

Evidence for a Boroxinate Based Brønsted Acid Derivative of VAPOL as the Active Catalyst in the Catalytic Asymmetric Aziridination Reaction

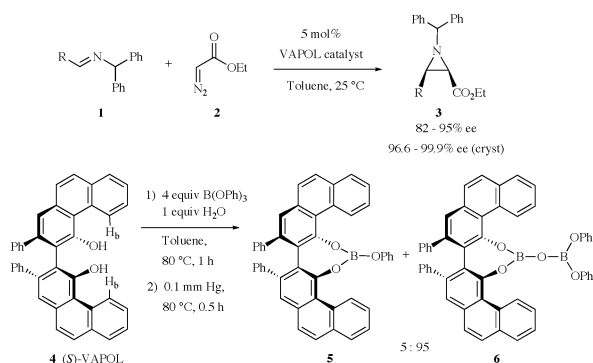
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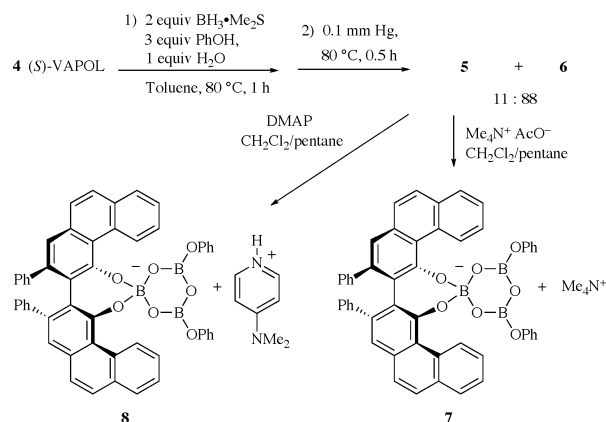
Investigations over the past decade have inveterated the privileged nature of VAPOL (and VANOL) as a ligand in the catalytic asymmetric aziridination reaction (AZ reaction) of imines with diazo compounds.^{1,2} With ethyl diazoacetate (EDA, **2**), ethyl aziridine-2-carboxylates are obtained with high cis-selectivity and enantioselectivity from benzhydryl imines derived from a range of aldehydes including 1°, 2°, and 3° aliphatic aldehydes and from a range of electron-rich and -poor aryl aldehydes (Scheme 1).^{1g} More recently, we reported that even higher asymmetric inductions could be obtained with certain substituted benzhydryl imine derivatives.^{1h} Our studies have revealed that the procedure for catalyst formation generates a mixture of two species which we tentatively identified as mesoborate **5** and pyroborate **6** (Scheme 1).^{1g} The present work suggests that the active catalyst is not a Lewis acid of the type **5** or **6** but in fact a Brønsted acid of singular structure.

Scheme 1



The structural assignment of pyroborate **6** was based on its ¹H and ¹¹B NMR spectra and on its high resolution mass spectrum.^{1g} Efforts to obtain solid state structural support for the assignment of pyroborate **6** were thwarted by the fact that **6** is not crystalline. In this regard, we were drawn to a report by Aldridge and co-workers who were able to structurally characterize a bis-Lewis base adduct of a simple pyroborate and acetate ion.³ In the procedure for the generation of **6** shown in Scheme 1, the excess B(OPh)₃ is not removed under high vacuum. In an effort to generate a cleaner sample of pyroborate **6**, the procedure outlined in Scheme 2 was developed with the more volatile BH₃·Me₂S which resulted in a 11:88 mixture of mesoborate **5** to pyroborate **6** with ≤10% of unreacted VAPOL remaining. Subsequent treatment of this mixture with 1 equiv of tetramethylammonium acetate followed by crystallization from CH₂Cl₂ and pentane gave diffraction quality crystals. X-ray diffraction analysis of these crystals revealed that the compound produced from this reaction was not the bis-Lewis base adduct of pyroborate **6** and an acetate ion. Quite remarkably, these crystals proved to be the ion pair **7** consisting of the tetramethylammonium cation and an anion formed from a boroxine ring in

Scheme 2



which one of the three borons forms a spiroborate anion (boroxinate) with a molecule of VAPOL.

