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The *iso*-VAPOL Ligand: Synthesis, Solid-State Structure and its Evaluation as a BOROX Catalyst

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ABSTRACT. The new vaulted biaryl ligand *iso*-VAPOL is an isomer of VAPOL but has the chiral pocket of VANOL. The synthesis of *iso*-VAPOL involves a cycloaddition/electrocyclization cascade (CAEC) similar to one that is used for VAPOL except that the starting material for *iso*-VAPOL is less than one-tenth the cost. The solid-state structure of *iso*-VAPOL was determined as well as that of VANOL since it had not been previously reported. The structures of *iso*-VAPOL and VANOL are compared to the known solid-state structure of VAPOL and it is found that all three ligands have the cisoid conformations in the solid-state; the dihedral angle between the two aryl groups is less than 90°. In addition, all three ligands pack in the solid-state with no inter-molecular hydrogen bonds. This is the opposite to what has been reported for BINOL where all known structures exist with transoid conformations where the dihedral angle is >90° and where the BINOL units pack with hydrogen bonds between neighboring BINOL units. Spectroscopic evidence including ^{1}H and ^{11}B NMR spectra are presented which indicate that the *iso*-VAPOL ligand will form BOROX catalysts with $B(OPh)_3$ in much the same way as VAPOL catalysts which have previously reported and characterized both by spectroscopy and X-ray crystallography. Support for the BOROX catalysts can also be taken from the fact that *iso*-VAPOL BOROX catalysts give essentially the same asymmetric inductions as the VAPOL BOROX catalyst over a range of substrates.

1. Introduction

We first introduced the vaulted biaryl ligands VANOL and VAPOL in 1993 as ligands for an aluminium catalyst in an asymmetric catalytic Diels-Alder reaction.[1] In that particular system, an aluminum Lewis acid derived from VAPOL gave much higher asymmetric inductions than did the corresponding VANOL catalyst. Since that time these ligands have been incorporated into a variety of catalysts whose effectiveness has been evaluated in over two-dozen different catalytic asymmetric reactions. Given the deeper chiral pocket of the VAPOL ligand it might have been expected that VAPOL would be superior to VANOL in all applications. This is not the case as VANOL catalysts have proven dominant in a substantial fraction of these applications. While VAPOL was the optimal ligand for an aluminum catalyst in the Diels-Alder reaction,[1] a VANOL aluminum catalyst proved preeminent in a Baeyer-Villiger reaction.[2] VAPOL was the ligand of choice in a Mannich reaction with a zirconium catalyst,[3] whereas, VANOL was found optimal in a titanium catalyst for asymmetric hydrogenation.[4] For those reactions in which there is turnover of the free ligand, VAPOL proved paramount in a boron mediated Petassis reaction,[5] while VANOL proved the most viable in a boron mediated propargylation of ketones[6] and also in a zinc mediated Michael addition of alkynes.[7] The deeper chiral pocket of VAPOL does seem to have won out for hydrogen phosphate derivatives of VANOL and VAPOL since all twelve of the applications reported to date with these Brønsted acid catalysts have faired better with VAPOL. These include the amidation[8] and imidation[9] of imines, the asymmetric reduction of imines,[10] desymmetrization of aziridines,[11] benzoyloxylation of aryloxindoles,[12] aza-Darzens reaction,[13] chlorination and Michael reactions of oxindoles,[14] pinacol rearrangement,[15] and reduction of aminals.[16] This is not the case for phosphoramidite derivatives since a VAPOL derivative was superior for hydroarylation of alkenes[17] and a VANOL derivative for a hydroacylation of alkenes.[18] The other major class of catalysts that are known for VANOL and VAPOL are the BOROX catalysts which are chiral anionic species comprised of a boroxinate core (Figure 1). These catalysts can function as chiral anion catalysts as in the Ugi reaction where there is an ion-pair with an iminium ion and the VAPOL boroxinate functions far better than the VANOL analog.[19] Alternatively, the BOROX catalysts can

function as a Brønsted acid in heteroatom Diels-Alder reactions where the VAPOL BOROX catalyst is superior to that of VANOL,[20] and in 2-aza-Cope rearrangements where the VANOL BOROX catalyst is superior to that of VAPOL.[21] The VANOL and VAPOL BOROX catalysts also serve as highly efficient chiral catalytic asymmetric aziridination of imines with diazo compounds. In contrast to nearly all of the known reactions mediated by VANOL and VAPOL catalysts, the catalytic asymmetric aziridination reaction is equally effective with each ligand. This is true of the reactions of imines with diazo compounds (two component),[22] or of the reactions of aldehydes, amines and diazo compounds (three component)[23] with BOROX derivatives which gives essentially the same asymmetric induction with VANOL and VAPOL (±1% ee) averaged over nearly a dozen imine substrates.[22,24] We have recently reported the preparation of 44 new VANOL ligands as a result of introduction of substituents in all five of the open positions in VANOL (positions 4 to 8). The BOROX catalysts from these ligands were screened in the catalytic asymmetric aziridination reaction with the hot spots found at positions 5, 6 and 7 with the highest inductions favoring substitution at position 7.[25]

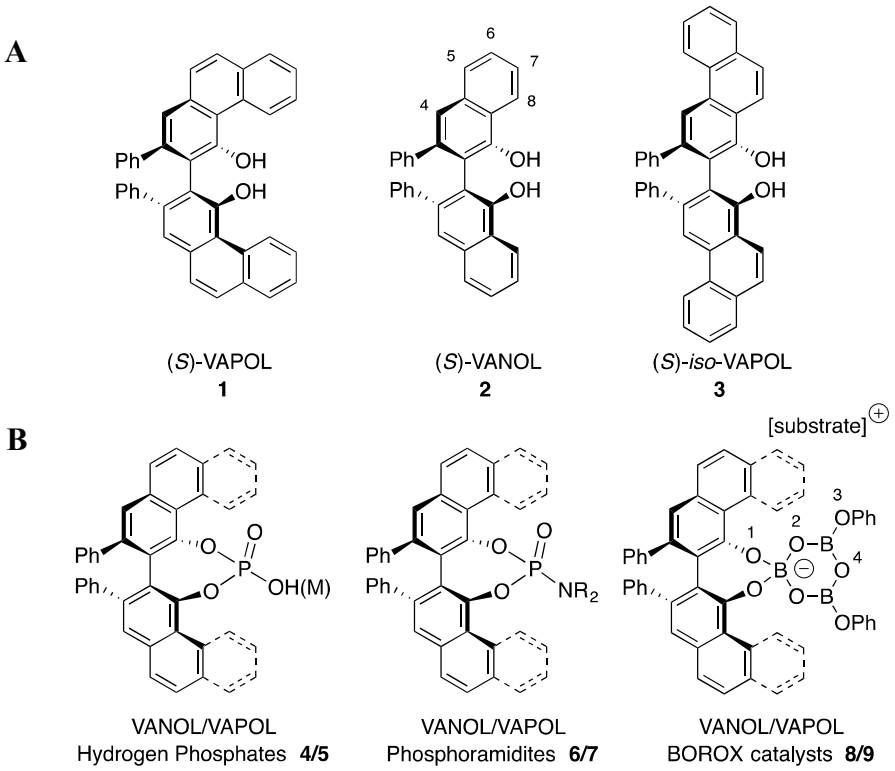


Figure 1 (**A**) Different chiral diols from the vaulted biaryl ligands. (**B**) Different catalysts derived from VAPOL and VANOL.

