Catalytic Asymmetric Epoxidation of Aldehydes with Two VANOL-Derived Chiral Borate Catalysts

Anil K. Gupta[+], Xiaopeng Yin[+], Munmun Mukherjee, Aman A. Desai, Aliakbar Mohammadlou, Kelsee Jurewicz, and William D. Wulff*

Abstract: *A highly diastereo- and enantioselective method for the epoxidation of aldehydes with α-diazoacetamides has been developed with two different borate ester catalysts of VANOL. Both catalytic systems are general for aromatic, aliphatic, and acetylenic aldehydes, giving high yields and inductions for nearly all cases. One borate ester catalyst has two molecules of VANOL and the other only one VANOL. Catalysts generated from BINOL and VAPOL are ineffective catalysts. An application is shown for access to the side-chain of taxol.*

*T*he tactical repertoire for the conversion of either an aldehyde or ketone into an epoxide largely consists of two transformations (Scheme 1): 1) the Darzens condensation of an α-halo stabilized carbanion with the a carbonyl compound,[1,2] 2) the Corey–Chaykovsky reaction which involves a sulfur ylide as a carbene surrogate in the synthesis of epoxides.[3–7] A third method involving the formation of epoxides from the reactions of diazo compounds are not that common and have not been particularly useful.[8–10] However,

efficient catalytic asymmetric versions have been more recently reported by Gong and co-workers for the reactions of aldehydes with secondary α-diazoacetamides.[11a,b] These reactions gave high asymmetric inductions with chiral complexes of titanium or zirconium with BINOL and BINOL derivatives. Two additional titanium complexes have also been reported.[11c,d] We report herein the first non-transition metal catalyzed asymmetric epoxidation of aldehydes with diazo compounds. We also report the discovery of two different chiral borate catalysts that are nearly equally effective for this reaction. Prior to this work, chiral borate esters were not engaged in aldehyde activation other than for Diels–Alder reactions.[12,13]

We previously reported asymmetric methods for the synthesis of both *cis*- and *trans*-substituted aziridines by the addition of diazo compounds to imines with a BOROX catalyst derived from either VANOL or VAPOL (Scheme 2).

Scheme 1. Epoxides from ketones and aldehydes. EWG = electron-withdrawing group.

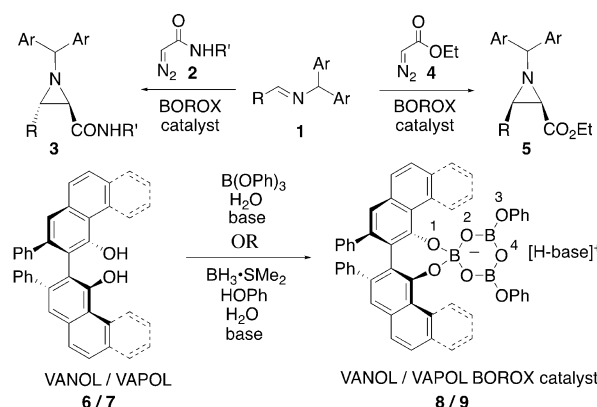***Scheme 2.*** The *cis*- and *trans*-aziridination with BOROX catalysts.

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The diazo ester **4** reacts to give *cis*-aziridines,[14] whereas, the diazo acetamide **2** reacts with the same imine and the same catalyst (either VANOL or VAPOL) to give *trans*-aziridines.[15,16] The structure of the BOROX catalyst (**8/9**) for the aziridination reactions was determined to have a boroxine ring by NMR spectroscopy, and X-ray analysis, as well as KIE and computational studies.[15b,17a,c] The BOROX catalyst can be assembled in situ by the imine substrate from the ligand by a number of methods, but the most common method is that with either B(OPh)₃ or BH₃·SMe₂ and phenol.[14e,17,18] Most amines and imines are basic enough to cause assembly of the BOROX catalyst.