The crystal structure of **7** reveals that three of the methyl groups in the tetramethylammonium ion have close contacts with the aromatic rings of the boroxinate anion (Figure 1). These contacts are less than the sum of the van der Waals radii of an sp³ carbon (2.0 Å) and an sp² carbon (1.7 Å) and are reminiscent of the cation-π interactions described by Dougherty and Stauffer.^{4,5} These interactions occur with one of the phenanthrene rings of the VAPOL ligand and also with one of the phenyloxy rings of the boroxinate core which folds up to meet the tetramethylammonium cation. The twist angle about the biaryl axis is 55° in boroxinate **7** which is to be compared with 79° in the free VAPOL ligand.⁶

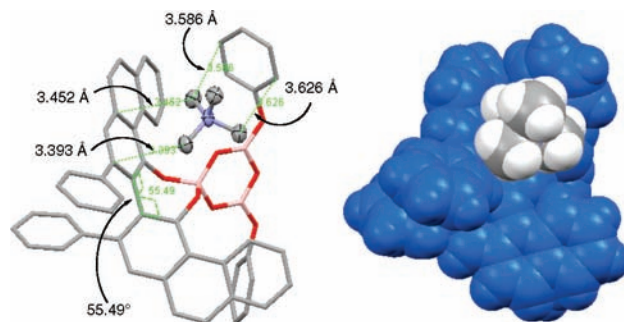


Figure 1. Crystal structure of the boroxinate ammonium salt **7** visualized by the Mercury Program.

The redistribution of the pyroborate **6** into the boroxinate **7** mediated by an acetate ion was quite unexpected. In an effort to determine if this was a function of the bidentate nature of the acetate ion, an attempt was made to trap the pyroborate **6** with a monodentate Lewis base, 4-dimethylamino pyridine (DMAP), that we hoped would mimic the imine substrates in the AZ reaction.

Treatment of the 11:88 mixture of **5** and **6** generated as shown in Scheme 2 with 1 equiv of DMAP gave the DMAP complex **8** which crystallized from solution in 23% yield. As indicated in Figure 2, this compound also has a boroxinate core that is complexed with a protonated DMAP. The key interaction in this complex is the hydrogen bond between the protonated nitrogen and one of the oxygens of the boroxine ring that is attached to the four-coordinate boron in which the N–O distance is 2.850 Å. The hydrogen was initially located closer to the nitrogen than to the oxygen, and further refinement was consistent with proton transfer to the nitrogen with an N–H bond of 1.006 Å. The hydrogen bond also appears to be bifurcated^{7,8} with an additional interaction with one of the oxygens on the VAPOL ligand. The H–O_{boroxine} distance is 1.844 Å, and the H–O_{VAPOL} distance is 2.458 Å. There also appears to be a π – π stacking interaction¹⁰ (3.489 Å) between a phenanthrene ring of the VAPOL ligand and the pyridinium ion of the protonated DMAP. The two ring systems are 6.5° from parallel. Finally, there appears to be a CH– π interaction⁵ (3.244 Å) between an *ortho*-hydrogen on the DMAP ring and one of the phenoxy rings of the boroxine system. It is interesting to note that this phenoxy ring seems to have folded to meet the DMAP unit, whereas the other phenoxy ring is projected out away from the boroxinate complex (Figure 2).

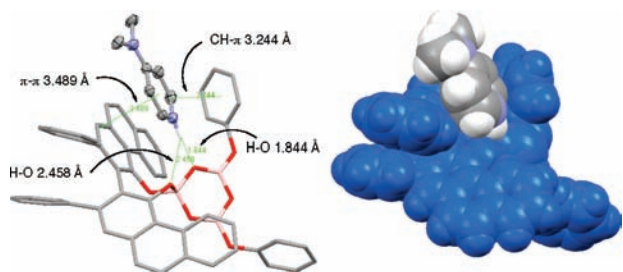


Figure 2. Crystal structure of boroxinate–pyridinium complex **8** visualized by the Mercury Program.

