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How the Binding of Substrates to a Chiral Polyborate Counterion Governs Diastereoselection in an Aziridination Reaction: H-Bonds in Equipoise

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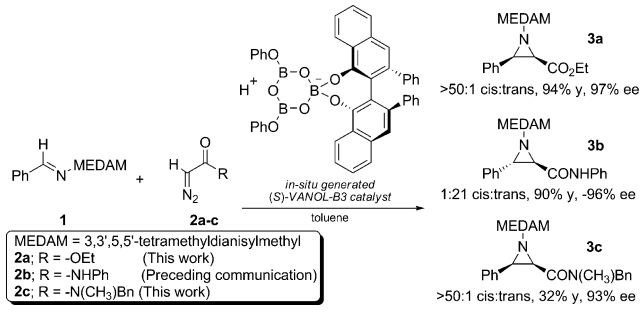
Abstract: The stereochemistry-determining step of the self-assembled chiral Brønsted acid-catalyzed aziridination reactions of MEDAM imines and three representative diazo nucleophiles has been studied using ONIOM(B3LYP/6-31G*:AM1) calculations. The origin of cis selectivity in the reactions of ethyldiazoacetate and trans selectivity in reactions of *N*-phenyldiazoacetamide can be understood on the basis of the difference in specific noncovalent interactions in the stereochemistry-determining transition state. A H-bonding interaction between the amidic hydrogen and an oxygen atom of the chiral counterion has been identified as the key interaction responsible for this reversal in diastereoselectivity. This hypothesis was validated when a 3° diazoamide lacking this interaction showed pronounced cis selectivity both experimentally and calculationally. Similar trends in diastereoselection were observed in analogous reactions catalyzed by triflic acid. The broad implications of these findings and their relevance to chiral Brønsted acid catalysis are discussed.

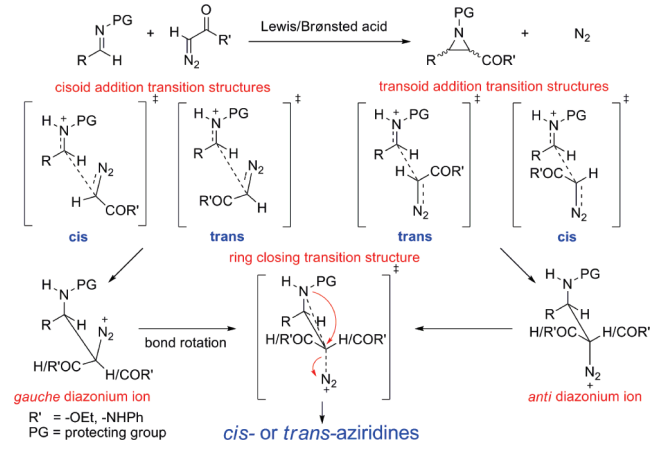
In the preceding communication (DOI 10.1021/ja1038648), we described the extension of our catalytic asymmetric *cis*-aziridination methodology[1] to the selective formation of *trans*-aziridines. This reversal of diastereoselectivity, which is accomplished by a simple change in one of the substrates used, was accompanied by the observation of the opposite facial selectivity to the imine (Scheme 1). Herein we present a combined experimental and computational study that examines the mode of catalysis of this unique catalyst and the origins of the enantio- and diastereoselection in this unprecedented universal catalytic asymmetric aziridination methodology.

Scheme 1. Universal Catalytic Asymmetric Aziridination



The mechanism of Lewis/Brønsted acid-catalyzed aziridination reaction of imines and diazo compounds has received little experimental and no calculational scrutiny.[2] The widely accepted mechanism invokes initial attack of the diazo nucleophile at the iminium carbon to form an α-diazonium-*β*-amino ester/amide intermediate. There are four limiting orientations for this attack: two cisoid approaches (quasi-[3 + 2]) and two antiperiplanar transoid approaches, as shown in Scheme 2.[3] This carbon−carbon bond-forming step is the enantioselectivity- and diastereoselectivity-determining step of the reaction.[4] Diastereoselection can be achieved if one of these approaches is preferred. This step is rendered enantioselective if the nucleophile can effectively discriminate between the *Si* and *Re* faces of the activated imine. After the carbon−carbon bond has been formed, N_2 is eliminated in an S_N2-like fashion from the diazonium intermediate (directly from the anti intermediates and after bond rotation from the gauche intermediates) to form the three-membered aziridine ring.

