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Vaulted Biaryls in Catalysis: A Structure-Activity Relationship Guided Tour of the Immanent Domain of the VANOL Ligand

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Abstract

The active site in the BOROX catalyst is a chiral polyborate anion (boroxinate) that is assembled in-situ from three equivalents of $B(OPh)_3$ and one of the VANOL ligand by a molecule of substrate. The substrates are bound to the boroxinate by H-bonds to oxygens O1-O3. The effects of introducing substituents at each position of the naphthalene core of the VANOL ligand are systematically investigated in an aziridination reaction. Substituents in the 4,4'- and 8,8'-positions have a negative effect on catalyst performance, whereas, substituents in the 7- and 7'-positions have the biggest impact in a positive direction.

1. INTRODUCTION

The vaulted biaryl ligands VANOL and VAPOL have been demonstrated to be effective in a variety of useful catalytic asymmetric reactions including amidation of imines,¹ aminoallylation of aldehydes,² aza-Darzens reaction³ *cis*-aziridination of imines^{4,5} *trans*-aziridination of imines,^{4q,6} Baeyer-Villiger reactions,⁷ benzyloxylation of aryloxindoles,⁸ desymmetrization of aziridines,⁹ Diels-Alder reactions,¹⁰ heteroatom Diels-Alder reactions,¹¹ hydroarylation of alkenes,¹² hydrogenation of alkenes,¹³ imidation of imines,¹⁴ Mannich reactions,¹⁵ multi-component aziridination of aldehydes,¹⁶ Petasis reaction,¹⁷ propargylation of ketones,¹⁸ reduction of imines,¹⁹ chlorination and Michael reactions of oxindoles,²⁰ hydroacylation of alkenes,²¹ pinacol rearrangement,²² reduction of amins²³ and Michael addition of alkynes.²⁴

Many of the reactions of imines with VANOL and VAPOL catalysts involve a chiral polyborate catalyst with a chiral boroxinate anionic core that exists as an ion pair with the protonated imine and these together constitute the catalyst-substrate complex (Scheme 1). These boroxinate, or BOROX catalysts, are assembled in-situ by the imine substrate from a molecule of the VANOL or VAPOL ligand and $B(OPh)_3$.^{4j,m,6b,16b} These catalysts have been shown to occur in *cis*-^{4,5} and *trans*-aziridination^{4q,6} reactions as well as in aza-Cope rearrangement² and are presumably involved in heteroatom Diels-Alder reactions of imines as well (Scheme 2).¹¹

2. BACKGROUND

The 3-D structure of the (*S*)-VANOL BOROX anion shown in Figure 1 is based on several X-ray structures determined for these boroxinate species with the corresponding cationic moiety removed.^{4j,m} In the calculated transition state for the first step^{6d} in the *cis*-

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Supporting Information: Procedures for the preparation for the 3-phenyl phenols **15** and the 44 new VANOL derivatives and the asymmetric syntheses of aziridines **12**.

aziridination reaction both substrates are H-bonded to various oxygens of the boroxinate anionic core.^{6b,6c} Both substrates are also H-bonded to the boroxinate anion in the transition state for the first step^{6d} in the *trans*-aziridination reaction as well.^{6b,6c} However, in the latter case the diazo compound (diazoacetamide) is bound to the catalyst by two H-bonds, one from the hydrogen of the diazo carbon and one from the amide hydrogen.

It can be anticipated that the introduction of substituents on any of the open positions (C4–C8) of the naphthalene core of VANOL may have an effect on the binding of either and/or both of the substrates in the aziridination reaction leading to either increased or decreased asymmetric inductions. However, the VAPOL ligand is nothing more than a VANOL ligand with substituents in the C7 and C8 positions in the form of a fused benzene ring and both VANOL and VAPOL BOROX catalysts give essentially identical asymmetric inductions ($\pm 1\%$) over the entire scope of imines that have been screened in the aziridination reaction.²⁵ Nonetheless, substituents of different shapes and sizes and electronic properties may have interactions with the bound substrates that are disparate from those of a flat rigidly projected benzene ring.

