at room temperature in a vial opened to air and the subsequent catalytic asymmetric aziridination as well (Figure 3). In the first Frame, a 20 mL vial is loaded with 0.1 mmol of (S)-VAPOL, 0.3 mmol B(OPh)₃, and 1.0 mmol of imine **1a**. When this mixture of three white solids is dissolved in 2 mL of toluene (used as commercially supplied), the resulting solution immediately takes on a red color (Frame 2). NMR analysis indicated that boroxinate species was generated in approximately 86% yield, similar to Figure 1, entry 2. After a few minutes, 1.2 mmol of ethyl diazoacetate is added and vigorous bubbling immediately ensues as indicated in Frame 3, and after 30 min, the red color has dissipated (Frame 4). After 60 min, the reaction is completed and the product is purified by column chromatography on silica gel to give aziridine **3a** in 82% yield and 92% ee which is essentially the same (82% yield, 94% ee) as previously reported⁵ for this reaction when initiated with the precatalyst and carried out under an argon atmosphere and rigorously dried glassware and solvents (Scheme 1). However, there are limits to the tolerance of water to this aziridination reaction. Addition of 1–3 equiv of water during catalyst formation with commercial B(OPh)₃ does not hinder the reaction of imine **1a**, but the addition of 5–10 equiv of water relative to the ligand results in extremely low conversion. Therefore, for reactions with very low catalyst loading (0.1–0.5 mol %), it is best to perform the reaction under an inert atmosphere with dried glassware and solvents under which conditions up to 500 turnovers have been observed for this reaction.⁵ Nevertheless, this simple procedure for one-pot catalyst generation and aziridination at room temperature under an argon atmosphere is effective with only 5 mol % catalyst as illustrated for imines ranging from the electron-rich **1e** to the electron-poor **1f** and to the aliphatic imine **1g** (Scheme 4).⁷ It should be pointed out that the asymmetric inductions in Scheme 4 are very close to those reported for catalysts prepared by first heating VAPOL and B(OPh)₃ to generate the precatalyst except for the *para*-methoxy imine **1e** where the % ee drops from 98% ee to 84% ee and the reason for this is not understood.^{7b} A variety of solvents are compatible with this protocol and give comparable results (Table S3 in Supporting Information).

Scheme 4

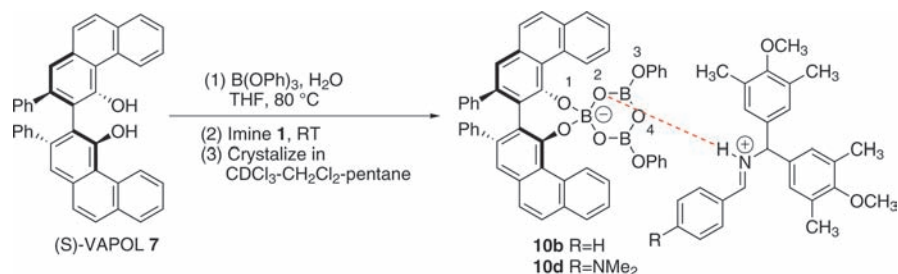


3. Crystallographic Studies

The chemzyme–substrate complex **10a** derived from the benzhydryl (Bh) imine **1a** could not be induced to form crystals suitable for an X-ray diffraction study. In a study directed to mapping the active site of this chemzyme, it was found that the *tetra*-methylidiansylmethyl (MEDAM) imines of the type **1b** as well as the *tetra*-*t*-butyldiansylmethyl (BUDAM) imines of the type **1c** proved to be superior substrates for the aziridination reaction giving higher asymmetric inductions and much greater rates of reaction (11–16 times faster than **1a**).⁷ We were delighted to find that both of the MEDAM imines **1b** and **1d** gave single crystals (both yellow) of the boroxinate–imine complexes **10b** and **10d** (Scheme 5). All of the data for the solid-state X-ray structures of **10b** and **10d** can be found in the Supporting Information. Structural parameters for **10b** and **10d** are available free of charge from the Cambridge Crystallographic Data Centre under reference number CCDC 784078 and 784079. The X-ray structure of **10b** not only confirms the boroxinate ion pair motif, but for the first time clarifies how the imine substrate docks with the catalyst. The structural analysis reveals the presence of an ion pair consisting of a protonated iminium ion and the boroxinate anion derived from a boroxine ring in which the tetra-coordinate boron is spiro-fused to the VAPOL ligand. This is a remarkable structure where the catalyst and substrate seem to fit together like a hand and a glove. This close fit makes possible the large number of noncovalent interactions observed between the boroxinate anion and the protonated iminium and these are summarized in Figure 4A.

