CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.201302451

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

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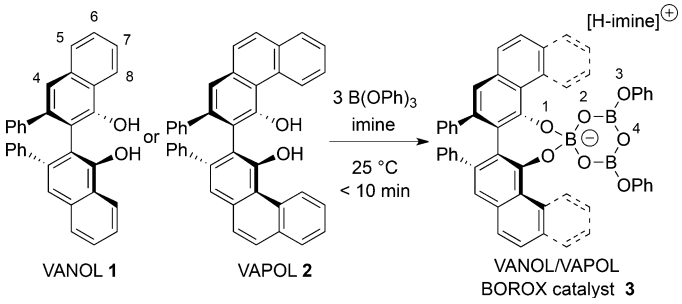
Abstract: The active site in the BOROX catalyst is a chiral polyborate anion (boroxinate) that is assembled in situ from three equivalents of $B(OPh)_3$ and one of the VANOL ligand by a molecule of substrate. The substrates are bound to the boroxinate by H bonds to oxygen atoms O1–O3. The effects of 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.

Keywords: asymmetric catalysis · biaryls · catalysis · structure–activity relationships

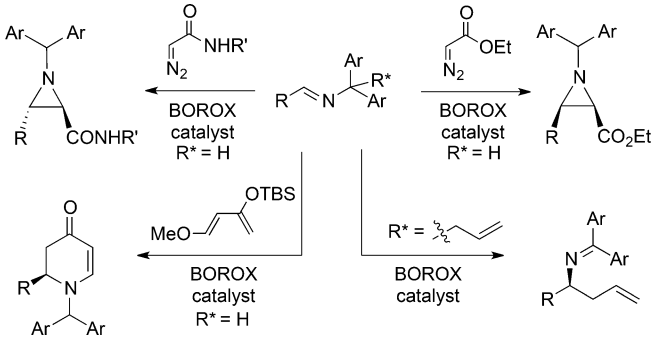
Introduction

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 reaction[3] *cis*-aziridination of imines[4,5] *trans*-aziridination of imines,[4q,6] Baeyer–Villiger reactions,[7] benzoyloxylation 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] multicomponent 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 aminals[23] 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 rearrangement[2] and are presumably involved in heteroatom Diels–Alder reactions of imines as well (Scheme 2).[11]



Scheme 1. Substrate assembled BOROX catalysts.



Scheme 2. Imine substrates in BOROX catalyzed reactions.

The 3D structure of the (*S*)-VANOL–BOROX anion (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*-aziridination reaction both substrates are H bonded to various oxygen atoms of the boroxinate anionic core.[6b,c] 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,c] However, in the latter case the diazo compound (diazoacetamide) is bound to the catalyst by two H bonds, one from the hy-

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201302451; including procedures for the preparation for the 3-phenyl phenols **15** and the 44 new VANOL derivatives and the asymmetric syntheses of aziridines **12**.

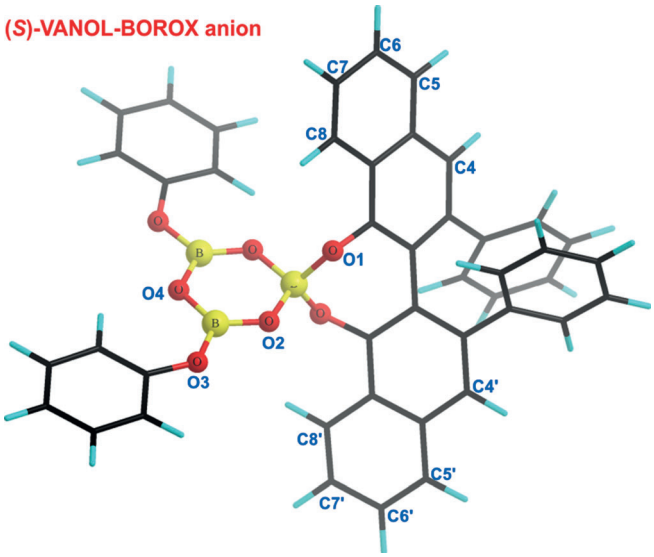


Figure 1. The 3D structure of the (*S*)-VANOL–BOROX anion.

drogen 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 (Figure 2). 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 (±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 its 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.