Scheme 2. General Mechanism of Aziridination Reactions of Imines and Diazo Compounds Catalyzed by Brønsted Acids (the Diastereomer of the Aziridine Formed from Each TS Is Indicated in Blue)



The active catalyst in our universal aziridination protocol is a self-assembled chiral polyborate Brønsted acid having a unique structure. Analogous to earlier studies with VAPOL, we found by ^{11}B and ^{1}H NMR spectroscopy that VANOL induces self-assembly of an identical VANOL-B_3 catalyst−imine complex.[5] The iminium ion can potentially be bound to one of the four oxygen atoms O1, O2, O3, or O4 of the chiral counterion (Figure 1). NBO analysis (RHF/3-21G) performed on the polyborate anion showed that the oxygen atom with the highest electron density is O2. Consequently, the O2-bound iminium ion was found to be the preferred geometry for the catalyst−iminium complex (Figure 1).[6] In addition to being bound to the most electron-rich oxygen, the O2-bound species also benefits from stabilizing noncovalent interactions between the MEDAM protecting group and the VANOL ligand. The biaryl system appears to effectively shield the *Re* face of the iminium ion, keeping the *Si* face accessible for nucleophilic attack. This is consistent with the absolute configuration of the *cis*-aziridine **3a**

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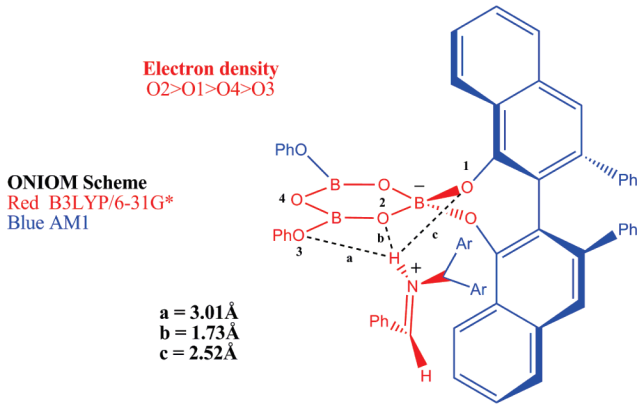


Figure 1. Optimized geometry of the (*S*)-VANOL-B_3 catalyst−imine complex. Also shown is the division of layers for the ONIOM calculations.

in the reaction of **1** and **2a**.[1] However, on the basis of Figure 1, one cannot rationalize the *Re*-facial attack that must occur in order to form the observed enantiomer of the *trans*-aziridine **3b** in the reaction of **1** and **2b**. There clearly must be some interaction between **2b** and the catalyst (which is absent in the reaction of **2a**) in the stereochemistry-determining transition state that reverses both the diastereoselectivity and the facial selectivity to the imine in this reaction.

Transition structures for the key carbon−carbon bond-forming step of the reactions of **1** with **2a**, **2b**, and **2c** catalyzed by the (*S*)-VANOL-B_3 catalyst were located using ONIOM(B3LYP/6-31G*:AM1) calculations.[7] The color scheme in Figure 1 illustrates the division of layers for the ONIOM calculations. In addition to the portions shown in red, the diazo compound was also calculated using the DFT method. All distances are reported in angstroms, and all reported energies are single-point energies of fully optimized geometries from the ONIOM calculations computed at the B3LYP/6-31+G* level of theory.[8] This approach has been reasonably successful in qualitative predictions of stereoselectivity in similar reactions.[9]

The lowest-energy transition structures TS1 and TS2 leading to the observed enantiomers of the *cis*- and *trans*-aziridines, respectively, in the reaction of **1** and **2a** are shown in Figure 2.[10] The key observation in both of these structures (and in all of the structures discussed below) is that unlike in the catalyst−imine complex depicted in Figure 1, the iminium proton is no longer closest to O2. As a general trend, protonated **1** is H-bonded to O1 in all of the cis transition structures and O3 in all of the trans transition structures. There also exists a stabilizing non-covalent interaction between the acidic α-CH of **2a** and O2/O1 of the catalyst core in TS1 and TS2.[11] In order to accommodate this interaction, attack of **2a** occurs via a syn-clinical approach relative to the iminium double bond in TS1 and via a trans-antiperiplanar approach in TS2 (similar to the cisoid and transoid transition structures in Scheme 2). TS1 is 3.1 kcal/mol lower in energy than TS2, and this difference is qualitatively consistent with the experimentally observed >50:1 cis/trans ratio for this reaction at room temperature. The transition structure for the formation of the minor enantiomer of the *cis*-aziridine was found to be 1.9 kcal/mol higher in energy than TS1, in good agreement with the experimental 97% ee.[12]