The purpose of the present work is to systematically map the contours of the VANOL BOROX catalyst to observe how alterations in its domain will effect reactions occurring at the chiral boroxinate core. The response to the introduction of various substituents at all five of the open positions on the naphthalene core on the VANOL ligand (C4–C8) is monitored as a function of the asymmetric induction in the *cis*-aziridination reaction.

It is clear at this point in the development of asymmetric catalysis, that universal catalysts will not be the norm. Each reaction class and catalyst type will typically require their own optimized ligand. This is no more readily evident than in the chemistry of BINOL ligands.²⁶ It is commonly observed that 3,3'-disubstituted BINOLs are superior to BINOL but for some reactions and with some catalysts the 6,6-disubstituted BINOLs are the best. It would be interesting to know how the same substituent introduced into each of the six open positions in BINOL would effect the asymmetric induction in a given reaction but to the best of our knowledge this type of study has not been done for BINOL. Given the established utility of VANOL in the broad range of asymmetric reactions outlined in the introduction, the synthetic methods for the preparation of 44 different VANOL derivatives described in this work would be deemed to be of value not only for boroxinate derived VANOL catalysts but also for many other types of catalysts based on VANOL.

3. RESULTS AND DISCUSSION

For each of the five positions on VANOL several different substituents were investigated including bromide, *p*-*t*-butylphenyl and *p*-trifluoromethylphenyl groups (Table 1). Substituents in the 4- and 8-positions of VANOL had the biggest negative impact on the asymmetric inductions falling to 3% ee with ligand **4q** and to 8% ee with ligand **8ah**. The large influence of substituents in the 4-position was not anticipated given the remoteness of these groups from the active site of the boroxinate catalyst. This may have to do with the influence of groups in the 4-position on the twist angle between the two naphthalene rings in the VANOL and the consequences that this might have on the stability of the boroxinate core since it is believed that its formation is equilibrium dependent. Nonetheless, the ¹¹B NMR spectrum reveals that at least some of the boroxinate species is formed, but it is certainly possible that there could be significant background reactions with non-chiral borate species (see supporting information). The significant negative effect of the substituents in the 8-position could also be due to an increase in background reaction as a result of incomplete boroxinate formation although, again ¹¹B NMR spectrum clearly shows that some boroxinate has formed. Alternatively, the negative effect of substituents in the 8-

position could also be due to a simple disruption of the binding or of the nature of the binding of the substrates to the boroxinate core.

Of all of the positional isomers of VANOL that were screened, the only ligand that gave an asymmetric induction that was significantly higher than VANOL or VAPOL was the ligand **7q** that has a *p-t*-butylphenyl group in the 7- and 7'-positions and, curiously, this was true for both imines **10d** and **10i** (Table 1, entry 6). The results from the octahydro-VANOL ligand **9** were quite intriguing. Although no overall increase in induction was observed for the catalyst from **9**, the induction for the imines **10d** and **10i** were reversed. The induction with the phenyl imine **10d** fell from 92 to 82% ee, the induction for the cyclohexyl imine **10i** rose from 81 to 90% ee.

The fact that the VANOL positional isomer screen identified the 7-position of VANOL as the “hot” position for effecting aziridination reactions occurring in the boroxinate active site, prompted the generation of a library of VANOL ligands that are substituted at the 7- and 7'-positions. The fact that the 7-position emerged as optimal was fortunate since, from the synthetic point of view, it is clear that this is the best position for diversity to proliferate with the greatest of ease. These ligands can be readily obtained from *p*-substituted phenyl acetic acids via a cycloaddition/ electrocyclization cascade (CAEC) process²⁷ and a few examples are indicated in Scheme 3. Simply heating the acid chloride **13** with phenyl acetylene leads to the corresponding 3-phenyl-1-naphthol **15** after liberation from the *iso*-butyrate ester **14**. *iso*-Butyric anhydride is added to the CAEC cascade to react with **15** and prevent it from being trapped by the aryl ketene intermediate generated from **13**. An oxidative phenol coupling reaction with air is used to acquire the racemic ligand in good to high yields. Although a large scale resolution method has been developed for VANOL,²⁷ on lab scale, the most convenient way to access the optical pure ligands is to perform a deracemization with a copper complex of (–)-sparteine (or (+)-sparteine) which give the (*S*)- or (*R*)-ligands **7** in >99% ee in all cases.²⁸ A thirty one member library of 7,7'-disubstituted VANOL ligands has been generated and their syntheses are all described in the supporting information. About a third of these were prepared from commercially available *p*-substituted phenyl acetic acids as outlined in Scheme 3 and the rest were prepared by a variety of different coupling reactions of the 7,7'-disubstituted dihalides (*S*)-**7d** and (*S*)-**7e**, or their enantiomers.