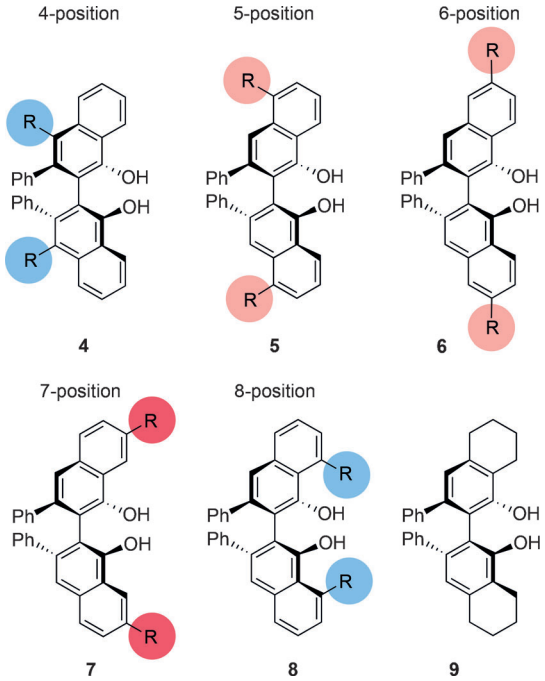
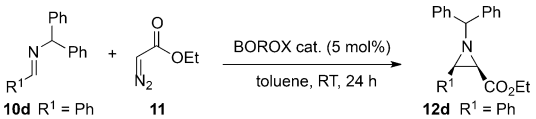


Figure 2. Positional isomers of the VANOL ligand.

Results and Discussion

For each of the five positions on VANOL several different substituents were investigated including bromide, *p*-*tert*-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 ^{11}B NMR spectrum revealed that at least some of the boroxinate species is formed, but it is certainly possible that there could be significant background reactions with nonchiral borate species (see the 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 the ^{11}B NMR

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

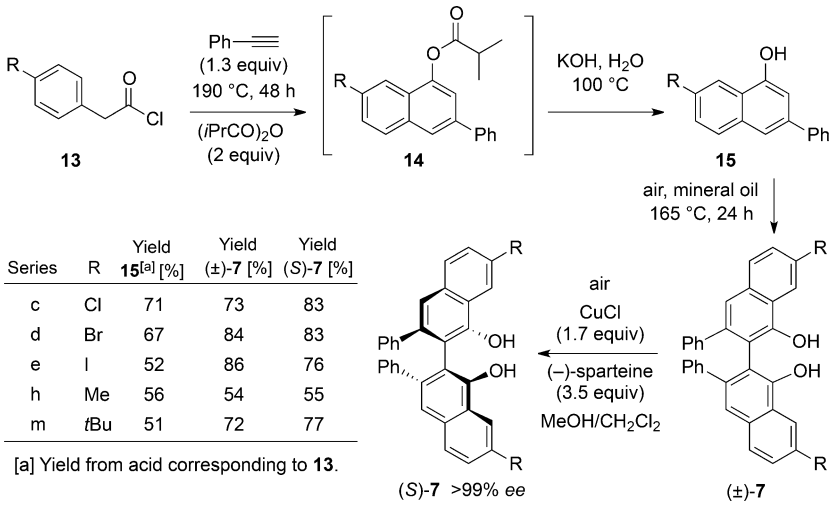
Entry	Ligand	R	**12d** R^1 = Ph		**12i** R^1 = Cy	
			Yield [b]	*ee* [%][c]	Yield [%][b]	*ee* [%][c]
1	VANOL	–	84	92	77	81
2	VAPOL	–	76	93	78	82
3	**4q**	*p*-*t*BuC$_6$H$_4$	75	3	68	1
4	**5q**	*p*-*t*BuC$_6$H$_4$	87	84	79	74
5	**6q**	*p*-*t*BuC$_6$H$_4$	82	89	77	82
6	**7q**	*p*-*t*BuC$_6$H$_4$	85	97	83	93
7	**4d**	Br	86	45	81	45
8	**5d**	Br	87	92	80	83
9	**6d**	Br	83	90	76	79
10	**7d**	Br	89	89	78	85
11	**5p**	*p*-CF$_3$C$_6$H$_4$	92	78	84	69
12	**6p**	*p*-CF$_3$C$_6$H$_4$	92	87	86	78
13	**7p**	*p*-CF$_3$C$_6$H$_4$	92	84	93	78
14	**8h**	Me	83	80	72	77
15	**8ah**	Ph	62[d]	8	26[e]	15
16	**9**	–	90	82	87	90