Transition structures TS3 and TS4 for the reaction of **1** and **2b** (Figure 2) were then located. Both TS3 and TS4 are characterized by non-covalent H-bonding interactions between (a) the iminium proton and O1/O3, (b) the α-CH of **2b** and O2, and (c) the amidic hydrogen of **2b** and O3/O1. While H-bonding interactions (a) and (b) are also present in TS1 and TS2, (c) is exclusive to TS3 and TS4. Therefore, the reversal of diastereoselectivity likely has its origins in the relative strength of H-bonding interaction (c) in TS3

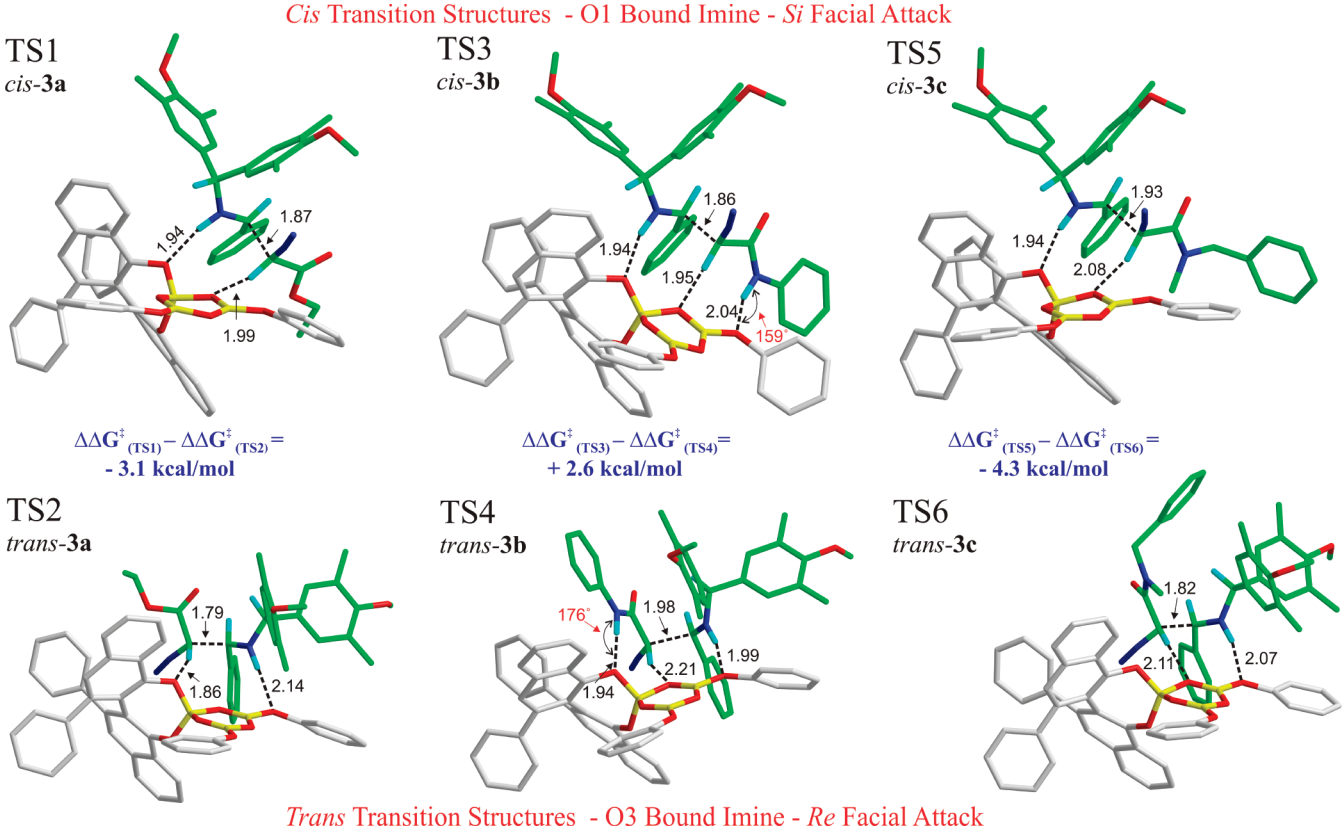


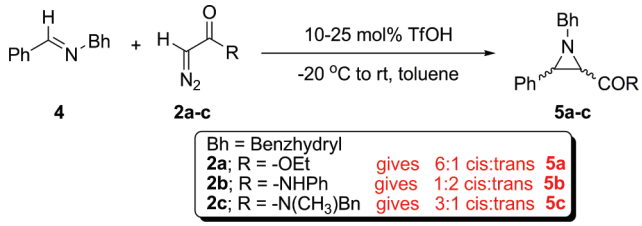
Figure 2. Geometries, key interactions, and relative energies of the diastereoselectivity-determining transition states in the reactions of **1** and **2a**−**c**.