The data in Table 2 reveal that the majority of all of the different substituents in the 7- and 7'-positions examined led to improved asymmetric inductions for both aziridines (20/31 for **12d** and 24/31 for **12i**). It was most remarkable to find that out of all thirty of the new VANOL ligands, the best ligand for the cyclohexyl imine **10i** was also the best ligand for the phenyl imine **10d**. Given this singularity for the 7,7'-di-*t*-butylVANOL ligand **7m**, it was not surprising to find that many of the other trends in asymmetric induction observed for the cyclohexyl imine **10i** were also observed for **10d**. The two groups of substituents that gave the largest increases were bulky alkyl groups and aromatic substituents. There are definite electronic effects that appear as well that can be observed for the halogens where the inductions are typically slightly decreased relative to a methoxyl group that gives rise to a sizable increase. The series of aryl substrates reveals that the interplay between sterics and electronics of the aryl group is indeed delicate. The 4-methylphenyl group in ligand **7o** leads to a definite jump in asymmetric induction compared with VANOL and a slight further increase is seen with the 4-*t*-butylphenyl substituent in **7q**. This increase is more than negated by a 4-trifluoromethyl group (**7p**). Any advantage of a phenyl substituent in the 7- and 7'-positions is lost with the introduction of *ortho*-groups on the phenyl ring (**7u** and **7v**).

All reactions in Table 2 were carried out for 24 h in order to ensure that any differences in rates for the various ligands could be accommodated. Most of the reactions in fact are

probably complete in substantially less time than 24 h. The reaction with the optimal ligand **7m** with imine **10d** was re-examined with regard to minimum reaction time to find that the reaction is complete in 4 h with 5 mol% catalyst to give an 89% yield of **12d** in 97.4% ee. This repeat reaction was performed on a sample of the ligand **7m** that was stored in the refrigerator under nitrogen for two years subsequent to the first run indicated in Table 2.

The boroxinate catalyst generated from the 7,7-di-*t*-butylVANOL ligand **7m** gave higher asymmetric inductions than the parent VANOL ligand **1** not only for the aziridination of the imines **10d** and **10i** (Tables 1 & 2), but all ten of the imines shown in Table 3. This set of imines was chosen since all have been previously examined with catalysts generated from VANOL and VAPOL.^{13h} The asymmetric inductions with the di-*t*-butylVANOL catalyst range from 94–99% ee over the ten substrates. It is clear that there is a dramatic increase in the average asymmetric induction over these ten substrates that result from the introduction of the *t*-butyl in the 7- and 7'-positions of VANOL (87 vs 97% ee). Not only are the asymmetric inductions dramatically improved with the di-*t*-butylVANOL catalyst, but the general efficiency of the reaction is also greatly improved with the average yield increasing by 11% over the VANOL catalyst. This increase in efficiency appears to be the result of a combination of two factors. A decrease in the amount of enamine side-products and an increase in the diastereoselectivity in favor of the *cis*-aziridine. The latter is particularly manifested in the aziridination of imines derived from *ortho*-substituted benzaldehydes. One of the weak points we had previously established for the AZ reaction with VANOL and VAPOL catalysts is the lower *cis*/*trans* selectivity and the lower asymmetric inductions observed for imines derived from *ortho*-substituted benzaldehydes.^{13h} For example, the reaction of the 2-bromophenyl imine **10c** with the VANOL catalyst gives a 1.9:1 ratio of *cis* to *trans* and the di-*t*-butylVANOL catalyst gives an 8:1 mixture. Improved diastereoselection is also observed for the *ortho*-methylphenyl imine **10f** with *cis*-*trans* ratios increasing from 12:1 to >100:1 for the VANOL and di-*t*-butylVANOL catalysts, respectively. Thus, the di-*t*-butylVANOL catalyst is superior to either VANOL or VAPOL catalysts in providing diastereoselective and enantioselective access to aziridines from benzhydryl imines.