[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 H_2O 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 %.

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*-*tert*-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 through a cycloaddition/electrocyclization cascade (CAEC) process[27] and a few examples are indicated in Scheme 3. Simply heating the acid chloride **13** with phenyl acetylene led to the corresponding 3-phenyl-1-naphthol (**15**) after liberation from the *iso*-butryate ester **14**. *iso*-Butyric anhydride was 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 was used to acquire the racemic ligand in good to high yields. Although a large-scale resolution method has been developed for VANOL,[27] on the laboratory scale, the most convenient way to access the optically 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 31-member library of 7,7′-disubstituted VANOL ligands was 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 (Scheme 3) and the rest were prepared by a variety of



Series	R	Yield **15**[a] [%]	Yield (±)-**7** [%]	Yield (*S*)-**7** [%]
c	Cl	71	73	83
d	Br	67	84	83
e	I	52	86	76
h	Me	56	54	55
m	*t*Bu	51	72	77

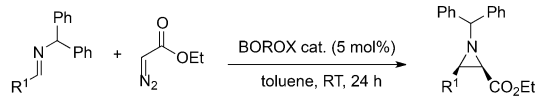
[a] Yield from acid corresponding to **13**.

Scheme 3. Library synthesis of 7,7′-disubstituted VANOLs.

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 31 different substituents in the 7- and 7′-positions examined led to improved asymmetric inductions for both aziridines (20 for **12d** and 24 for **12i**). It was most remarkable to find that out of all thirty of the new VANOL ligands, the best

Table 2. Screen of the 7,7′-disubstituted VANOL Library.[a]



10d R^1 = Ph **11** **12d** R^1 = Ph
10i R^1 = Cy **12i** R^1 = Cy

Ligand	R	**12d** R^1 = Ph		**12i** R^1 = Cy	
		Yield [%][b]	*ee* [%][c]	Yield [%][b]	*ee* [%][c]
VANOL	H	84	92	77	81
7b	F	80	83	76	82
7c	Cl	91	89	83	78
7d	Br	89[d]	89[d]	78	85
7e	I	85	92	80	88
7f	CF_3	96	86	88	85
7g	OMe	86	96	88	92
7h	Me	82[e]	86[e]	83	87
7i	Et	90	94	91	87
7j	*n*Bu	95	94	91	89
7k	*i*Pr	93	97	91	89
7l	Cy	94	94	90	87
7m	*t*Bu	82[f]	98[f]	88	94
7n	$SiPh_2tBu$	77	94	72	79
7o	4-MeC_6H_4	94	96	89	90
7p	4-$CF_3C_6H_4$	92	84	93	78
7q	4-$tBuC_6H_4$	85	97	83	93
7r	3,5-$Me_2C_6H_3$	82	95	88	92
7s	3,5-$(tBu)_2$-4-$MeOC_6H_2$	85	97	77	86
7t	3,5-$(CF_3)_2C_6H_3$	94	95	90	80
7u	2,6-$Me_2C_6H_3$	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_4H_3S	96	95	90	88
7z	2-C_4H_3O	95	96	77	76
7aa	3-C_4H_3S	96	96	91	90
7ab	3-C_4H_3O	98	95	90	89
7ac	−CH=CH	91	93	90	82
7ad	−C≡CH	86	93	85	84
7ae	−C≡C$SiMe_3$	86	92	79	88
7af	−C≡C-*t*Bu	94	94	87	87