versus TS4. H-bond strengths are characterized both by the bond distance and the donor−H−acceptor angle, with short, linear H-bonds having the strongest interactions.[13] The amidic hydrogen−oxygen H-bond is shorter (1.94 vs 2.04 Å) and closer to linearity (176 vs 159°) in TS4 than in TS3 (Figure 2). TS4 is 2.6 kcal/mol lower in energy than TS3, and this is consistent with the experimental trans selectivity.[14] Finally, the TS for the *Si*-facial attack of **2b** to give the minor enantiomer of the *trans*-aziridine was found to be 11.4 kcal/mol higher in energy than TS4.[12]

As a mechanistic probe of the importance of this third H-bonding interaction in impacting the diastereoselectivity, we decided to explore the aziridination reaction of **1** and *N*-methyl-*N*-benzyldiazoacetamide (**2c**). Being a 3° diazoamide, **2c** lacks the key amidic hydrogen, and we expected that the reaction of **1** and **2c** would revert to a cis-selective reaction analogous to the reaction of **1** and **2a**. Not surprisingly, this was indeed the case: the reaction carried out at room temperature gave almost exclusively the *cis*-aziridine (Scheme 1). Transition structures TS5 and TS6 were then located for the reaction of **1** and **2c** (Figure 2). Comparison of the pairs of transition structures TS3/TS5 and TS4/TS6 shows that all of the key distances are almost identical, and clearly, the only difference of note is the absence of the H-bond between the amidic hydrogen and O3/O1 in TS5 and TS6. As a result, TS5 is favored over TS6 by 4.3 kcal/mol, once again in complete accord with the experimental (>50:1) cis/trans ratio.

This is a unique template in asymmetric catalysis. We have shown that the polyborate catalyst self-assembles *only* in the presence of the imine substrate.[5] During a catalytic cycle, the boroxinate core executes key functions that are quintessential for asymmetric catalysis. It activates the imine electrophile by protonation and imparts enantioselection in nucleophilic additions to the imine by serving as a chiral counterion. Diastereoselection is achieved when the polyborate core *directs* the orientation and approach of the diazo nucleophile to the "active site". It also lowers the energy of the transition state via multiple H-bonding interactions with both substrates.

Scheme 3. Triflic Acid-Catalyzed Aziridination Reactions



On the basis of our understanding of the non-covalent interactions that stabilize the transition states in the aziridination reactions catalyzed by the B_3 catalyst and the idea that the triflate anion could function as a H-bonding counterion,[15] we decided to explore the aziridination reactions of **4** with **2a**,[2b] **2b**, and **2c** catalyzed by triflic acid. Our hypothesis was that in the event that the three oxygen atoms of the triflate anion could stabilize the aziridination transition state in a manner similar to our B_3 catalyst, we could have tunable diastereoselectivity even in this simple reaction, depending on the diazo nucleophile used. To our delight, identical to the trends observed in our system, we observed trans-selective aziridination in the reaction of **4** and **2b** and *c*is-selective aziridination in the reactions of **4** and **2a**/**2c** (Scheme 3).[16] The trans-antiperiplanar orientation of the double bonds of **4** and **2b** in TS8 (Figure 3) sets up the three strong H-bonding interactions with the triflate anion, virtually identical to the situation in TS4. While this result reinforces the validity of our model, it also emphasizes the importance of considering multiple non-covalent interactions as a control element in other Brønsted acid-catalyzed aziridinations.[17]

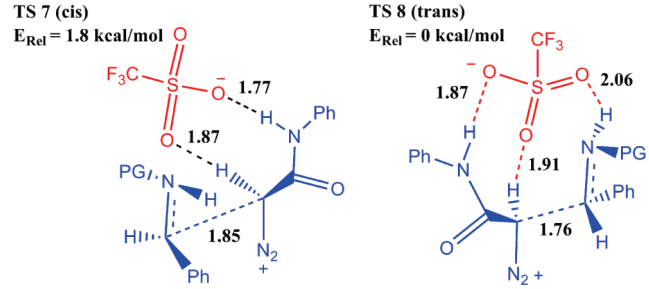


Figure 3. Transition structures TS7 and TS8 leading to the minor (cis) and major (trans) products in the triflic acid-catalyzed reaction of **4** and **2b**.