Foremost among these is a hydrogen bond from the protonated iminium to the oxygen in the boroxinate ring that is attached to the four coordinate boron (O2) (Scheme 5). The H–O distance of 2.02 Å (Figure 4A, *d*₁) suggests a strong to moderate hydrogen bond^{10,11} and the chemical shift of this

Scheme 5



proton at 13.7 ppm is consistent with related species in which proton is on nitrogen not oxygen.⁶

The crystal structure of **10b** perhaps provides some clues as to the increased reactivity and enantioselectivity of the BUDAM and MEDAM imines relative to their benzhydryl counterparts.⁷ There are several $\text{CH}-\pi$ interactions^{12,13} and perhaps the most interesting is from an ortho-hydrogen on the MEDAM phenyl ring to one of the phenyl rings on the back end of the VAPOL ligand (Figure 4, d_3 4.14 Å).¹⁴ There is also a CH/π interaction between one of the MEDAM methyl groups and this same phenyl ring (Figure 4, d_2 4.42 Å). These interactions are easiest to see in the crystal structure of **10b** shown in Figure 4A. There are other $\text{CH}-\pi$ interactions including one from a MEDAM methyl to the end ring of a phenanthrene unit in the VAPOL ligand (Figure 4, d_4 3.83 Å). Consistent with these $\text{CH}-\pi$ interactions placing these methyl groups in the shielding region of various arene rings is the fact that the methyl groups of the MEDAM rings are desymmetrized in the ^1H NMR spectrum of complex **10b** and are observed as two singlets which are shielded relative to the free imine **1b** by 0.42 and 0.54 ppm (Figure 5). A similar upfield shift also occurs for the methyl groups in *t*-butyl substituents of BUDAM imine–catalyst complex.⁶ We have evidence that this shielding effect is not due to the protonation of imine because the same methyl groups of the imine-HCl salts do not shift significantly from those of

the free imine on ^1H NMR (Figure 5). Thus, the $\text{CH}-\pi$ interactions of the methyl and *t*-butyl groups of the MEDAM and BUDAM imines may contribute, for reasons of increased binding to the catalyst in the transition state, to the increased rates and asymmetric inductions of these imines relative to the benzhydryl imines.⁷ These interactions may also be related to the ease with which complex **10b** could be crystallized but not **10a**.

Another important noncovalent interaction between the catalyst and the substrate is a $\pi-\pi$ stacking interaction between the protonated benzyldiene iminium moiety and the phenanthrene rings of the VAPOL ligand. This can be seen in the space-filling model of the catalyst–substrate complex **10b** shown in Figure 4B where the boroxinate anion is in green. The $\pi-\pi$ stacking interaction occurs with an angle between the two planes of 4.4° from parallel and with a distance of 3.44 Å that seems to be in the optimal range for such an interaction.¹⁵ As a consequence of this $\pi-\pi$ stacking interaction, it is clear from Figure 4B that attack by a nucleophile from below would be blocked. Attack from the top face would correspond to *Si*-face addition which is what is observed with catalysts derived from (*S*)-VAPOL and (*S*)-VANOL ligands for both the aziridination and aza Diels–Alder reactions.³

The crystal structure of the catalyst–substrate complex **10d** with the *p*-dimethylaminophenyl imine **1d** has many of the same