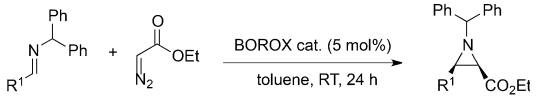
[a] Unless otherwise specified, all reactions were run at 0.5 M in imine in toluene on a 0.5 mmol scale with 1.2 equiv EDA at 25 °C for 24 h and went to 100 % completion with 5 mol % catalyst. The catalyst was prepared as indicated in Table 1. [b] Yield of isolated *cis*-aziridine by chromatography on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

ligand for the cyclohexyl imine **10i** was also the best ligand for the phenyl imine **10d**. Given this singularity for the 7,7′-di-*tert*-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, in which 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-*tert*-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 were 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-*tert*-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 and 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-*tert*-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 in-

Table 3. Substrate scope: VANOL **1** versus 7,7′-tBu_2VANOL **7m**.[a]



10 **11** **12**

Series	R^1	VANOL BOROX[b]		7,7′-tBu_2VANOL BOROX	
		Yield **12** [%][c]	*ee* **12** [%][d]	Yield **12** [%][c]	*ee* **12** [%][d]
a	4-$NO_2C_6H_4$	86	89	96	98
b	4-BrC_6H_4	86	94	90	98
c	2-BrC_6H_4	43[e]	82	78[f]	95
d	C_6H_5	87	93	82	98
e	1-naphthyl	80	93	91	99
f	2-MeC_6H_4	67[g]	90	92[h]	97
g	4-$MeOC_6H_4$	67	87	71	98
h	*n*-propyl	54	77	77	94
i	cyclohexyl	79	82	88	94
j	*tert*-butyl	89	85	89	96
	average	74	87	85	97

[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); [h] *cis*/*trans* > 100:1.

troduction of the *tert*-butyl in the 7- and 7′-positions of VANOL (87 vs. 97% *ee*). Not only are the asymmetric inductions dramatically improved with the di-*tert*-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 aziridination 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-*tert*-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-*tert*-butylVANOL catalysts, respectively. Thus, the di-*tert*-butylVANOL catalyst is superior to either VANOL or VAPOL catalysts in providing diastereoselective and enantioselective access to aziridines from benzhydryl imines.

Conclusion

A systematic mapping of the sensitivity of the active site in a VANOL boroxinate catalyst in response to steric and electronic effects of substitutions in the naphthalene core to the catalytic transfer of chirality in an aziridination reaction 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-*tert*-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 unsubstituted VANOL for every imine with an overall average of 10% higher *ee* and 11% higher yield. The 7,7′-di-*tert*-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 diphenylmethylamine. 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 disubstituted 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.

Experimental Section

Preparation of 7-(*tert*-butyl)-3-phenylnaphthalen-1-ol (15m) through the cycloaddition/electro-cyclization cascade: A single-neck 500 mL round bottom flask equipped with a condenser was charged with 4-*tert*-butylphenylacetic acid **22m** (13.44 g, 70.0 mmol) and $SOCl_2$ (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 SO_2). 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 second liquid N_2 trap to protect the pump. Under N_2 phenylacetylene (10.3 mL, 94 mmol) and $(i\mathrm{PrCO})_2O$ (23.4 mL, 141 mmol) were added to the flask containing the acyl chloride. The mixture was stirred at 190 °C for 48 h with a gentle nitrogen flow across the top of the condenser. Sometimes two condensers are required to ensure the efficient return of phenylacetylene. 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 H_2O (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 $MgSO_4$, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (50 mm × 250 mm, CH_2Cl_2/hexanes 1:3 to 1:1 to 1:0) gave **15m** as an off-white solid (9.78 g, 35.4 mmol, 51%). M.p.: 135–137 °C; R_f = 0.40 (CH_2Cl_2). Spectral data for **15m**: ^{1}H NMR ($CDCl_3$, 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 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 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 ppm; IR (thin film): $\tilde{\nu}$ = 3505 (br s), 2961 (s), 1601 (s), 1559 (s), 1458 (s), 1408 (s), 1273 cm^{-1} (s); MS: *m/z* (%): 276 $[M]^+$ (54), 261 (96), 233 (15), 202 (24), 189 (15), 165 (9), 130 (13), 116 (100); elemental analysis calcd for $C_{20}H_{20}O$: C 86.92, H 7.29; found: C 86.92, H 7.04.