Attempts to utilize the BOROX catalyst for the generation of epoxides from aldehydes and ethyl diazoacetate have

been unsuccessful, undoubtedly because of the fact that neither substrate is capable of generating the BOROX catalyst.[14e] First an aldehyde is not a strong enough base to assemble a BOROX catalyst. Second, ethyl diazoacetate reacts with VAPOL and B(OPh)$_3$ to only give the alkylated VAPOL derivative **14a** in 80% yield, and thus prevents the formation of the BOROX catalyst (Scheme 3). The actual reaction of ethyl diazoacetate with benzaldehyde in the presence of VAPOL and B(OPh)$_3$ has been previously carried out for a different purpose and the epoxide **12** (R = Ph) was produced along with other products but only in 3% yield.[14e]
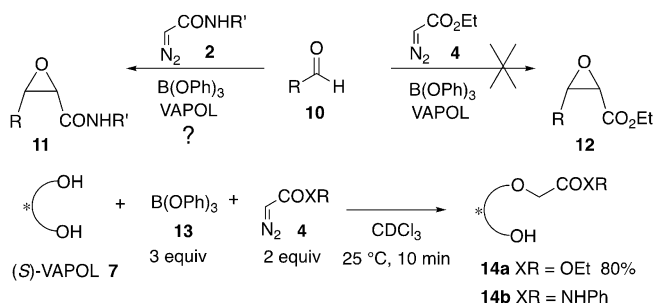
Scheme 3. Epoxides from aldehydes with a BOROX catalyst and reaction of the VAPOL ligand.

The question remains whether the epoxidation of an aldehyde with a diazoacetamide can be effected with a BOROX catalyst. VAPOL and B(OPh)$_3$ do not react by themselves, but in the presence of **2a**, a reaction occurs, however, unlike ethyl diazoacetate, the O−H insertion product **14b** was not observed. A small amount of a boron species that could be assigned as a BOROX complex was observed but other three-coordinate boron species were evident. At this point it was thought that it might be possible to add a non-reacting basic species that could cause the assembly of the BOROX catalyst but not interfere with the reaction itself. Various bases were screened and many were found to be efficacious in the reaction of benzaldehyde (**15**) and **2a**, including aniline and DMSO (dimethyl sulfoxide) with VANOL the optimal ligand (see the Supporting Information).

A suitable protocol for the epoxidation of aldehydes was found (Table 1). The catalyst was prepared by heating 3 equivalents of BH$_3$·SMe$_2$, 2 equivalents of phenol, 1 equivalent of VANOL, and 3 equivalents H$_2$O in toluene at 100°C followed by exposure to high vacuum to remove volatiles and then exposure of the pre-catalyst to 1 equivalent of DMSO at 25°C for an hour. With 10 mol% of this catalyst, the epoxidation of **15** with **2a** is achieved in 88% yield and 99% *ee* with greater than 100:1 selectivity for the *cis*-diastereomer (entry 1). The formation of the *cis*-epoxide was unexpected since the same diazo compound gives *trans*-aziridines with imines (see Scheme 2). The origins of this stereochemical outcome is not understood presently. Excellent asymmetric inductions were observed for the epoxidation of aldehydes, including electron-rich and electron-poor aryl aldehydes. Slightly lower inductions were observed for *ortho*-

substituted aryl aldehydes (Table 1, entries 6 and 14) and for aliphatic aldehydes (entries 17 and 18).

There is the question of the nature of the catalyst for the reaction in Table 1. Is it a BOROX catalyst of the type **8** that is effective in the aziridination reaction? To probe whether a BOROX-type catalyst is involved, the catalyst was prepared by leaving out the water and the phenol with the result that the reaction in entry 1 of Table 1 was unaffected (92% yield and 99% *ee*; see the Supporting Information). This result certainly means that the BOROX species **8** cannot be the catalyst.