4. CONCLUSIONS

A systematic mapping of the sensitivity of the active site in a VANOL boroxinate catalyst in responding to steric and electronic effects of substitutions in the naphthalene core to the catalytic transfer of chirality in an aziridination reactions has been carried out. A screen of all five positional isomers of VANOL revealed that the chirality transfer was most sensitive in a positive direction to substitution in the 7- and 7'-positions. A subsequent screen of a set of 31 members of the 7,7'-disubstituted VANOL ligands identified the 7,7'-di-*t*-butylVANOL as optimal. A screen of this ligand for the catalytic asymmetric aziridination of a set of ten different imines found that this ligand gave higher asymmetric inductions than the un-substituted VANOL for every imine with an overall average of 10% higher ee and 11% higher yield. The 7,7'-Di-*t*-butylVANOL **7m** is clearly the ligand of choice for the catalytic asymmetric aziridination reaction with benzhydryl imines which can be readily prepared from the commercially available diphenylmethanamine. However, given the fact that the vaulted biaryl ligands VANOL and VAPOL ligands have been demonstrated to be effective in over twenty other catalytic asymmetric reactions, the family of di-substituted VANOL ligands described here (not just the 7,7'-derivatives) may well provide the diversity necessary to identify ligands of optimal performance for other asymmetric catalysts for a broad range of reactions. A prime reason for the consideration of such diversity screens is the ease of synthesis of the various VANOL derivatives.

5. EXPERIMENTAL SECTION

Preparation of 7-(*tert*-butyl)-3-phenylnaphthalen-1-ol **15m** via the Cycloaddition/Electrocyclization Cascade

A single-neck 500 mL round bottom flask equipped with a condenser was charged with 4-*tert*-butyl-phenylacetic acid **22m** (13.44 g, 70.0 mmol) and SOCl₂ (18.7 mL, 256 mmol). The top of the condenser was vented to a bubbler and then into a beaker filled with NaOH (sat. aq.) to trap acidic gases (HCl and SO₂). The mixture was heated to reflux for 1 h in a 90 °C oil bath, and then all of the volatiles were carefully removed by swirling it under high vacuum (1 mm Hg) for 1 h with a 2nd liquid N₂ trap to protect the pump. To the flask containing the acyl chloride was added phenylacetylene (10.3 mL, 94 mmol) and (*i*-PrCO)₂O (23.4 mL, 141 mmol) under N₂. The mixture was stirred at 190 °C for 48 h with a gentle nitrogen flow across the top of the condenser. The brown reaction mixture was cooled to below 100 °C (*ca.* 60 °C, oil bath temperature) and a solution of KOH (23.3 g, 415 mmol) in H₂O (93 mL) was then added slowly. This two-phase mixture was stirred at 100 °C overnight. The mixture was cooled to room temperature and ethyl acetate (200 mL) was added and the mixture stirred for 10 min before the organic layer was separated. The aqueous layer was extracted twice with ethyl acetate (100 mL × 3) and the combined organic layer was washed with brine (100 mL), dried over MgSO₄, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (50 mm × 250 mm, CH₂Cl₂:hexanes 1:3 to 1:1 to 1:0) gave **15m** as an off-white solid (9.78 g, 35.4 mmol, 51%). mp 135–137 °C; R_f = 0.40 (CH₂Cl₂). Spectral data for **15m**: ¹H NMR (CDCl₃, 500 MHz) δ 1.43 (s, 9H), 5.25 (s, 1H), 7.06 (d, 1H, *J* = 2.0 Hz), 7.32–7.37 (m, 1H), 7.42–7.47 (m, 2H), 7.59–7.62 (m, 2H), 7.64–7.67 (m, 2H), 7.80 (d, 1H, *J* = 8.5 Hz), 8.08–8.10 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 31.31, 35.10, 108.41, 116.25, 118.40, 123.31, 125.80, 127.24, 127.29, 127.81, 128.78, 133.22, 138.19, 141.06, 148.30, 151.66; IR (thin film) 3505br s, 2961s, 1601s, 1559s, 1458s, 1408s, 1273s cm⁻¹; mass spectrum, *m/z* (% rel intensity) 276 M⁺ (54), 261 (96), 233 (15), 202 (24), 189 (15), 165 (9), 130 (13), 116 (100). Anal calcd for C₂₀H₂₀O: C, 86.92; H, 7.29. Found: C, 86.92; H, 7.04.