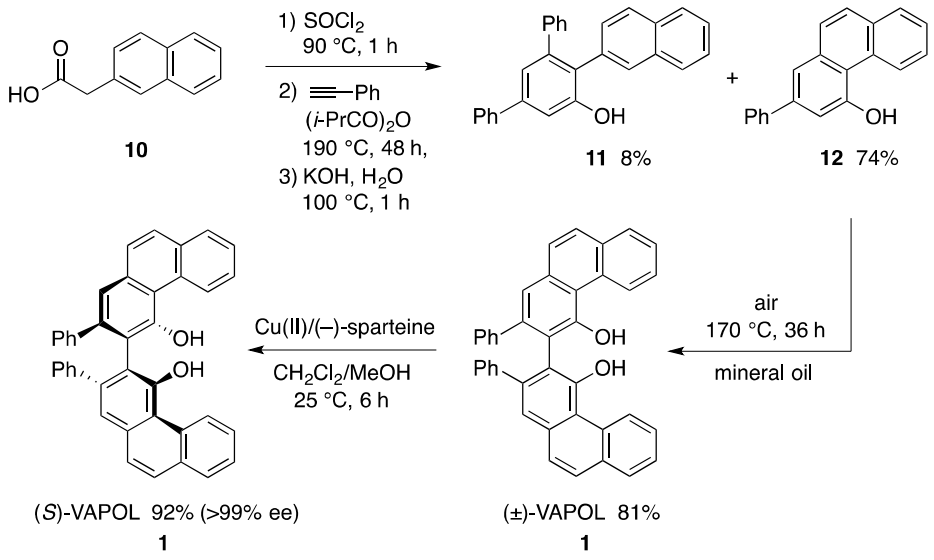
The vaulted biaryl **3** is an isomer of VAPOL and would be expected to have a distinct profile from either VAPOL or VANOL in catalysts for the many reactions described above that have been documented for VANOL and VAPOL. This ligand would formally result from moving the benzene ring that is fused to the 7,8-positions of VANOL to the 5,6-positions of VANOL. We were attracted to compound **3**, or *iso*-VAPOL, since it could potentially be prepared in a manner that would be less expensive than VAPOL by a substantial margin. We describe herein, a successful synthesis of (*S*)-*iso*-VAPOL **3** in an overall yield similar to that reported for VAPOL and from starting materials that are more than a factor of ten cheaper than those for VAPOL. Thereafter, the solid-state structures of the (*R*)-VANOL **2** and (*S*)-*iso*-VAPOL **3** were compared. Finally, the BOROX catalysts of (*S*)-*iso*-VAPOL and (*R*)-VANOL **2** were evaluated and compared for the catalytic asymmetric aziridination reaction and it was found that results using (*S*)-*iso*-VAPOL **3** were comparable to the same catalysts prepared from VANOL and VAPOL.

2. Background

The original method for the synthesis of VANOL and VAPOL involved the benzannulation of a Fischer carbene complex.[26] While this method is highly efficient giving racemic VAPOL in ~45% overall yield in four steps and since no chromatography was required until the final step, this reaction could be readily adapted to large scale. Unfortunately, the cost of chromium hexacarbonyl greatly hampers the utilization of this method on large scale. We have also developed a synthesis of VAPOL based on the Snieckus phenol synthesis but this has not been evaluated on large scale.[27] We have also developed a very efficient method for the large scale synthesis of VANOL based on a dienone-phenol rearrangement but this method is not applicable to VAPOL or *iso*-VAPOL.[28] The most efficient route for the synthesis of VANOL and VAPOL that is both scalable and flexible for access to derivatives involves a cycloaddition/electrocyclization cascade (CAEC).[29] In the case of VAPOL, this begins with 2-naphthyl acetic acid, and after conversion to the corresponding acid chloride, thermolysis with

phenyl acetylene initiates the cycloaddition/electrocyclization cascade (CAEC) that concludes in the formation of 2-phenyl-4-phenanthrol **12** in 74% yield (Scheme 1).[29] Approximately ten percent of the flux in this reaction proceeds to the naphthyl-substituted phenol **11** which has incorporated two molecules of phenyl acetylene. An oxidative phenol coupling reaction of **12** gives rise to racemic VAPOL in 81% yield. All the steps to racemic VAPOL can be performed on large scale with purification by crystallization thus avoiding chromatography.[29] This includes the ability to separate the phenanthrol **12** from the side-product **11** since the latter is ~100 times less soluble in *iso*-propanol than the former. A combination of crystallization and quick filtration through silica gel to remove colored impurities allows for the isolation of phenanthrol **12** in 64% yield from 57 g of the acid **10**. The overall yield of **12** varies with the commercial source of 2-naphthyl acetic acid and can range from 57 to 75%. Optically pure VAPOL can be obtained on large scale via its hydrogen phosphate and a classical resolution with (–)-cinchonidine.[29] On small scale, the most convenient way to secure optically pure VAPOL is via a deracemization with a copper complex of either (+)- or (–)-sparteine (Scheme 1).[25,30]

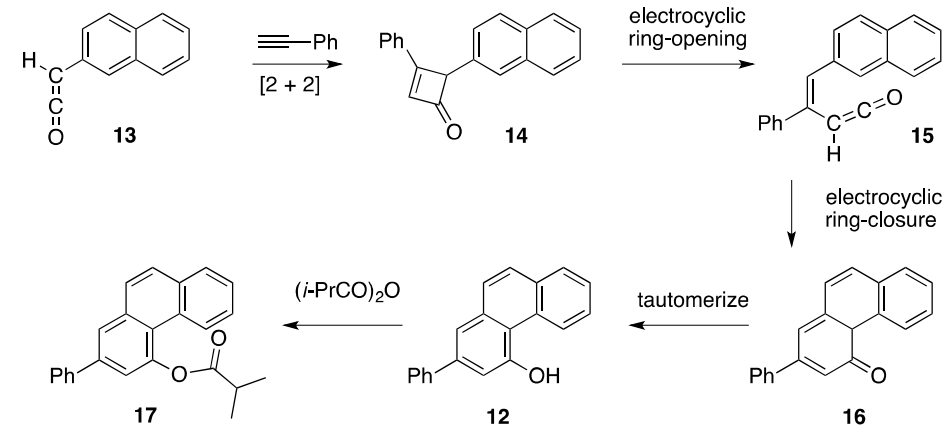
Scheme 1



The cycloaddition/electrocyclization cascade involves a [2+2] cycloaddition of 2-naphthyl ketene **13** with phenyl acetylene to give the cyclobutenone **14**. At the temperature of the reaction (190 °C), the cyclobutenone **14** will undergo a 4π e^- electrocyclic ring opening to give the *β*-naphthyl vinyl ketene **15**

which is readily transformed by a 6π e^- electrocyclic ring closure to generate the cyclohexadienone **16** that upon tautomerization gives 2-phenyl-4-phenanthrol **12**. *iso*-Butyric anhydride is added to the reaction to trap the phenol function in **12** to give the *iso*-butyrate ester **17**. If this is not done, the phenanthrol **12** is trapped by the ketene **13** to give a 2-naphthyl acetic ester which diverts half of the starting 2-naphthyl acetic acid to an unproductive course and drops the yield of phenanthrol **12** by a factor of two.[29]

Scheme 2



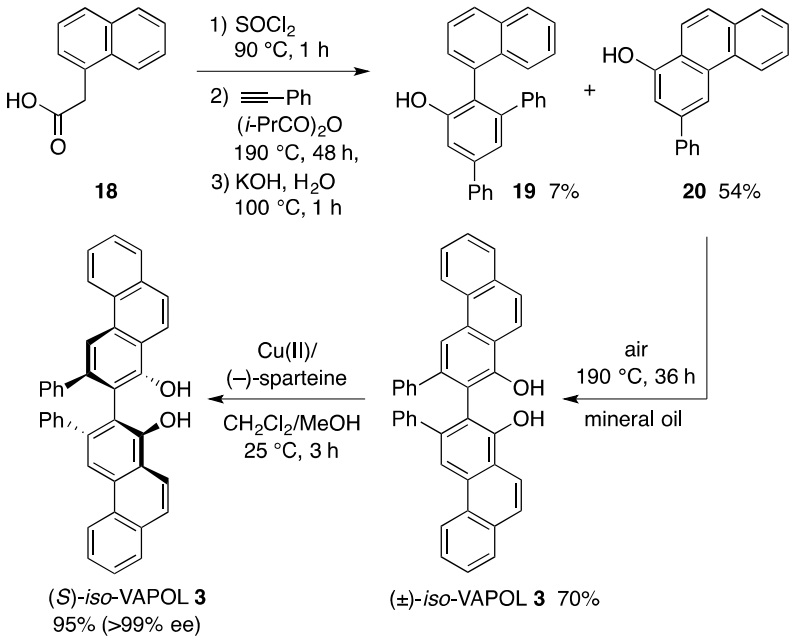
3. Results and Discussion

Synthesis of iso-VAPOL.