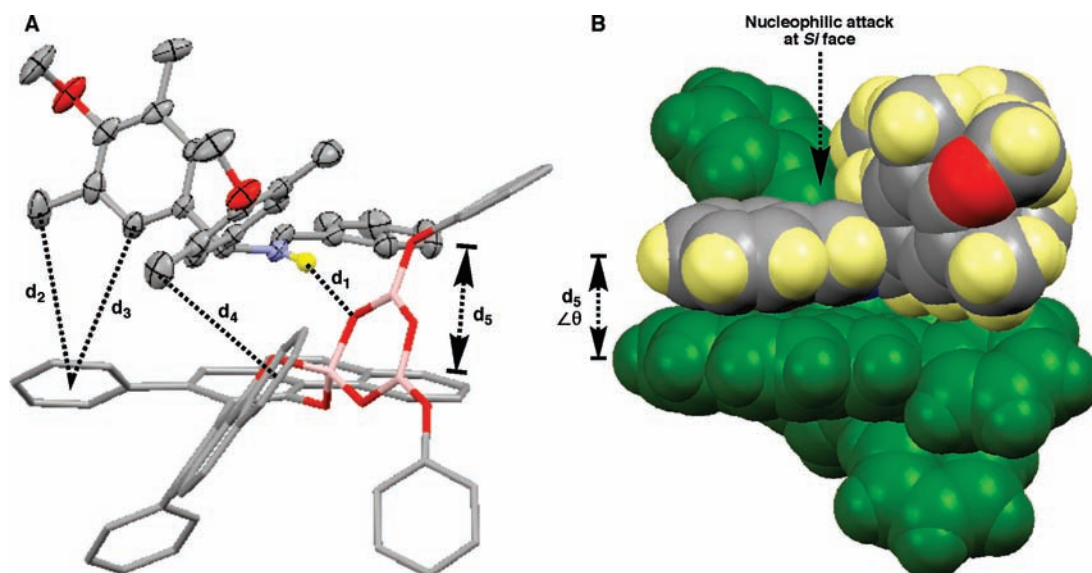


Figure 4. (A) Solid state structure of the chemzyme–substrate complex **10b** visualized by the Mercury program (C, gray; O, red; N, blue; B, purple; H, yellow). Calculated hydrogen atoms and solvent molecules were omitted for clarity. Some secondary interactions were proposed and highlighted: $d_1 = 2.02$ Å (H-bonding), $d_2 = 4.42$ Å ($\text{CH}-\pi$), $d_3 = 4.14$ Å ($\text{CH}-\pi$), $d_4 = 3.83$ Å ($\text{CH}-\pi$), $d_5 = 3.44$ Å ($\pi-\pi$ stack), $\theta = 4.4^\circ$ ($\pi-\pi$ stack). The iminium phenyl ring is displaced from the middle ring and end ring of phenanthrene by 1.44 and 1.33 Å, respectively (data not shown in figure). (B) Space-filling model of the complex **10b** rotated $\sim 180^\circ$ vertically relative to panel A to bring the $\pi-\pi$ stacking interaction into view. The boroxinate anion is given in green and the iminium cation is in traditional colors.

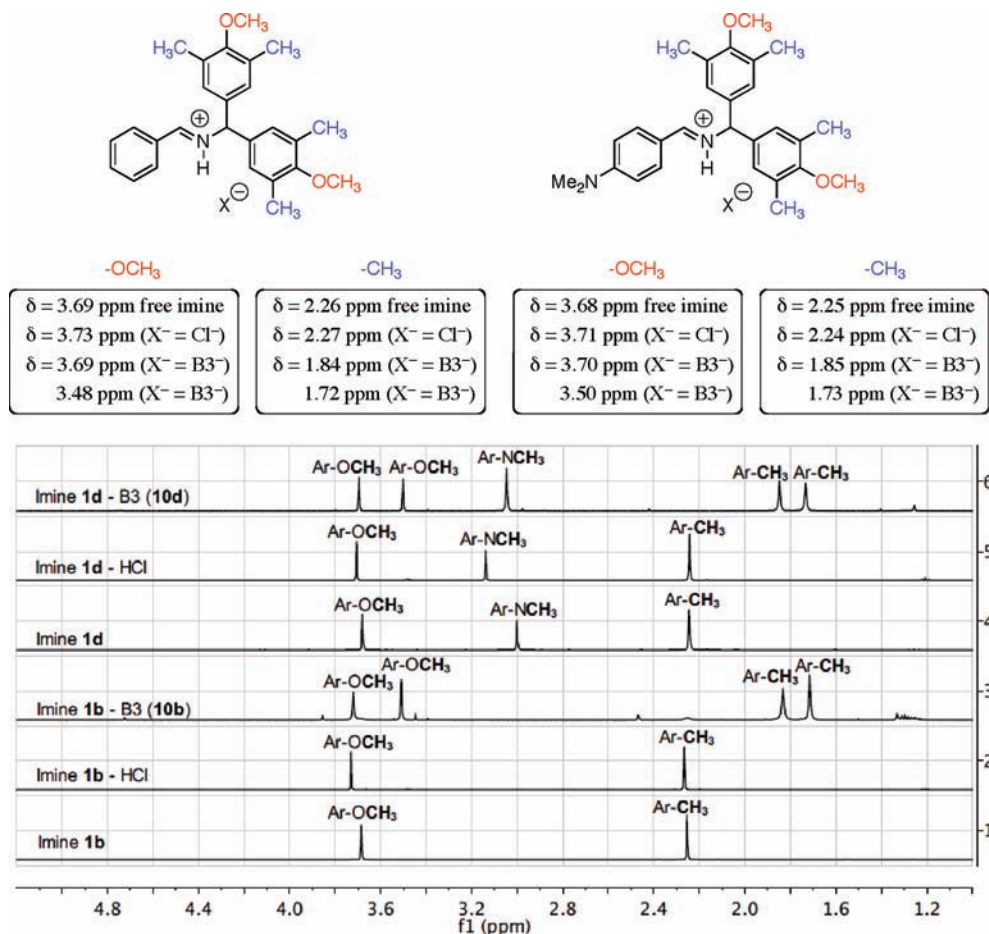


Figure 5. Chemical shifts of methyl and methoxy groups in various imines and iminiums in CDCl_3 with TMS as internal standard.