Preparation of (S)-7,7'-di-*t*-butyl VANOL **7m**

Air-Mediated Phenol Coupling—To a 500 mL flame-dried three neck round bottom flask equipped with a cooling condenser was added 7-(*tert*-butyl)-3-phenylnaphthalen-1-ol **15m** (201 mg, 0.73 mmol) and mineral oil (1 mL). Airflow was introduced from one side neck via a needle located one inch above the mixture. The airflow rate is about one bubble per second. The mixture was stirred at 165 °C for 24 h. After cooling to room temperature, CH₂Cl₂ (1 mL) and hexanes (2 mL) were added to the flask and the mixture was stirred until all large chunks had been broken up. Purification by column chromatography on silica gel (30 mm × 250 mm, CH₂Cl₂/hexanes 1:2) gave racemic **7m** as an off-white solid (145 mg, 0.26 mmol, 72%).

Deracemization^{28,29}—To a 50 mL round bottom flask was added (–)-sparteine (782 mg, 3.34 mmol), CuCl (160 mg, 1.62 mmol) and MeOH (26 mL) under an atmosphere of air. The reaction mixture was sonicated²⁹ in a water bath for 60 minutes with exposure to air.²⁹ The flask was then sealed with a septum and purged with argon, which was introduced by a needle under the surface for 60 minutes. At the same time, to a 250 mL flame-dried round bottom flask was added racemic **7m** (525 mg, 0.95 mmol) and CH₂Cl₂ (103 mL). The resulting solution was purged with argon for 60 minutes under the surface. The green Cu(II)-sparteine solution was then transferred via cannula to the solution of racemic **7m** under argon and then the combined mixture was sonicated²⁹ for 15 minutes and then allowed to stir at room temperature overnight with an argon balloon attached to the flask which was covered with aluminum foil. The reaction was quenched by slow addition of sat aq NaHCO₃.

(12 mL), H₂O (40 mL) and most of the organic solvent was removed under reduced pressure. The residue was then extracted with CH₂Cl₂ (30 mL × 3). The combined organic layer was dried over MgSO₄, filtered through Celite and concentrated to dryness. The product was purified by column chromatography on silica gel (30 mm × 250 m, CH₂Cl₂/hexanes 1:2) to afford (*S*)-**7m** as an off-white foamy solid (404 mg, 0.73 mmol, 77%). The optical purity was determined to be >99% *ee* by HPLC analysis (Pirkle D-Phenylglycine column, 99:1 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: *R*_t = 8.67 min for (*R*)-**7m** (minor) and *R*_t = 10.19 min for (*S*)-**7m** (major). mp 154–156 °C; *R*_f = 0.26 (1:2 CH₂Cl₂/hexanes). Spectral data for **7m**: ¹H NMR (CDCl₃, 500 MHz) δ 1.48 (s, 18H), 5.81 (s, 2H), 6.61 (dd, 4H, *J* = 8.0, 1.0 Hz), 6.95 (t, 4H, *J* = 8.0 Hz), 7.03–7.07 (m, 2H), 7.28 (s, 2H), 7.66 (dd, 2H, *J* = 8.5, 2.0 Hz), 7.73 (d, 2H, *J* = 8.5 Hz), 8.29–8.30 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 31.33, 35.19, 112.72, 117.71, 121.63, 122.65, 126.39, 127.43, 127.45, 128.90, 132.83, 140.01, 140.40, 148.58, 150.24 (1 sp² C not located); IR (thin film) 3519br s, 3058w, 2961s, 1597s, 1497s, 1385s, 1265s cm⁻¹; mass spectrum, *m/z* (% rel intensity) 550 M⁺ (47), 535 (13), 275 (29), 260 (89), 232 (29). Anal calcd for C₄₀H₃₈O₂: C, 87.23; H, 6.95. Found: C, 86.90; H, 7.16. [α]_D²⁰ = −215.2 (c 1.0, CH₂Cl₂) on >99% *ee* (*S*)-**7m** (HPLC).