The synthesis of *iso*-VAPOL **3** was envisioned via a cycloaddition/electrocyclization cascade (CAEC) akin to that developed for VAPOL shown in Scheme 1. The extension of this strategy for the synthesis of *iso*-VAPOL did in fact prove viable and the details of the synthesis are shown in Scheme 3. The difference is that while the synthesis of VAPOL begins with 2-naphthyl acetic acid **10**, the synthesis of *iso*-VAPOL begins with 1-naphthyl acetic acid **18**. While both acids are commercially available, 1-naphthyl acetic acid is more than an order of magnitude less costly than its 2-naphthyl isomer. 1-Naphthyl acetic acid **18** is a plant hormone and it is used in agriculture for a variety of purposes. When the acid chloride derived from **18** is subjected to thermolysis with phenyl acetylene the desired 3-phenyl-1-phenanthrol **20** was isolated in 54% yield on a 9.4 g scale which is accompanied by the formation of

the side-product **19** in 7% yield. The success of the synthesis depends on the quality of the 1-naphthyl acetic acid. Some technical grade samples of 1-naphthyl acetic acid were found to contain up to 7% of 2-naphthyl acetic acid. The use of technical grade quality leads to a reaction mixture that contains the VAPOL monomer **12** and the isolation of compound **20** in pure form from this mixture proved to be tedious. Thus it is best to use commercial 1-naphthyl acetic acid that is devoid of its 2-naphthyl isomer which we find is the case with material that is rated as plant cell culture tested (≥95%). As in the VAPOL synthesis with 2-naphthyl acetic acid, the side product in the reaction of 1-naphthyl acetic acid resulted from the incorporation of two molecules of phenyl acetylene. The completion of the synthesis of racemic (±)-*iso*-VAPOL **3** followed from the oxidative phenol coupling of 3-phenyl-1-phenanthrol **20** which was effected by heating in mineral oil in the presence of air at 190 °C to give (±)-**3** in 70% yield. Deracemization with a copper-(–)-sparteine complex gave (*S*)-*iso*-VAPOL **3** in 95% yield and >99% optically purity (Scheme 3).[25,30]

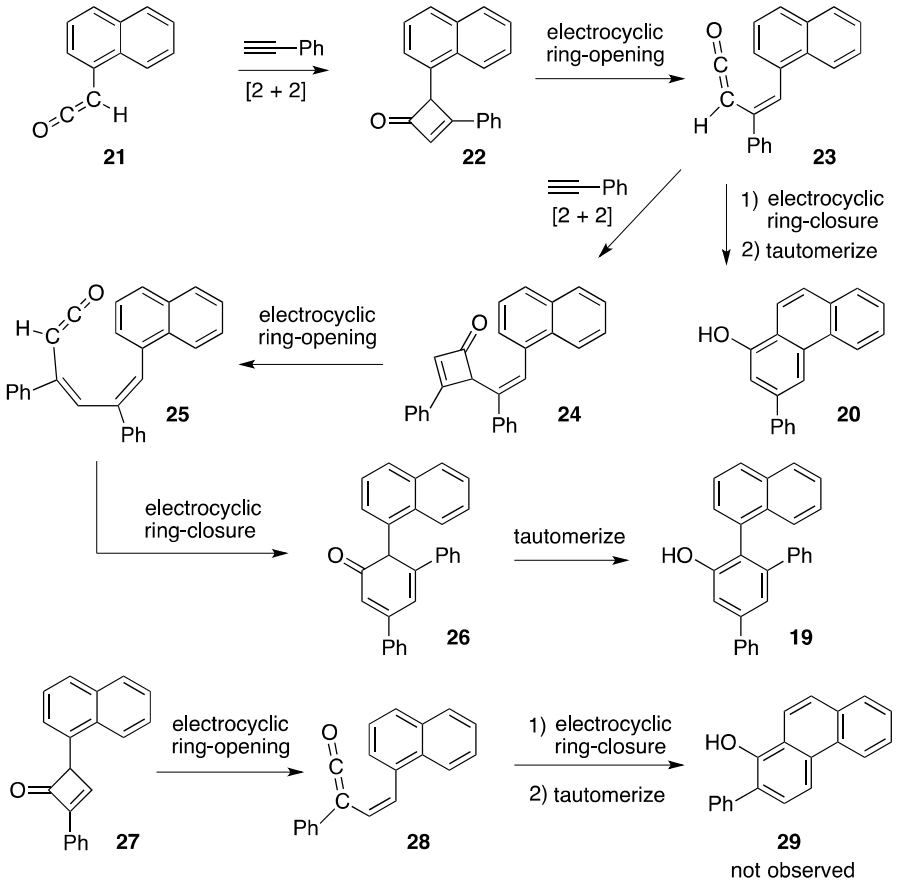
Scheme 3



A mechanistic accounting of the products produced in the cycloaddition/electrocyclization cascade with the acid halide from 1-naphthyl acetic acid **18** and phenyl acetylene is presented in Scheme 4. The [2+2] cycloaddition of the 1-naphthyl ketene **21** and phenyl acetylene is highly regioselective

giving only the cyclobutene **22** and none of the regioisomer **27**. If the regioisomer **27** had been formed, this would have lead to the formation of 2-phenyl-1-phenanthrol **29** but this was not observed in the reaction. Electrocyclic ring opening of the cyclobutene **22** gives the ketene **23** which can undergo electrocyclic ring closure and tautomerization to give the desired product **20**. The second alkyne in the side-product **19** is presumed to result from a [2+2] cycloaddition of phenyl acetylene with the β-naphthyl vinyl ketene **23** to give the cyclobutenone **24** and then a 4π e^- electrocyclic ring opening to ketene **25** followed a 6π e^- electrocyclic ring closure to dienone **26** and finally a tautomerization.

Scheme 4

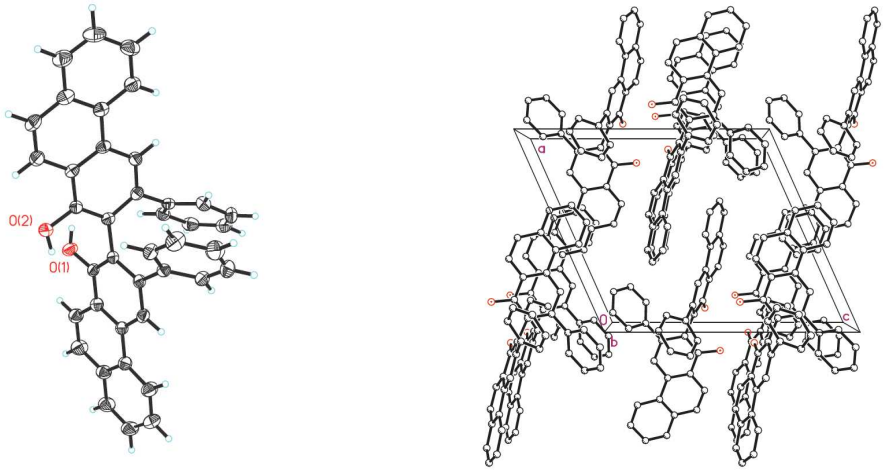


Comparison of the Solid-State Structures of iso-VAPOL and VANOL.