The mode of catalysis described in this work adds a new dimension to counterion catalysis by integrating into it some of the key features of H-bonding catalysis. We are currently investigating the application of this highly tunable "template catalyst" to a wide variety of nucleophilic additions to imines and carbonyl compounds.

Acknowledgment. This work was supported by NSF Grant CHE-0750319.

Supporting Information Available: Experimental details, coordinates of all calculated structures, alternative transition structures, mechanistic discussions, and pdb files. This material is available free of charge via the Internet at http://pubs.acs.org.

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(3) Intermediate orientations are also possible on the basis of the steric bulk of the substrates. If both faces of the imine are considered, there are eight limiting orientations. Cisoid attack leads to gauche intermediates, whereas transoid attack leads to anti intermediates. The terminology used here is similar to that in the following reference: Aggarwal, V. K.; Harvey, J. N.; Richardson, J. *J. Am. Chem. Soc.* **2002**, *124*, 5747–5756.
(4) On the basis of the relative rates for *p*-substituted imines, it has been proposed that the C−C bond-forming step might also be the rate-determining step of a Lewis acid-catalyzed aziridination reaction (see ref 2c).
(5) See the Supporting Information for spectra showing the existence of the VANOL-B_3 catalyst. For VAPOL-B_3 studies, see: Hu, G.; Huang, L.; Huang, R. H.; Wulff, W. D. *J. Am. Chem. Soc.* **2009**, *131*, 15615–15617.
(6) See the Supporting Information for higher-energy optimized complexes.
(7) (a) Svensson, M.; Humbel, S.; Morokuma, K. *J. Chem. Phys.* **1996**, *105*, 3654–3661. (b) Vreven, T.; Morokuma, K. *J. Comput. Chem.* **2000**, *21*, 1419–1432. (c) Dapprich, S.; Koma'romi, I.; Byun, K. S.; Morokuma, K.; Frisch, M. J. *J. Mol. Struct.* **1999**, *461*, 1–21.
(8) The reported energies do not include zero-point energy (zpe) or entropy corrections, since frequency calculations at the B3LYP/6-31+G* level of theory would have been prohibitive. The zpe- and entropy-corrected energies from the ONIOM calculations, PCM single-point energy calculations using other DFT methods, and relevant discussions are included in the Supporting Information.
(9) (a) Dudding, T.; Houk, K. N. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5770–5775. (b) Simón, L.; Goodman, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 4070–4077. (c) Anderson, C. D.; Dudding, T.; Gordillo, R.; Houk, K. N. *Org. Lett.* **2008**, *10*, 2749–2752. (d) Li, N.; Chen, X.-H.; Song, J.; Luo, S.-W.; Fan, W.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 15301–15310.
(10) See the preceding communication for a discussion of facial bias in the formation of *cis*- and *trans*-aziridines in the reactions of **1** and **2a**/**2b**.
(11) The acidity of the α-H of diazo compounds is well-established. Even a simple base such as DBU has been shown to cause deprotonation. See: (a) Jiang, N.; Wang, J. *Tetrahedron Lett.* **2002**, *43*, 1285–1287. (b) Xiao, F.; Liu, Y.; Wang, J. *Tetrahedron Lett.* **2007**, *48*, 1147–1149. (c) Wang, W.; Shen, K.; Hu, X.; Wang, J.; Lui, X.; Feng, X. *Synlett* **2009**, 1655–1658. For a review, see: (d) Maas, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 8186–8195. Numerous other transition structures similar to TS1 and TS2 that did not have this non-covalent interaction were also located. While they

reproduced the diastereoselectivity, they were on an average 2−4 kcal/mol higher in energy than either TS1 or TS2 (see the Supporting Information).
(12) See the Supporting Information for structures and detailed discussion.
(13) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543.
(14) Isomerization of **1** to the (*Z*)-imine and approach of **2b** identical to TS3 would also result in the observed enantiomer of *trans*-**3b**. This possibility was considered and found to be higher in energy (see the Supporting Information for coordinates of this structure).
(15) Jacobsen and co-workers recently illustrated the concept of "cooperative catalysis" in Brønsted acid-catalyzed reactions using chiral ureas/thioureas in a series of elegant publications. In one example, hydrogen bonding to a triflate anion is invoked (reference 15d). See: (a) Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968–970. (b) Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 15358–15374. (c) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887–890. (d) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986–990.
(16) These reactions are slow (imine consumption is not always complete in 24 h) and are typically accompanied by some decomposition. See the Supporting Information for full experimental details.
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