Asymmetric Catalytic Aziridination with a BOROX Catalyst Prepared from (*S*)-7,7'-Di-*t*-butyl VANOL **7m**

A 25 mL pear-shaped single necked Schlenk flask which had its 14/20 joint replaced by a threaded high vacuum Teflon valve was flame dried (with a stir bar in it) and cooled to room temperature under N₂ and charged with (*S*)-*t*-Bu₂VANOL **7m** (13.8 mg, 0.025 mmol) and triphenyl borate (29 mg, 0.10 mmol). The mixture was dissolved in dry toluene (1 mL). After the addition of H₂O (0.45 μL, 0.025 mmol), the Teflon valve was closed and the flask was heated at 80 °C for 1 h. Toluene was carefully removed by exposing to high vacuum (0.1 mmHg) by slightly cracking the Teflon valve. After removal of the solvent, the Teflon valve was completely opened and the flask was heated to 80 °C under high vacuum for 30 min. To the Schlenk flask containing the catalyst were added imine **10d** (136 mg, 0.50 mmol) and dry toluene (1 mL). The reaction mixture was stirred at room temperature for 5 minutes and then ethyl diazoacetate (62 μL, 0.6 mmol) was added via syringe. The Teflon valve was closed and the reaction mixture was stirred at room temperature for 24 h. The mixture was then diluted with hexanes (5 mL) and transferred to a 25 mL round bottom flask. Rotary evaporation of the solvent followed by exposure to high vacuum (0.5 mm Hg) for 30 minutes gave the crude mixture as an off-white solid. The conversion was determined from the ¹H NMR spectrum of the crude reaction mixture by integration of the aziridine ring methine protons relative to either the imine methine proton or the H on the imine carbon. The *cis/trans* ratio was determined to be >100:1 from the ¹H NMR spectrum of the crude reaction mixture by integration of the ring methine protons for each aziridine. The *cis* (*J* = 6–8 Hz) and the *trans* (*J* = 1–3 Hz) coupling constants were used to differentiate the two isomers. The yields of the acyclic enamine products were determined to be <1% from the ¹H NMR spectrum of the crude reaction mixture by integration of the N-H proton of the enamine relative to the aziridine ring methine protons with the aid of the isolated yield of the *cis*-aziridine. The crude product was purified by column chromatography on silica gel (35 mm × 400 mm, EtOAc:hexanes 1:19) to afford **12d** as a white solid (146 mg, 0.41 mmol, 82%). The optical purity was determined to be 98% *ee* by HPLC (Chiralcel OD-H column, 222 nm, 90:10 hexane/*i*PrOH, flow rate: 0.7 mL/min). Retention time: *R*_t = 4.42 min for (2*S*, 3*S*)-**12d** (minor) and *R*_t = 8.17 min for (2*R*, 3*R*)-**12d** (major). The reaction was repeated and stopped after a reaction time of 4 h to give an 89% yield of **12d** with 97.4% *ee*. mp 126–127 °C; *R*_f = 0.13 (1:9 EtOAc:hexanes). Spectral data for **12d**: ¹H NMR (CDCl₃, 500 MHz) δ 0.96 (t, 3H, *J* = 7.0 Hz), 2.65 (d, 1H, *J* = 7.0 Hz), 3.19 (d, 1H, *J* = 7.0 Hz), 3.93 (s, 1H), 3.90–3.94 (m, 2H), 7.14–7.20 (m, 2H), 7.20–7.26 (m, 5H), 7.30–7.34 (m, 2H), 7.37–7.40