In the past, the solid-state structure of the VAPOL ligand has been reported by Matzger and coworkers.[31] During the purification of (*S*)-*iso*-VAPOL **3** by silica gel chromatography, a few crystals were formed serendipitously in one of the fractions collected. The crystals were then subjected to the X-

ray diffraction analysis and the resulting ORTEP diagram of the crystal structure is shown in Figure 2A. As was the case in the crystal structure of (*S*)-VAPOL **1**,[31] the solid-state form of (*S*)-*iso*-VAPOL **3** lacks intermolecular hydrogen bonding that prevails for BINOL. The dihedral angle between the phenanthrene rings of the (*S*)-**3** is 70.6°. It varies from 80.1° to 88.5° in the case of the VAPOL ligand.[31] The dihedral angle is <90° and corresponds to the cisoid conformation,[32,33] which alters the preferred packing motif. Also, as in the case of VAPOL, [31] the hydroxyl groups are buried in the pocket created by the phenanthrene rings of the (*S*)-**3**. The steric repulsion of these phenanthrene groups inhibits any possible hydrogen bonding. Although the VANOL ligand has been reported and used in many asymmetric reactions, its solid-state structure has not been studied yet. White needles were obtained when (*R*)-VANOL **2** was crystallized from dichloromethane. In the case of (*R*)-VANOL **2**, three conformations of the unit cell were observed with the dihedral angles of 69.6°, 74.6°, 76.9° respectively (Figure 2B). Thus (*R*)-VANOL **2** exists in a cisoid conformation and surprisingly, it lacks inter molecular hydrogen bonding. It must be noted that in the case of the BINOL ligand, hydrogen

A



B

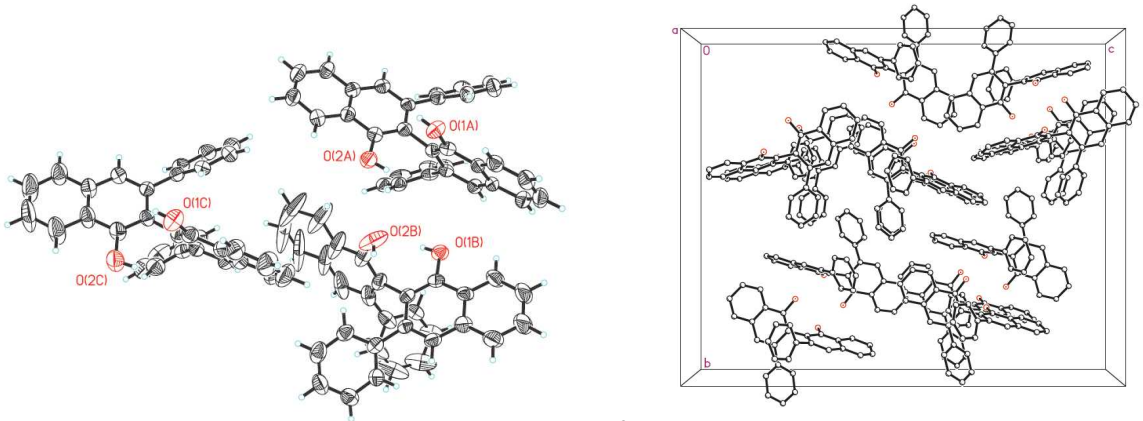


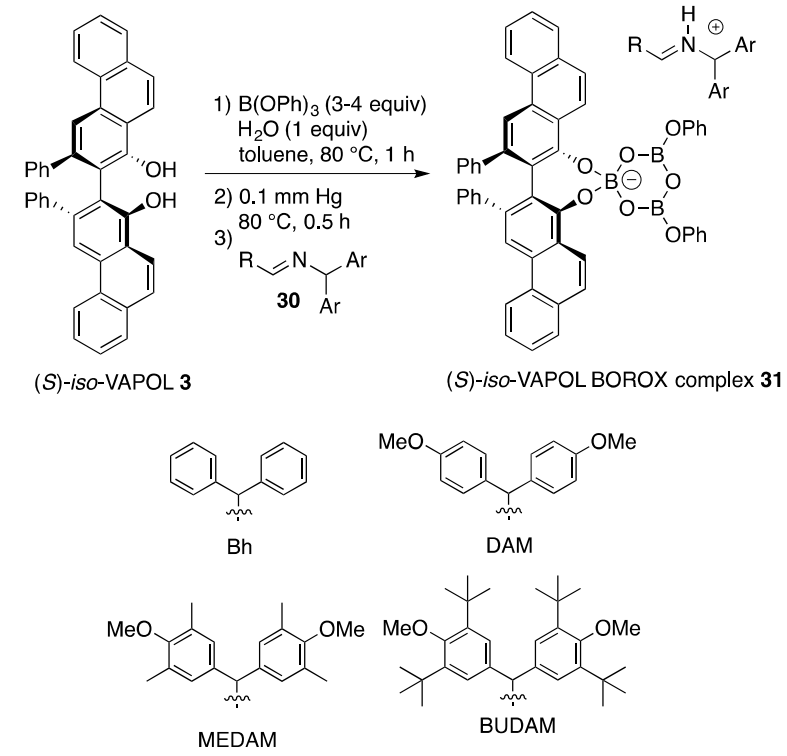
Figure 2 (**A**) ORTEP drawing of X-ray crystal structure of (*S*)-**3** and ORTEP drawing of crystal packing of (*S*)-**3** along b-axis. (**B**) ORTEP drawing of X-ray crystal structure of all three conformations (in the unit cell) of (*R*)-**2** and ORTEP drawing of crystal packing of (*R*)-**2** along b-axis.

bonding occurs in both the enantiopure and racemic crystal structures.[34] The dihedral angle between the naphthalenes of all known solid-state forms of BINOL is >90° and thus exists in transoid conformations.[33]

Evaluation of the BOROX catalyst of iso-VAPOL and VANOL in the Aziridination Reaction

The generation of the *iso*-VAPOL BOROX catalyst **31** was undertaken with the protocol shown in Scheme 5 that is one of the protocols that has been established for the corresponding VANOL and VAPOL BOROX catalysts.[22c,e] This protocol involves the generation of a pre-catalyst by heating the ligand, $B(OPh)_3$ and H_2O in toluene at 80 °C for 1 h and then removal of all of the volatiles at this temperature under vacuum (0.1 mm Hg). Addition of the imine **30** should then initiate the assembly of the BOROX catalyst species **31** and then finally addition of the ethyl diazoacetate should allow for aziridine formation to begin. The catalytic asymmetric aziridination reaction (AZ reaction) was originally developed with a benzhydryl group (Bh)[22c] on the imine **30** but latter it was found that the diaryl methyl groups DAM, MEDAM and BUDAM were much easier to remove from the nitrogen to

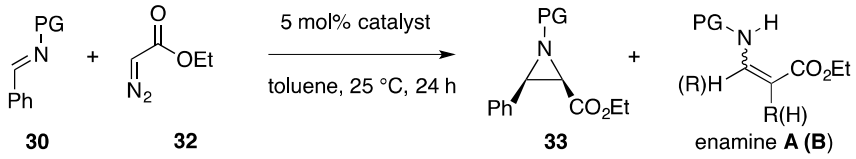
Scheme 5



give N-H aziridines,[35] and in addition, that these groups gave much higher asymmetric induction in the aziridination reaction.[22e] Thus, all four nitrogen protecting groups were investigated in aziridination reactions catalyzed by the *iso*-VAPOL BOROX catalyst and the results are presented in Table 1.

The initial evaluation of *iso*-VAPOL ligand was performed with the four imines **30a-30d** prepared from benzaldehyde and ethyl diazoacetate **32**. Each reaction was performed with 5 mol% catalyst in toluene at room temperature for 24 h although undoubtedly most of the reactions were complete in far less time. The catalyst was prepared by heating 1 equiv of the ligand with 4 equiv of $B(OPh)_3$ and 1 equiv H_2O in toluene at 80 °C for 1 h followed by removing all volatiles under vacuum at this temperature for 0.5 h. The imine (20 equiv) was added to assemble the BOROX catalyst and then ethyl diazoacetate (24 equiv) was added to start the reaction. Each of the imines has been previously examined in the aziridination reaction with ethyl diazo acetate with both VANOL and VAPOL ligands. However, in the present study the reaction of each imine was carried out with *iso*-VAPOL and with VANOL where the latter serves as the control. The data for VAPOL from the literature is also included in Table 1. In all cases, only the *cis*-isomer of the aziridine **33** is observed with a cis:trans ratio of

≥50:1. The error is these reactions is usually larger for the yields than it is for the asymmetric induction and for the latter it has been found that the measurements are usually within ±1% ee.[22c,e] Even with that caveat the differences between the VANOL, VAPOL and *iso*-VAPOL ligand are quite small. The *iso*-VAPOL ligand is more like the VAPOL ligand with the benzhydryl imine **30a** and slightly better that either VANOL or VAPOL with the DAM imine **30b**. All the ligands perform about the same with the MEDAM imine and with the BUDAM imine the *iso*-VAPOL ligand behaves more like the VANOL ligand.