After extensive additional investigational studies (see the Supporting Information), it was found that the epoxidation reaction can be optimized to give a catalyst prepared from two molecules of the VANOL ligand and only one molecule of BH$_3$·SMe$_2$. A survey of aldehydes with the catalyst **B** is given in Table 2. A wide range of electron-poor and electron-rich aryl aldehydes were epoxidized with excellent asymmetric induction. The reaction of *para*-methoxybenzaldehyde is far too slow to be useful, however, its surrogate *para*-acetoxybenzaldehyde gives the epoxide **49a** in 92% yield and 99% *ee* (entry 12 versus 13). With aliphatic aldehydes, it was found that asymmetric inductions of greater than 99% *ee* could be realized with unbranched, α-branched, and α,α-bis-branched aliphatic aldehydes (entries 27, 31, 33, and 35). The reaction could also be extended to acetylenic aldehydes with excellent induction, but not to alkenyl aldehydes (entries 36–39). The absolute configurations of **41b**, **60b**, and **62b** are known[10] and that of **41a** was determined by conversion into the taxol side-chain **72** (Scheme 4). The rest were assumed to
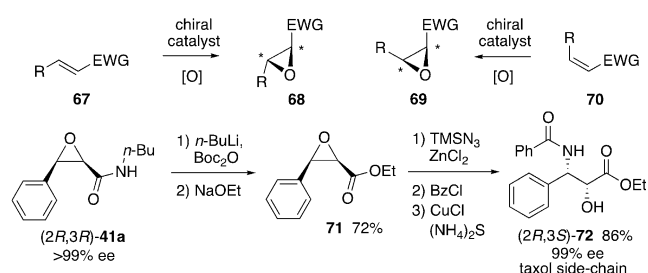
Scheme 4. Application of *cis*-epoxides.

be homochiral. The reaction of **2a** with **15** could be scaled up tenfold to 6.0 mmol and in 20 minutes gives a 95% yield of **41a** (1.25 g) with greater than 99% *ee*. The reaction of **15** is slightly slower (ca. 5X) with the catalyst **A** than it is with the catalyst **B** (Table 1, entry 3 vs. Table 2, entry 1). The reactions without DMSO tend to be a little slower with the inductions dropping slightly with **2a** and **2b**. However, for **2c** there is either a small or no difference between reactions run with or without DMSO (Table 2, entries 3, 18, 31, 33, and 39).

The approach to epoxides involving the formal addition of a carbene to a carbonyl, exemplified by the present work, is complimentary to that which involves a formal addition of an oxygen atom to an α,β-unsaturated carbonyl compound (Scheme 4). A significant body of literature exists on the asymmetric epoxidation of electron-deficient alkenes.[19] However, most all methods involve the epoxidation of

Table 1: Asymmetric epoxidation of aldehydes with the VANOL Catalyst **A**.[a]
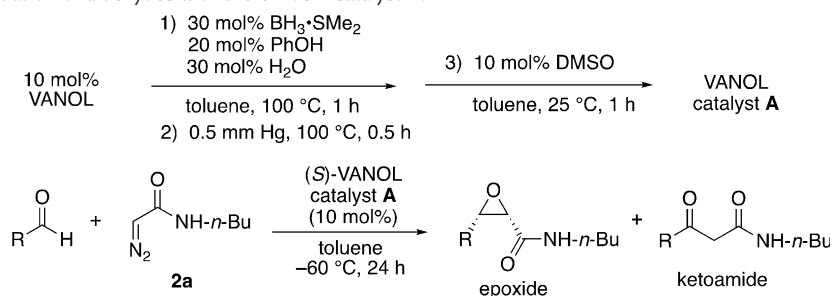
Entry	R	Aldehyde		Epoxide Yield [%][b]	ee [%][c]	cis/trans[d]	Ketoamide Yield [%][e]
1	C_6H_5	**15**	**41a**	88 (79)	99 (90)	>100:1	<1 (5)
2[f]	C_6H_5	**15**	**41a**	90 (76)	98 (72)	>50:1	5
3[g]	C_6H_5	**15**	**41a**	38	90	n.d.	n.d.
4[h]	C_6H_5	**15**	**41a**	21	54	n.d.	51
5[i]	C_6H_5	**15**	**41a**	20[e]	37	n.d.	52
6	2-MeC_6H_4	**16**	**42a**	60	80	>100:1	<1
7	4-MeC_6H_4	**17**	**43a**	80	98	>100:1	<1
8	1-naphthyl	**18**	**44a**	97	92	35:1	<1
9	2-naphthyl	**19**	**45a**	92	98	>100:1	<1
10	3-MeOC_6H_4	**21**	**47a**	80	90	31:1	6
11	4-AcOC_6H_4	**23**	**49a**	82	97	>100:1	4
12	3-BrC_6H_4	**25**	**51a**	88	96	>100:1	4
13	4-BrC_6H_4	**26**	**52a**	88	99	>100:1	<1
14	2-F-4-BrC_6H_3	**29**	**55a**	70	80	39:1	9
15	4-CNC_6H_4	**31**	**57a**	84	96	>100:1	<1
16	$4\text{-NO}_2C_6H_4$	**32**	**58a**	70	92	13:1	8
17	*n*-propyl	**34**	**60a**	65	78	n.d.	9
18	*n*-octyl	**35**	**61a**	84	90	n.d.	6