close contacts present in **10b** that can be seen in Figure 4A including a hydrogen bond between the protonated iminium and O-2 of the boroxinate which is 2.05 Å (Figure 6, d_1). Two of the $\text{CH}-\pi$ interactions in **10d** are similar to those in **10b** where the same methyl groups are interacting with the same aromatic ring (Figure 6, d_2 and d_4). A third $\text{CH}-\pi$ interaction (Figure 6, d_3) is present in **10d** that may also be present in **10b** but is a little outside of the normal range for $\text{CH}-\pi$ interactions in **10b**. The main difference between the structures **10b** and **10d** is that for **10d** the interaction of the aryl substituent of the iminium with the phenanthrene ring of the ligand forms an angle between the planes of these rings of 47°. This disfavoring of the $\pi-\pi$ stacking interaction in **10d** is consistent with the increased electron density that the dimethylamino groups imparts to the iminium and may be related to the fact that imine **1d** is not a substrate of the reaction.¹⁶

The structure of the chemzyme–substrate complex **10b** provides some insight as to why the VANOL and VAPOL ligands (Scheme 1) both give nearly identical asymmetric

inductions in the aziridination reaction.^{5,7} The $\pi-\pi$ stacking of the iminium ion involves the conjugated phenyl of the iminium stacked over the central ring of the phenanthrene of the VAPOL ligand and apparently the end ring of the phenanthrene is not needed. Removing the end ring from VAPOL **7** would of course produce the VANOL ligand **6** (Scheme 1) which would be expected to be capable of similar $\pi-\pi$ stacking observed for VAPOL in the complex **10b** bearing in mind that optimal $\pi-\pi$ stacking occurs when the rings are slipped.¹³

Finally, the chemzyme–substrate complex **10b** is capable of functioning as a catalyst for the aziridination reaction. Crystals of **10b** (10 mol %) catalyze the reaction of the MEDAM imine **1b** with ethyl diazoacetate and give the aziridine **3b** in 94% yield and 97% ee in methylene chloride at room temperature (Scheme 6) which is essentially identical to that previously reported with methylene chloride as reaction solvent⁷ and in the present work with toluene as solvent (Scheme 4). Thus, while this does not prove that the catalyst–substrate complex **10b** is part of the catalytic cycle, it does reveal that **10b** is not an artifact of crystallization and can at least return to the catalytic cycle. While the crystal structure of **10b** gives us a picture of how the imine substrates bind to the VAPOL boroxinate catalyst in the solid state, and perhaps in solution as well, the next step presumably involves the interaction of **10b** with ethyl diazoacetate and it is not clear what the structure of the chemzyme–substrate complex **10b** would tell us about the structure of the transition state for this process.

(10) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520.

(11) Jeffrey, G. A.; *An Introduction to Hydrogen Bonding*; Oxford University Press: New York, 1997.

(12) Nishio, M. *Tetrahedron* **2005**, *61*, 6923.

(13) Plevin, M. J.; Bryce, D. L.; Boisbouvier, J. *Nat. Chem.* **2010**, *2*, 466.

(14) Distances for CH/π interactions are defined as described in ref 13.

(15) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 1210.

(16) While the reaction of *p*-methoxyphenyl imine **1e** is slow (Scheme 4), the *p*-dimethylaminophenyl imine **1d** will not react with ethyl diazoacetate in 24 h.