30 **32** **33** enamine **A** (**B**)

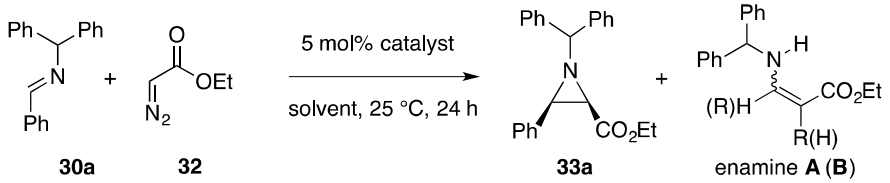
Table 1 Comparison of Vaulted Biaryl Ligands with Different Imine Protecting Groups [a]

entry	imine	PG	ligand	% yield *cis*-**33** [b]	% ee *cis*-**33** [c]	% yield **A** (**B**) [d]
1 [f]	**30a**	Bh	(*S*)-*iso*-VAPOL	82	92	3(7)
2			(*R*)-VANOL	87	–89	<1(<1)
3			(*S*)-VAPOL [g]	89	93	4(3)
4 [f]	**30b**	DAM	(*S*)-*iso*-VAPOL	91	96	6(<1)
5			(*R*)-VANOL	89	–92	1(<1)
6			(*R*)-VAPOL [g]	95	–92	1(<1)
7	**30c**	MEDAM	(*S*)-*iso*-VAPOL	96	98	2(1)
8			(*R*)-VANOL	98	–97	1(1)
9			(*S*)-VAPOL [g]	98	99	2(2)
10	**30d**	BUDAM	(*S*)-*iso*-VAPOL	97	96	<1(<1)
11			(*R*)-VANOL	98	–96	<1(<1)
12			(*S*)-VAPOL [g]	98	99	<1(<1)

[a] Unless otherwise specified, all reactions were performed with 1 mmol of imine **30** in toluene (0.5 M) with 1.2 equiv **32** and 5 mol% catalyst at 25 °C for 24 h and went to 100% completion. In all cases the cis:trans ratio for **33** was ≥ 50 : 1. The pre-catalyst was prepared by heating ligand (1 equiv) with commercial $B(OPh)_3$ (4 equiv) and H_2O (1 equiv) in toluene at 80 °C for 1 h, followed by removal of all volatiles under vacuum (0.1 mm Hg) for 0.5 h at 80 °C. [b] Isolated yield after chromatography on silica gel. [c] Determined by chiral HPLC. [d] Determined by integration of the NH signals of the enamines relative to the methine proton on aziridine ring in *cis*-**33** in the crude reaction mixture. [f] 94% and 96% conversion for entries 1 and 4, respectively. [g] Data from reference 22e.

The effect of solvent on the aziridination of imine **30a** with the *iso*-VAPOL BOROX catalyst **31** was also examined and the results are presented in Table 2. There is a significant drop in asymmetric

induction (~10% ee) in diethyl ether and ethyl acetate compared to toluene but the cis:trans selectivity is not effected. The drop in asymmetric induction for the VANOL catalyst in these solvents was only about half as much. Methylene chloride and 1,2-dichloroethane proved to be suitable solvents for the *iso*-VAPOL catalyst giving essentially equivalent results to those in toluene.



30a **32** **33a** enamine **A** (**B**)

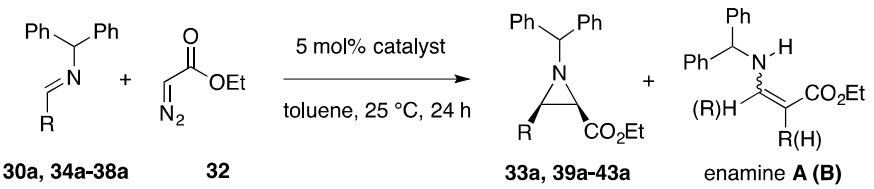
Table 2. Effect of Solvent on Aziridination with VANOL and iso-VAPOL Catalysts. [a]

entry	solvent	ligand	% conv [b]	% yield *cis*-**33a** [c]	% ee *cis*-**33a** [d]	cis:trans **33a** [e]	% yield **A** (**B**) [f]
1	EtOAc	(*S*)-iso-VAPOL	45	36	81	20:1	5(4)
2		(*R*)-VANOL	55	43	–84	> 50:1	7(4)
3	Et_2O	(*S*)-iso-VAPOL	95	83	80	≥ 50:1	5(6)
4		(*R*)-VANOL	96	83	–84	≥ 50:1	4(5)
5	CH_2Cl_2	(*S*)-iso-VAPOL	94	79	91	25:1	4(9)
6		(*R*)-VANOL	100	83	–89	50:1	4(8)
7	$ClCH_2CH_2Cl$	(*S*)-iso-VAPOL	94	81	91	≥ 50:1	4(8)
8		(*R*)-VANOL	100	83	–90	≥ 50:1	4(8)
9	toluene	(*S*)-iso-VAPOL	94	82	92	50:1	3(7)
10		(*R*)-VANOL	100	87	–89	≥ 50:1	<1(<1)

[a] Unless otherwise specified, all reactions were performed with 1 mmol of imine **30a** in toluene (0.5 M) with 1.2 equiv **32** and 5 mol% catalyst at 25 °C for 24 h. The pre-catalyst was prepared as indicated in Table 1. [b] Determined from the ^{1}H NMR spectrum of the crude reaction mixture. [c] Isolated yield after chromatography on silica gel. [d] Determined by HPLC. [e] Determined by integration of the methine protons of the aziridine ring for the cis and trans isomers of **33a** in the ^{1}H NMR spectrum of the crude reaction mixture. [f] Determined from the ^{1}H NMR spectrum of the crude reaction misture by integration of the NH signals of the enamines relative to the methine proton on the aziridine ring in *cis*-**33a**.

The scope of the aziridination reaction for the *iso*-VAPOL BOROX catalyst with imines derived from various aldehydes was carried out on the benzhydryl series since it gives the lowest asymmetric induction of the four imines and thus would more likely lead to a difference that would distinguish between the *iso*-VAPOL and VANOL ligands. However, as can be seen from the data in Table 3, there is very little difference between the inductions observed for the *iso*-VAPOL and VANOL BOROX catalysts. This is true for imines derived from both electron-rich and electron-poor aromatic aldehydes.

If there is any difference, it would be in favor of *iso*-VAPOL which gives higher inductions for four substrates and a lower induction for only one substrate. The cis:trans ratio is ≥50:1 in all cases except for the *p*-methoxyphenyl imine **36a** where the selectivity falls to ~10:1, but this happens for both the *iso*-VAPOL and VANOL catalysts (entries 7 & 8).