[a] Unless otherwise specified, all reactions were run with 10 mol% (*S*)-VANOL-BOROX catalyst and 0.2 mmol of **2a** as a 0.05 M solution in toluene with 1.1 equiv of aldehyde at −60°C for 24 h. Reactions proceeded with 100% completion. The precatalyst was prepared by heating (*S*)-VANOL (10 mol%), H_2O (30 mol%), BH₃·SMe₂ (30 mol%) and PhOH (20 mol%) in toluene at 100°C for 1 h, followed by removal of all volatiles under high vacuum (0.1 mm Hg) for 0.5 h at 100°C. The precatalyst was treated with 1 equiv DMSO (10 mol%) in toluene for 1 h at 25°C and then cooled to −60°C, and **2a** was added as a solution in toluene prior to the addition of the aldehyde. [b] Yield of isolated product; data within parentheses are reactions run without DMSO. [c] Determined by HPLC; data within parentheses are reactions run without DMSO. [d] The *cis/trans* ratio was determined by integration of the methine protons of the *cis*- and *trans*-epoxides in the ¹H NMR spectrum of the crude reaction mixture. [e] Determined from the ¹H NMR spectrum of the crude reaction mixture with the aid of Ph₃CH as an internal standard. [f] Reaction at −40°C for 1 h. [g] Reaction at −40°C for 10 min with 5 mol% catalyst. [h] Catalyst prepared from (*S*)-BINOL. [i] Catalyst prepared from (*S*)-VAPOL. n.d. = not determined.

trans-alkenes of the type **67**. There are several asymmetric catalysts that have been reported for the asymmetric epoxidation of electron-deficient *cis*-alkenes of the type **70**, but most led to mixtures of *cis*- and *trans*-isomers and/or low asymmetric induction.[20] Two catalysts give both high diastereo- and enantioselection.[21] *cis*-Epoxides of the type **69** are desirable intermediates for access to the *syn*-diastereomer of products resulting from nucleophilic ring-opening of the epoxide, much like the case of *cis*-aziridines.[14f] A case in point is the taxol side-chain **72**.[22] Conversion of **41a** into the the ester **71** and then ring-opening with trimethylsilyl azide gives a *syn*-azido alcohol, which is benzoylated on oxygen, and upon azide reduction[23] undergoes benzoyl migration to give **72**.