Preparation of (*S*)-7,7′-di-*tert*-butyl VANOL 7m

Air-mediated phenol coupling: 7-(*tert*-Butyl)-3-phenylnaphthalen-1-ol **15m** (201 mg, 0.73 mmol) and mineral oil (1 mL) were added to a 500 mL flame-dried three neck round bottom flask equipped with a cooling condenser. Airflow was introduced from one side neck via a needle located one inch above the mixture. The airflow rate was about one bubble per second. The mixture was stirred at 165 °C for 24 h. After being cooled to room temperature, CH_2Cl_2 (1 mL) and hexanes (2 mL) were added to the flask and the mixture was stirred until all large pieces were broken up. Purification by column chromatography on silica gel (30 mm × 250 mm, CH_2Cl_2/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 sonicated[29] in a water bath for 60 min 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 min. At the same time, to a 250 mL flame-dried round bottom flask was added racemic **7m** (525 mg, 0.95 mmol) and CH_2Cl_2 (103 mL). The resulting solution was purged with argon for 60 min 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 sonicated[29] for 15 min 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. $NaHCO_3$ (12 mL), H_2O (40 mL) and most of the organic solvent was removed under reduced pressure. The residue was then extracted with CH_2Cl_2 (30 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through Celite and concentrated to dryness. The product was purified by column chromatography on silica gel (30 mm × 250 m, CH_2Cl_2/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^{-1}). Retention times: t_R = 8.67 min for (*R*)-**7m** (minor) and t_R = 10.19 min for (*S*)-**7m** (major). M.p.: 154–156 °C; R_f = 0.26 (1:2 CH_2Cl_2/hexanes). Spectral data for **7m**: ^{1}H NMR ($CDCl_3$, 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 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 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 ppm (1 sp^2 C not located); IR (thin film): $\tilde{\nu}$ = 3519 (br s), 3058 (w), 2961 (s), 1597 (s), 1497 (s), 1385 (s), 1265 cm^{-1} (s); MS: *m/z* (%): 550 $[M]^+$ (47), 535 (13), 275 (29), 260 (89), 232 (29); elemental analysis calcd for $C_{40}H_{38}O_2$: C 87.23, H 6.95; found: C 86.90, H 7.16; $[\alpha]_D^{20}$ = −215.2 (*c* 1.0, CH_2Cl_2) on >99% *ee* (*S*)-**7m** (HPLC).

Asymmetric catalytic aziridination with a BOROX catalyst prepared from (*S*)-7,7′-di-*tert*-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 N_2 and charged with (*S*)-*t*Bu$_2$VANOL **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 H_2O (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 mm Hg) 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. Imine **10d** (136 mg, 0.50 mmol) and dry toluene (1 mL) were added to the Schlenk flask containing the catalyst. The reaction mixture was stirred at room temperature for 5 min 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 min gave the crude mixture as an off-white solid. The conversion was determined from the ^{1}H 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 ^{1}H 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 ^{1}H 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^{-1}). Retention time: t_R = 4.42 min for (2*S*,3*S*)-**12d** (minor) and t_R = 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*. M.p.: 126–127 °C; R_f = 0.13 (1:9 EtOAc/hexanes). Spectral data for **12d**: ^{1}H NMR ($CDCl_3$, 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 ppm (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 ppm (1 sp^2 C not located); IR (thin film): $\tilde{\nu}$ = 3031 (w), 2982 (w), 1738 (s), 1456 (m), 1204 cm^{-1} (s); MS: *m/z* (%): 357 $[M]^+$ (0.05), 190 (46), 167 (100), 117 (61); $[\alpha]_D^{20}$ = +36.2 (*c* 1.0, CH_2Cl_2) on 98% *ee* (2*R*,3*R*)-**12d**.

Acknowledgements

This work was supported by the National Institute of General Medical Sciences (GM 094478).

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Received: June 25, 2013
Published online: October 2, 2013