(m, 2H), 7.46–7.49 (m, 2H), 7.57–7.60 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 13.93, 46.38, 48.03, 60.55, 77.71, 127.19, 127.21, 127.31, 127.40, 127.54, 127.75, 127.78, 128.48, 135.03, 142.38, 142.52, 167.72 (1 sp^2 C not located); IR (thin film) 3031w, 2982w, 1738s, 1456m, 1204s cm^{-1} ; mass spectrum, m/z (% rel intensity) 357 M^+ (0.05), 190 (46), 167 (100), 117 (61). $[\alpha]_{\text{D}}^{20} = +36.2$ (c 1.0, CH_2Cl_2) on 98% *ee* (2*R*,3*R*)-**12d**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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29. Sonification is called for in the original procedure reported in reference 28 and is employed in the present work, but we have recently found that the deracemization of VAPOL gives the same result whether or not sonication is employed: Y. Guan, W. D. Wulff, unpublished results.

Figure 1.
3-D structure of the (S)-VANOL BOROX anion.

Figure 2.
Positional Isomers of the VANOL Ligand.

Scheme 1.
Substrate Assembled BOROX catalysts.

Scheme 2.
Imine Substrates in BOROX catalyzed reactions.

Scheme 3.
Library Synthesis of 7, 7'-disubstituted VANOLs.

Table 1

VANOL positional isomer screen in the aziridination reaction^[a]

10d R ¹ = Ph 10i R ¹ = Cy		11	12d R ¹ = Ph 12i R ¹ = Cy		
entry	Ligand	R	12d R ¹ = Ph % yield ^[b]	12i R ¹ = Cy % yield ^[b]	% ee ^[c]
1	VANOL	—	84	92	77
2	VAPOL	—	76	93	78
3	4q	<i>p</i> ^t BuC ₆ H ₄	75	3	68
4	5q	<i>p</i> ^t BuC ₆ H ₄	87	84	79
5	6q	<i>p</i> ^t BuC ₆ H ₄	82	89	77
6	7q	<i>p</i> ^t BuC ₆ H ₄	85	97	83
7	4d	Br	86	45	81
8	5d	Br	87	92	80
9	6d	Br	83	90	76
10	7d	Br	89	89	78
11	5p	<i>p</i> CF ₃ C ₆ H ₄	92	78	84
12	6p	<i>p</i> CF ₃ C ₆ H ₄	92	87	86
13	7p	<i>p</i> CF ₃ C ₆ H ₄	92	84	93
14	8h	Me	83	80	72
15	8ah	Ph	62 ^[d]	8	26 ^[e]
16	9	—	90	82	87

^[a] Unless otherwise specified, all reactions were run at 0.5 M in imine in toluene on a 0.5 mmol scale with 1.2 equiv EDA at 25 °C for 24 h and went to 100% completion with 5 mol% catalyst. The catalyst was prepared from 1 equiv ligand, 4 equiv B(OPh)₃ and 1 equiv H₂O at 80 °C in toluene for 1 h, followed by removal of volatiles under vacuum (0.5 mm Hg) at 80 °C for 0.5 h.

^[b] Yield of isolated *cis*-aziridine by chromatography on silica gel.

^[c] Determined by HPLC on a Chiralcel OD-H column.

[d] The reaction time was 4 d and conversion was 88%.

[e] The reaction time was 4 d and conversion was 78%.

Table 2

Screen of the 7,7'-disubstituted VANOL Library^[a]

10d R ¹ = Ph 10i R ¹ = Cy	11	12d R ¹ = Ph 12i R ¹ = Cy	
ligand	R	12d R ¹ = Ph % yield ^[b]	12i R ¹ = Cy % ee ^[c]
VANOL	H	84	92
7b	F	80	83
7c	Cl	91	89
7d	Br	89 ^[d]	89 ^[d]
7e	I	85	92
7f	CF ₃	96	86
7g	OMe	86	96
7h	Me	82 ^[e]	86 ^[e]
7i	Et	90	94
7j	<i>n</i> -Bu	95	94
7k	<i>i</i> -Pr	93	97
7l	Cy	94	94
7m	<i>t</i> -Bu	82 ^[f]	98 ^[f]
7n	SiPh ₂ <i>t</i> -Bu	77	94
7o	4-MeC ₆ H ₄	94	96
7p	4-CF ₃ C ₆ H ₄	92	84
7q	4- <i>t</i> -BuC ₆ H ₄	85	97
7r	3,5-Me ₂ C ₆ H ₃	82	95
7s	3,5-(<i>t</i> -Bu) ₂ -4-MeOC ₆ H ₂	85	97
7t	3,5-(CF ₃) ₂ C ₆ H ₃	94	95