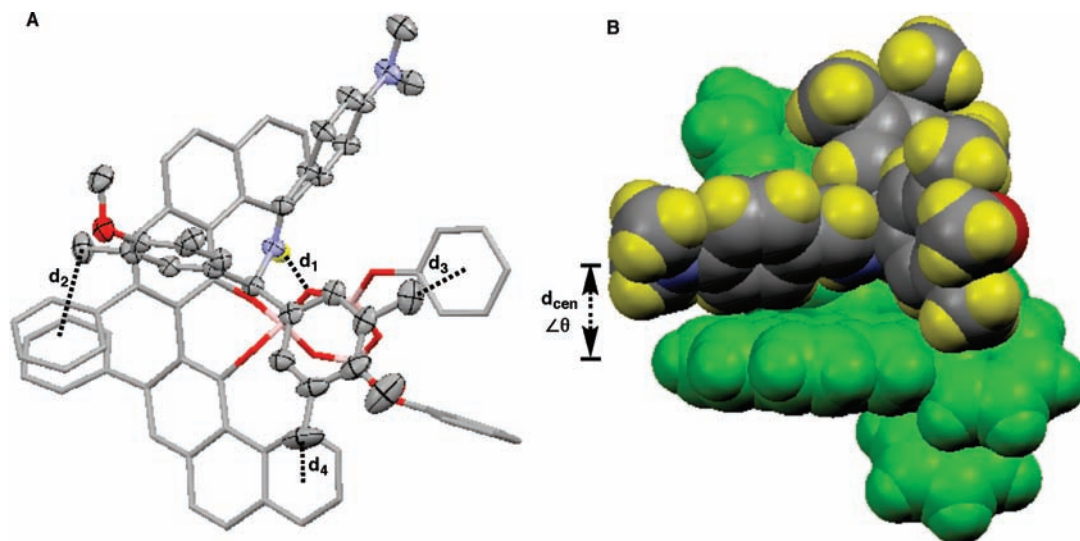
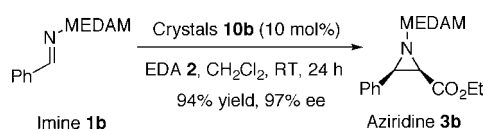


Figure 6. Crystal structure of B3-imine complex **10d** visualized by Mercury program. (A) Capped stick (anion) and ellipsoid (cation) display of the crystal structure. All calculated hydrogens and solvent molecules are omitted for clarity. Selected parameters are shown: $d_1 = 2.05$ Å (H-bonding), $d_2 = 3.87$ Å (CH- π), $d_3 = 3.65$ Å (CH- π), $d_4 = 4.14$ Å (CH- π), distances d_2 , d_3 and d_4 are from a methyl group to the center of aromatic ring. (B) Space-filling drawing of the structure with $d_{\text{cen}} = 4.52$ Å (distance from the center of phenyl ring of iminium cation to the end ring of phenanthrene), $\theta = 48.2^\circ$ (angle between iminium cation plane and phenanthrene plane). The boroxinate anion is colored in green to enhance contrast.

Scheme 6



4. Conclusions

Polyborate anions have been well documented in the literature and show richness in the diversity of their intrinsic structures.^{17–19} However, the mechanisms by which these structures are formed have not been investigated in detail and the applications of polyborate anions in asymmetric catalysis have, to the best of our knowledge, not been previously reported. The present work provides structural details of a new class of a highly organized chemzyme scaffold consisting of a polyborate anionic core assembled around a chiral vaulted bis-phenol ligand. The chemzyme assembly is induced by the imine substrate of the chemzyme. It has been suggested that substrate templating has played a role in the covalent formation of prebiotic catalysts and an example has been reported for a dipeptide-zinc

“mini-enzyme”.^{20,21} In the present case, the polyborate core of the chemzyme is assembled by an imine whose nitrogen substituent has been evolved to provide the greatest rates and highest enantioselectivities in an aziridination reaction.⁷ Crystal structures of the chemzyme–substrate complexes provide a particularly appealing vista of the variety and diversity of noncovalent interactions that are involved in the binding of the substrate to the chemzyme. These observations should hopefully serve to initiate new applications of polyborate chemistry and provide new insights into molecular recognition between a chemzyme and its substrate that would be important in the design of function in chemzymes.

Acknowledgment. This work was supported by a grant from the National Science Foundation (CHE-0750319). Professor Daniel Jones is acknowledged for assistance in mass spectrometric analysis and Dr. Daniel Holmes for insightful discussions on NMR experiments.

Supporting Information Available: Procedures for the preparation of new compounds and characterization data for all new compounds including cif files for **10b** and **10d**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (17) Beckett, M. A.; Coles, S. J.; Light, M. E.; Fischer, L.; Stiefvater-Thomas, B. M.; Varma, K. S. *Polyhedron* **2006**, *25*, 1011.
 (18) Schubert, D. M.; Visi, M. Z.; Knobler, C. B. *Inorg. Chem.* **2008**, *47*, 2017.
 (19) Beckett, M. A.; Bland, C. C.; Horton, P. N.; Hursthouse, M. B.; Varma, K. S. *Inorg. Chem.* **2007**, *46*, 3801.

- (20) Kochavi, E.; Bar-Nun, A.; Fleminger, G. *J. Mol. Evol.* **1997**, *45*, 342.
 (21) Fleminger, G.; Yaron, T.; Eizensstein, M.; Bar-Nun, A. *Origins Life Evol. Biosphere* **2005**, *35*, 369.