30a, 34a-38a **32** **33a, 39a-43a** enamine **A (B)**

Table 3 Comparing VANOL and *iso*-VAPOL and VAPOL with Various Imines. [a]

entry	imine	R	ligand	aziridine	% yield azir [b]	% ee azir [c]	% yield **A** (**B**) [d]
1	**30a**	C_6H_5	(*S*)-*iso*-VAPOL	**33a**	82	92	3(7)
2	**30a**		(*R*)-VANOL	**33a**	87	–89	<1(<1)
3	**34a**	4-BrC_6H_4	(*S*)-*iso*-VAPOL	**39a**	80	94	2(6)
4	**34a**		(*R*)-VANOL	**39a**	83	–91	4(6)
5	**35a**	4-MeC_6H_4	(*S*)-*iso*-VAPOL	**40a**	82	94	3(7)
6	**35a**		(*R*)-VANOL	**40a**	79	–92	3(6)
7 [e]	**36a**	4-MeOC_6H_4	(*S*)-*iso*-VAPOL	**41a**	62	89	<1(6)
8 [f]	**36a**		(*R*)-VANOL	**41a**	62	–91	<1(3)
9	**37a**	cyclohexyl	(*S*)-*iso*-VAPOL	**42a**	72	79	9(4)
10	**37a**		(*R*)-VANOL	**42a**	70	–77	5(4)
11	**38a**	*t*-butyl	(*S*)-*iso*-VAPOL	**43a**	83	84	6(<1)
12	**38a**		(*R*)-VANOL	**43a**	86	–84	<1(8)

[a] Unless otherwise specified, all reactions were performed with 1 mmol of the imine in toluene (0.5 M) with 1.2 equiv **32** and 5 mol% catalyst at 25 °C for 24 h and gave ≥50:1 cis:trans selectivity and went to 94-100% completion. The pre-catalyst was prepared as indicated in Table 1. [b] Isolated yield after chromatography on silica gel. [c] Determined by chiral HPLC. [d] Determined from the ^{1}H NMR spectrum of the crude reaction mixture by integration of the NH signals of the enamines relative to the methine proton on the aziridine ring. [e] Cis/trans = 9:1. [f] Cis/trans = 10:1.

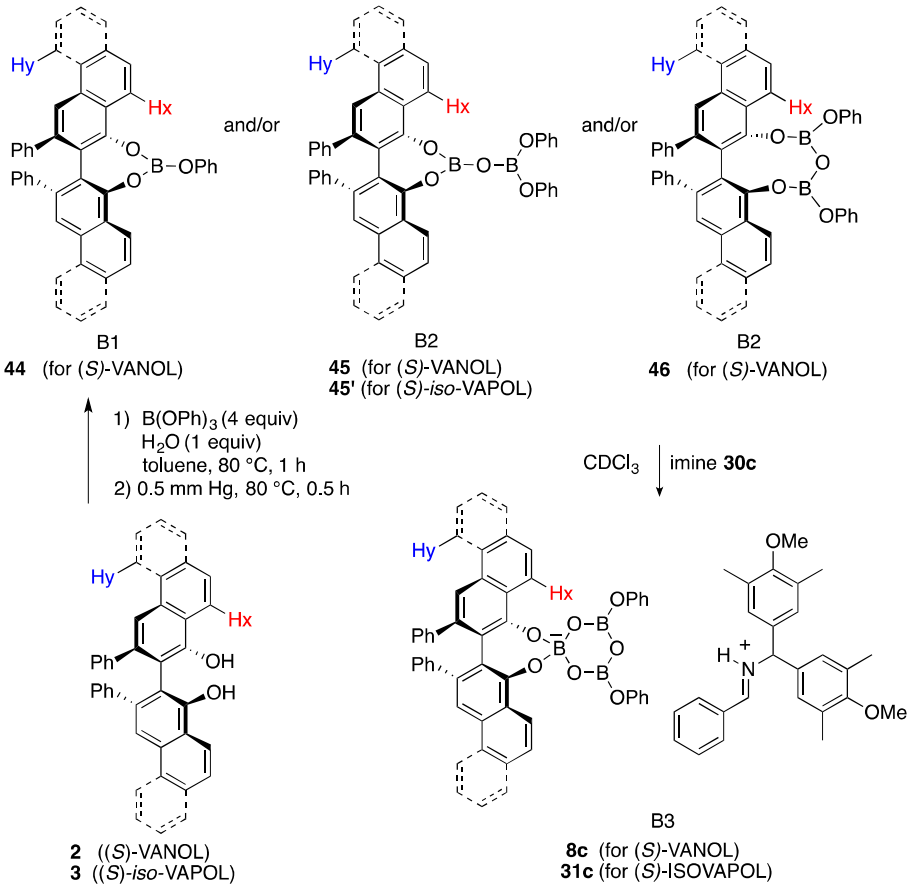
Investigation of the VANOL BOROX catalyst 8 and iso-VAPOL BOROX catalyst 31 using NMR Spectroscopy

We have reported a detailed NMR and crystallographic study of the VAPOL BOROX catalyst in 2010.[22f] The structure of the VANOL BOROX catalyst has been supported by calculations and NMR experiments and the very characteristic ^{11}B NMR spectra of the BOROX VAPOL catalyst is also observed for the VANOL BOROX catalyst.[22h] In order to gain the evidence for the generation of the

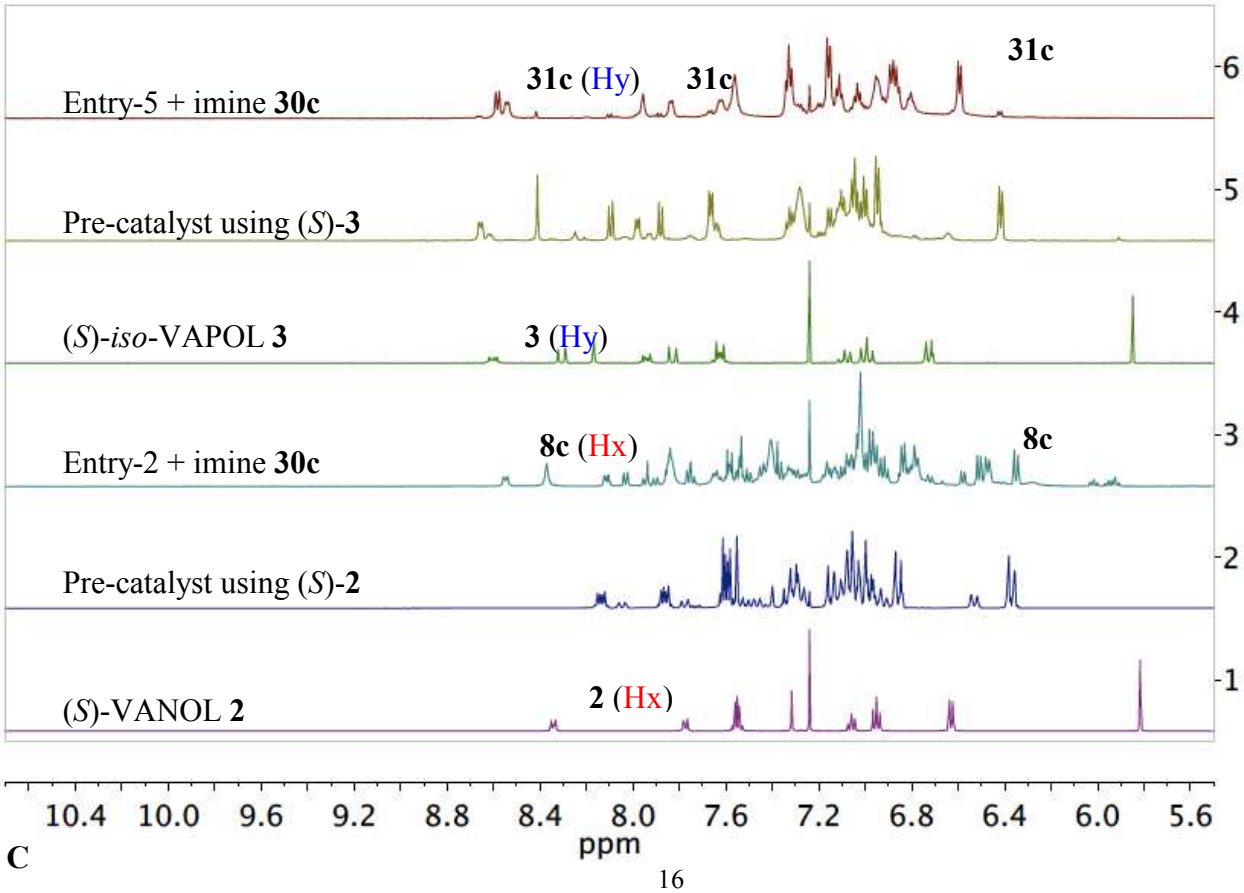
BOROX catalyst **31** from the *iso*-VAPOL ligand, a series of NMR experiments was performed (Figure 3). Various species were identified based on the characteristic peaks obtained from Hx and Hy for VANOL **2** and *iso*-VAPOL **3** respectively (Figure 3A).