The ¹¹B and ¹H NMR spectra of the DMAP–boroxinate complex **8** are quite distinctive (Figure 3, spectra b and e). Three-coordinate borate esters typically have broad absorptions for the boron between 16–20 ppm in CDCl₃. The ¹¹B NMR spectrum of B(OPh)₃ reveals an absorption at 16.5 ppm. The unsymmetrical pyroborate **6** has two broad absorptions at 18.3 and 16.2 ppm in CDCl₃, and for comparison this spectrum is shown in Figure 3 (spectrum a).¹⁸ Since ¹¹B is a quadrupole, the sharpness of the absorption is related to the spherical symmetry around the boron, and this is reflected in the appearance of the ¹¹B NMR spectrum of the DMAP complex **8** (Figure 3, spectrum b). The two three-coordinate borons in **8** appear as a very broad absorption at 19.31 ppm, and the four-coordinate boron as a very sharp peak at 5.54 ppm with an integration of 2:1, respectively (not shown). An upfield shift for the four coordinate boron is expected as a result of the increased electron density around the boron in the borate anion. For example, the ¹¹B NMR absorption for LiB(OPh)₄ is at 3.0 ppm.¹¹ We are not aware of any boroxinate structures with which to compare the ¹¹B shifts in the DMAP complex **8**, but an adduct of piperidine and trimethylboroxine has been reported to have two signals in CD₂Cl₂ at 32.4 and 6.0 ppm.¹²

The most distinctive absorption for the DMAP complex **8** in the ¹H NMR spectrum is the bay-region doublet at 10.38 ppm (Figure 3, spectrum e). The bay proton of VAPOL (H_b in **4** in Scheme 1) is a very useful spectroscopic handle since it is shifted downfield by ~2 ppm from all other protons in the VAPOL ligand. The bay proton for free VAPOL is found at 9.77 ppm, that for the VAPOL

mesoborate **5** at 9.51 ppm, and that for the pyroborate **6** at 9.22 ppm (Figure 3, spectrum d).

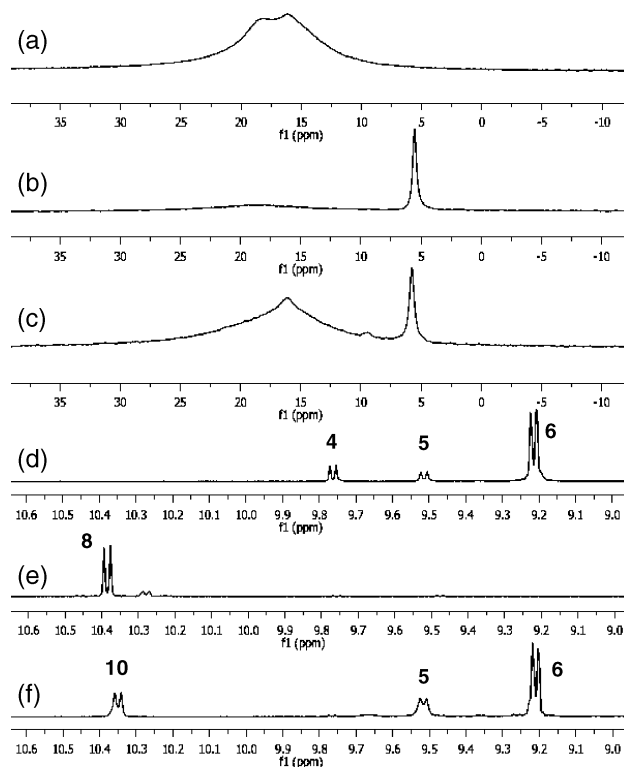
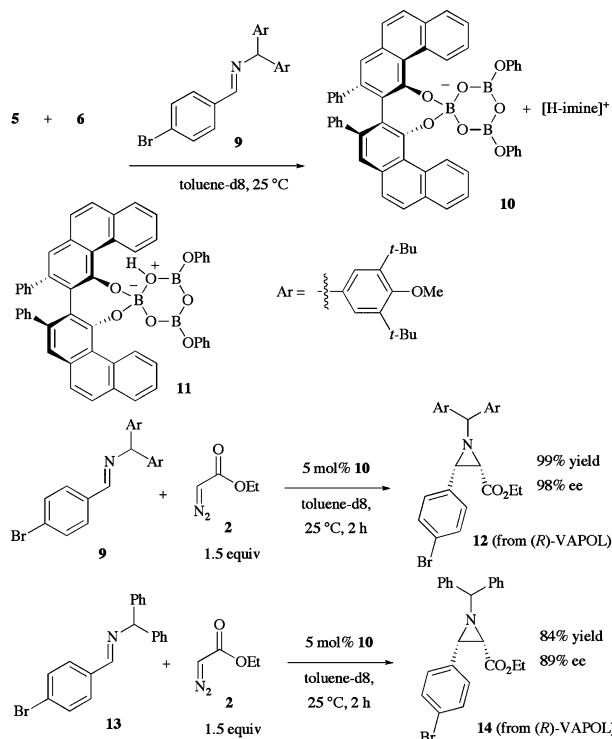


Figure 3. (a and d) ¹¹B and ¹H NMR spectra of a mixture of **4**, **5**, and **6**. (b and e) ¹¹B and ¹H NMR spectra of DMAP complex **8**. (c and f): ¹¹B and ¹H NMR spectra of **5**, **6**, and imine complex **10**.