$\text{10d R}^1 = \text{Ph}$ 11 $\text{12d R}^1 = \text{Ph}$
 $\text{10e R}^1 = \text{Cy}$ $\text{12e R}^1 = \text{Cy}$

ligand	R	$\text{12d R}^1 = \text{Ph}$	$\text{12e R}^1 = \text{Cy}$
		% yield ^[b] % ee ^[c]	% yield ^[b] % ee ^[c]
7u	2,6-Me ₂ C ₆ H ₃	77 91	72 82
7v	1-naphthyl	92 92	87 81
7w	2-naphthyl	91 95	94 90
7x	9-anthracenyl	88 84	72 63
7y	2-C ₄ H ₃ S	96 95	90 88
7z	2-C ₄ H ₃ O	95 96	77 76
7aa	3-C ₄ H ₃ S	96 96	91 90
7ab	3-C ₄ H ₃ O	98 95	90 89
7ac	-CH=CH	91 93	90 82
7ad	-C≡CH	86 93	85 84
7ae	-C≡CSiMe ₃	86 92	79 88
7af	-C≡C- <i>i</i> -Bu	94 94	87 87

^[a] Unless otherwise specified, all reactions were run at 0.5 M in imine in toluene on a 0.5 mmol scale with 1.2 equiv EDA at 25 °C for 24 h and went to 100% completion with 5 mol% catalyst. The catalyst was prepared as indicated in Table 1.

^[b] Yield of isolated *cis*-aziridine by chromatography on silica gel.

^[c] Determined by HPLC on a Chiralcel OD-H column.

^[d] A repeat of this reaction on 1.0 mmol scale gave 80% yield and 88% ee.

^[e] A repeat of this reaction on 1.0 mmol scale gave 87% yield and 86% ee.

^[f] A repeat of this reaction revealed that it was complete in 4 h to give 89% yield and 97.4% ee.

Table 3

Substrate Scope: VANOL **1** vs 7,7'-*t*-Bu₂VANOL **7m**^[a]

10	11	12
VANOL BOROX ^[b]				
series	R ¹	% yield 12 ^[c]	% ee 12 ^[d]	% ee 12 ^[d]
a	4-NO ₂ C ₆ H ₄	86	89	96
b	4-BrC ₆ H ₄	86	94	90
c	2-BrC ₆ H ₄	43 ^[e]	82	78 ^[f]
d	C ₆ H ₅	87	93	82
e	1-naphthyl	80	93	91
f	2-MeC ₆ H ₄	67 ^[g]	90	92 ^[h]
g	4-MeOC ₆ H ₄	67	87	71
h	<i>n</i> -propyl	54	77	77
i	cyclohexyl	79	82	88
j	<i>t</i> -butyl	89	85	89
	average	74	87	85

^[a] unless otherwise specified, all reactions were run at 0.5 M in imine in toluene on a 0.5 mmol scale with 1.2 equiv EDA at 25 °C for 24 h and went to 100% completion with 5 mol% catalyst. The catalyst was prepared as indicated in Table 1.

^[b] data taken from ref 4h.

^[c] yield of isolated *cis*-aziridine by chromatography on silica gel.

^[d] determined by HPLC on a Chiralcel OD-H column.

^[e] plus 23% yield *trans*-**6c** (*cis*/*trans* = 1.9:1).

^[f] plus 10% yield *trans*-**6c** (*cis*/*trans* = 8:1).

^[g] plus 6% yield *trans*-**6f** (*cis*/*trans* = 12:1).

$[\eta]_{cis/trans} > 100:1.$

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