The chemical shift of the proton Hx in the 8,8'-positions in VANOL **2** is assigned as δ = 8.35 ppm (d, $CDCl_3$). This assignment is based on the fact that the most downfield absorption in VANOL is missing in the ^1H NMR spectrum of 8,8-dimethyl-VANOL for which the most downfield signal is a doublet at δ = 7.57 ppm.[30] The method for pre-catalyst formation involves heating (*S*)-VANOL with 4 equiv of commercial $B(OPh)_3$ and 1 equiv of H_2O of at 80 °C. This resulted in the generation of two species which have been previously tentatively identified as the *pyro*-borate B2 **45** and the *meso*-borate **44.**[22c] It is also possible that one of the two observed species could be the the cyclic *pyro*-borate **46**; further elucidation of the structure of these two species will have to await additional studies. Treatment of this mixture with 1 equiv of the imine **30c** at room temperature within a few minutes results in the conversion of the colorless solution of **44** and **45** (or **46**) to a red solution of boroxinate **8c** (δ□ □x = 8.55 ppm, d, *J* = 9.0 Hz, $CDCl_3$) (entry 3, Figure 3B).

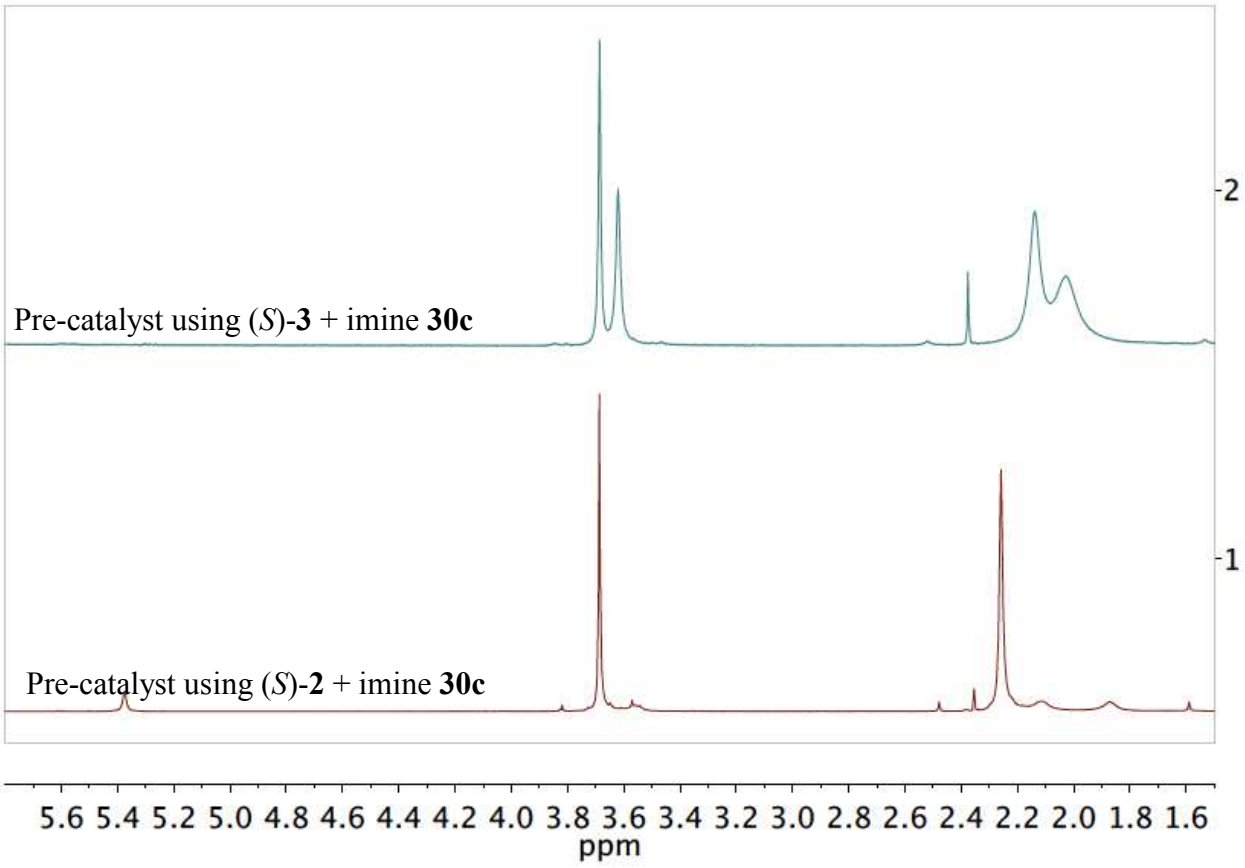
A


Hy
Hx
Ph
Ph
O
B–OPh
O
and/or
B1
44 (for (S)-VANOL)
B–O–B
OPh
OPh
B2
45 (for (S)-VANOL)
45' (for (S)-iso-VAPOL)
B2
46 (for (S)-VANOL)
1) B(OPh)3 (4 equiv)
H2O (1 equiv)
toluene, 80 °C, 1 h
2) 0.5 mm Hg, 80 °C, 0.5 h
CDCl3
imine 30c
OH
OH
2 ((S)-VANOL)
3 ((S)-iso-VAPOL)
OMe
OMe
B3
8c (for (S)-VANOL)
31c (for (S)-ISOVAPOL)

B


Entry-5 + imine 30c
31c (Hy)
31c
31c
Pre-catalyst using (S)-3
(S)-iso-VAPOL 3
3 (Hy)
Entry-2 + imine 30c
8c (Hx)
8c
Pre-catalyst using (S)-2
(S)-VANOL 2
2 (Hx)
6
5
4
3
2
1
10.4
10.0
9.6
9.2
8.8
8.4
8.0
7.6
7.2
6.8
6.4
6.0
5.6
ppm