We have recently shown that tetrabutylidiansylmethyl (BUDAM) imines of the type **9** (Scheme 3) will react with ethyl diazoacetate in the presence of the VAPOL–B(OPh)₃ catalyst to give aziridines with exceptionally high asymmetric inductions.^{1h} Treatment of the mixture of **5** and **6** prepared as indicated in Scheme 2 with 1 equiv of the imine **9** leads to the formation of a complex that did not form single crystals. This complex has been tentatively assigned as the ion pair **10** consisting of the VAPOL boroxinate anion and the protonated form of imine **9**. This assignment is made on the basis of its ¹¹B and ¹H NMR spectra, part of which are shown in Figure 3 (spectra c and f). The ¹¹B NMR spectrum reveals a sharp peak for **10** at 5.7 ppm similar to that observed for the DMAP complex **8** (5.5 ppm). In addition, a bay region doublet for **10** is observed at 10.35 ppm which is also similar to that observed for the DMAP complex **8** (10.38 ppm). The proton of the protonated DMAP in **8** is found at 12.32 ppm, and that for the protonated imine **9** in **10** is found at 13.65 ppm (see Supporting Information).

The initial preparation of the mixture of **5** and **6** from VAPOL and 2 equiv of BH₃·Me₂S (Scheme 2) was developed with the intention of optimizing the formation of the pyroborate **6**. This stoichiometry does not provide enough boron for the formation of the boroxinate **10**, and this is presumably the reason that the ¹H NMR spectrum of **10** reveals the substantial presence of the mesoborate **5** (9.51 ppm) and the pyroborate **6** (9.22 ppm) (Figure 3, spectrum f). However, if **10** is prepared from VAPOL, 4 equiv of B(OPh)₃, 1 equiv of H₂O, and then 3 equiv of imine **9**, a clean solution of **10** is generated containing 1% VAPOL, <1% of **5**, and 5% of **6** (see Supporting Information). The viability of the species **10** to function as a catalyst for the AZ reaction was then examined. Treatment of **9** and EDA with 5 mol % of **10** gave the aziridine **12**

Scheme 3



in 99% yield and 98% ee which compares with the reported data for this reaction in the AZ reaction (98% yield and 99% ee).^{1h,13} The ion pair **10** generated from the imine **9** will also catalyze the reaction of an imine with a different *N*-substituent. The aziridine **14** was produced in 84% yield and 89% ee, and we have previously observed that this aziridine can be obtained from imine **13** in 78% yield and 90% ee with catalysts generated from B(OPh)₃.^{1g,13}

The original optimized procedure^{1g} for the preparation of the aziridination catalyst involved reacting VAPOL with 3 equiv of B(OPh)₃, and this is consistent with a boroxinate as the active catalyst. The same 1:3 stoichiometry was also optimal in a catalyst for an asymmetric heteroatom Diels–Alder reaction.¹⁴ Neither procedure however involved the addition of any H₂O. The formation of a boroxine requires 3 equiv of H₂O. The success and reproducibility of the AZ reaction apparently have depended on the fact that commercial B(OPh)₃ is never pure and contains partially hydrolyzed boron-containing compounds.

Thus if the boroxinate is the active catalyst in the AZ reaction, then after the aziridine is liberated, the resulting species would be the protonated boroxinate **11** although we have not been able to detect this species. Treatment of **10** with 1.2 equiv of EDA results in the quantitative formation of **12** and to the loss of all absorptions below 10 ppm in the ¹¹B NMR (see Supporting Information). Ostensibly, **11** could be either a chiral Lewis acid or a chiral

Brønsted acid, but given the structure of the DMAP boroxinate complex **8** and the similarities of the ¹H and ¹¹B NMR spectra of **8** and **10**, it is considered likely that the imine **9** is bound in **10** in a protonated form and that the AZ reaction involves a chiral Brønsted acid and not a chiral Lewis acid as had been assumed.¹⁵ The implications of the discovery of this new class of chiral Brønsted acids will be reported in due course.

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Supporting Information Available: Synthetic procedures and spectral data for all new compounds and X-ray diffraction data and cif files for **7** and **8**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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