C



D

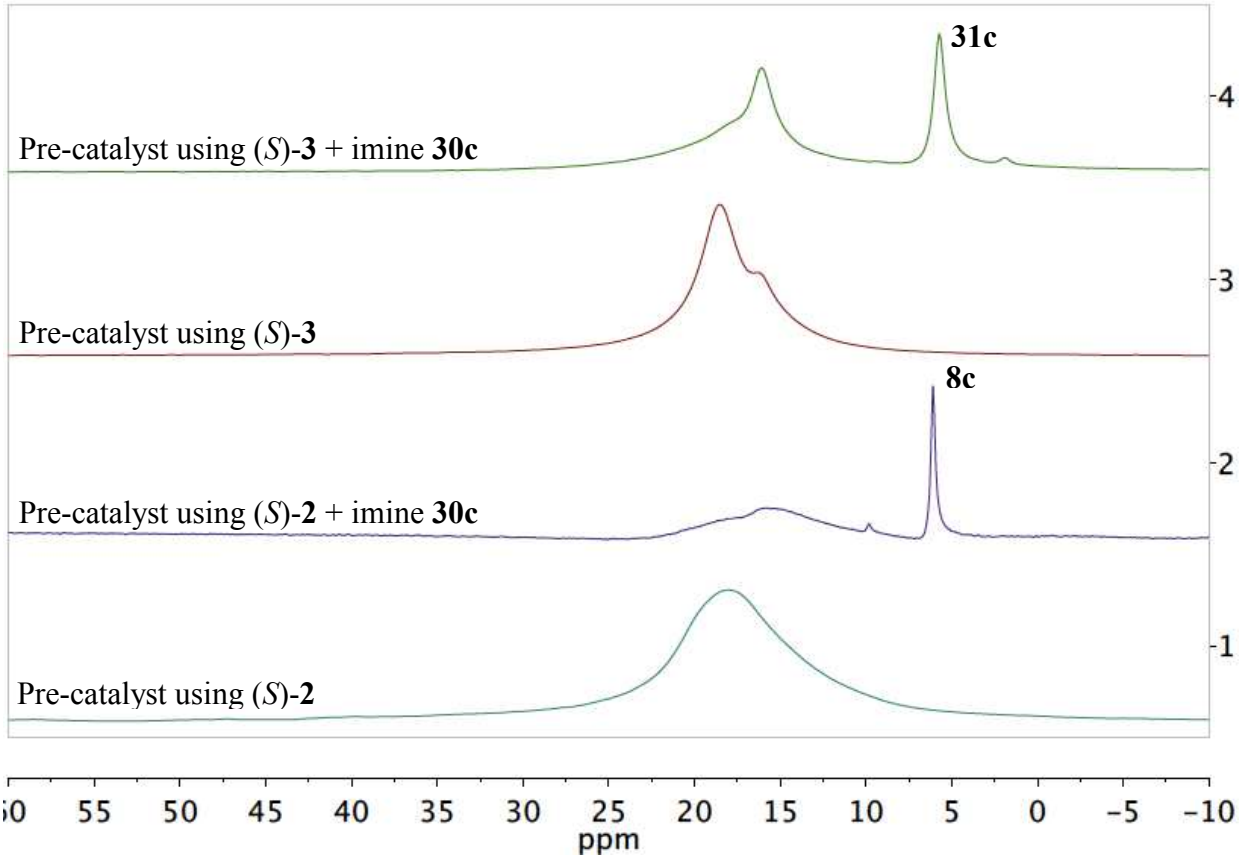


Figure 3 (**A**) Treatment of (*S*)-**2** and (*S*)-**3** with $_{17}B(OPh)_3$ and imine **30c**. (**B**) ^1H NMR spectra of the

reaction mixture in $CDCl_3$. Entry 1: pure (*S*)-**2**. Entry 2: (*S*)-**2** (0.1 mmol) plus 4 equiv $B(OPh)_3$ and 1 equiv H_2O were heated at 80 °C in toluene for 1 h followed by removal of volatiles under vacuum for 0.5 h. Entry 3: 1.0 equiv of imine **30c** was added to the entry 2 (pre-catalyst) for 10 min at 25 °C. Entry 4: pure (*S*)-**3**. Entry 5: (*S*)-**3** (0.1 mmol) plus 4 equiv $B(OPh)_3$ and 1 equiv H_2O were heated at 80 °C in toluene for 1 h followed by removal of volatiles under vacuum for 0.5 h. Entry 6: 1.0 equiv of imine **30c** was added to the entry 2 (pre-catalyst) for 10 min at 25 °C. (**C**) ^{1}H NMR spectra (methyl and methoxy region) corresponding to the entry 3 and 6 in ^{1}H NMR spectra in Figure 3B. (**D**) ^{11}B NMR spectra corresponding to entries 2,3,5 and 6 in the ^{1}H NMR spectra in Figure 3B.

It is well known that most three coordinate aryl borate esters show very broad absorptions at 16-18 ppm in the ^{11}B NMR. The VANOL BOROX catalyst **8c** has a sharp absorption at δ□□□6.09 ppm in ^{11}B NMR (entry 2, Figure 3D).[22h] This is due to the increased spherical symmetry of a four coordinate boron in the BOROX catalyst. Additionally, a very broad absorption was also observed at δ□□□16.10 ppm, which can be attributed to the two 3-coordinate borons present in the catalyst. The ratio of the 3-coordinate:4-coordinate borons is 2:1 which is in perfect agreement of the structure of the catalyst (integration not shown).

The formation of the pre-catalyst from the reaction of *iso*-VAPOL **3** seemed to be little cleaner giving a major species with a doublet at δ = 8.65 ppm (entry 5, Figure 3B). This species is tentatively identified as the pyro-borate **45′** but additional studies will be needed to rule out 44 ‘ or 46’ as the structure of this species. A new doublet is observed at δ = 8.58 ppm (J = 8.8 Hz, $CDCl_3$) for proton Hy for the boroxinate **31c** when 1 equiv of imine **30c** was added (entry 6, Figure 3B). In support of the formation of **31c**, a peak at δ = 5.72 ppm in the ^{11}B NMR spectrum for the tetra-coordinate boron where the ratio of the 3-coordinate to 4-coordinate borons = 2.3:1 (entry 4, Figure 3D, integration not shown). Nearly identical ^{11}B NMR spectra are observed for the VANOL BOROX[22h] and VAPOL BOROX[22f] catalysts. The presence of a single doublet at δHx = 8.55 ppm and at δ Hy = 8.58 ppm for both the boroxinate complexes **8c** and **31c** respectively, indicates that the exchange of the iminium ion from the top face of the catalyst to the bottom is fast on the NMR time scale in both the cases. A striking difference between the two boroxinates **8c** and **31c** was that the splitting in the methyl and methoxy region of the MEDAM

group was absent in the case of the VANOL ligand derived catalyst **8c** (Figure 3C). The splitting of methyl and methoxy into two singlets has been observed for VAPOL derived catalysts.[22f] This may be due to differentiation of the two dimethylmethoxyphenyl groups in the catalyst bound iminium. The chemical shifts of the protons associated with the nitrogen of the protonated imines in the complexes **8c** and **31c** are δ=13.74 ppm and δ=13.67 ppm respectively.

4. Conclusions

Iso-VAPOL is a new member of the vaulted biaryl family of atropisomeric ligands and its syntheses and characterization is described. This ligand is prepared by a cycloaddition /electrocyclization cascade similar to that reported for VAPOL, however, the starting material is an order of magnitude cheaper than that for VAPOL. The solid-state structures of *iso*-VAPOL and VANOL were determined and it was found that both do not display intermolecular H-bonds and both have cisoid conformations. These two characteristics are shared with the vaulted biaryl VAPOL which is in contrast to linear biaryl ligands such as BINOL which exists in a transoid conformation and has intermolecular H-bonds in the solid state. It was shown that *iso*-VAPOL can form a BOROX catalyst with $B(OPh)_3$ and that this species is capable of catalyzing the aziridination of imines with ethyl diazo acetate to give aziridine-2-carboxylates in high yield and with high enantio- and diastereo-selectivity. *Iso*-VAPOL is an isomer of VAPOL but has a chiral pocket similar to that of VANOL. This fact will be expected to play out and its value to be defined in the differences in asymmetric inductions between it and VANOL and VAPOL in a variety of catalysts for a number of different asymmetric reactions.

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24) See pages S26 to S28 in the Supporting Information of footnote 22e.

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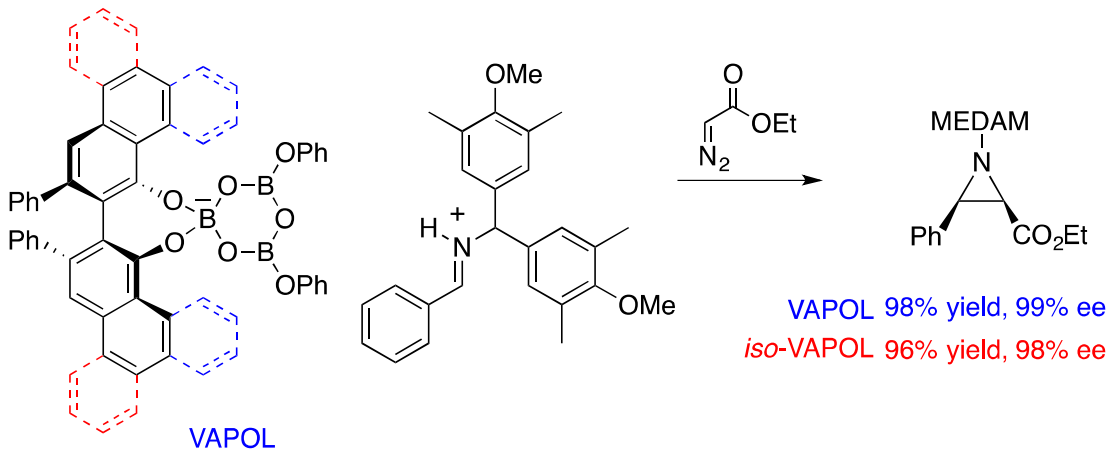
Table Contents Graphic



The *iso*-VAPOL ligand is just as effective as VAPOL in the catalytic asymmetric synthesis of aziridines at one-tenth the cost.