The catalyst **B** for the reactions in Table 2 is not a BOROX catalyst of the type **8** since neither phenol nor water were added to the catalyst preparation protocol. From the optimized stoichiometry, **B** appears to consist of two molecules of VANOL and one boron atom, suggesting the
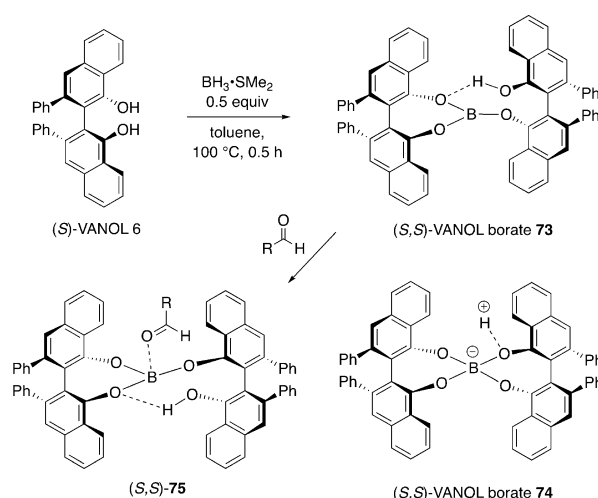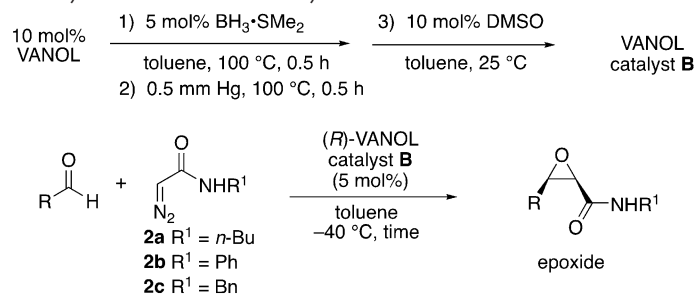

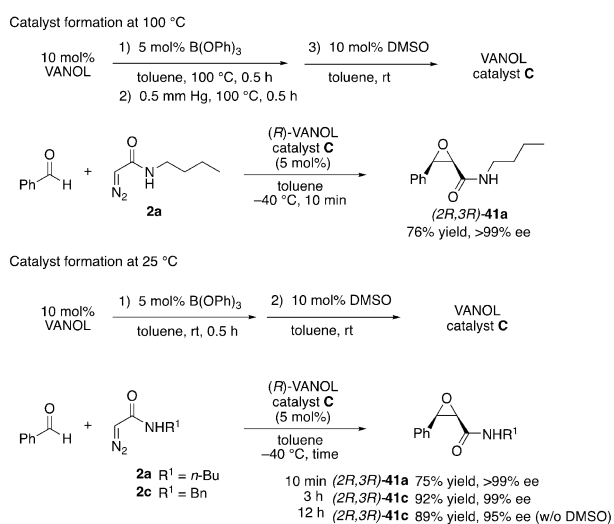***Scheme 5.*** Possible structures of the catalyst **B**.

Table 2: Asymmetric epoxidation of aldehydes with the VANOL catalyst **B**.[a]

Entry	R	Aldehyde	t [h][b]	Epoxide	Yield [%][b,c]	ee [%][b,d]
1	C_6H_5	**15**	0.17 (2)	**41a**	99 (86)	> 99 (93)
2	C_6H_5	**15**	12	**41b**	93	98
3	C_6H_5	**15**	1 (3)	**41c**	93 (98)	> 99 (97)
4[e]	C_6H_5	**15**	24	**41a**	3	n.d.
5[f]	C_6H_5	**15**	24	**41a**	13	n.d.
6	$2\text{-}MeC_6H_4$	**16**	2	**42a**	89	97
7	$4\text{-}MeC_6H_4$	**17**	0.17	**43a**	94	99
8	1-naphthyl	**18**	1	**44a**	88	97
9	2-naphthyl	**19**	0.25	**45a**	91	> 99
10	$2\text{-}MeOC_6H_4$	**20**	0.17	**46a**	92	94
11	$3\text{-}MeOC_6H_4$	**21**	0.17	**47a**	92	97
12[g]	$4\text{-}MeOC_6H_4$	**22**	24	**48a**	19	n.d.
13	$4\text{-}AcOC_6H_4$	**23**	0.25	**49a**	92	> 99
14	$2\text{-}BrC_6H_4$	**24**	0.5	**50a**	94	90
15	$2\text{-}BrC_6H_4$	**24**	(1)	**50c**	(96)	(97)
16	$3\text{-}BrC_6H_4$	**25**	0.17	**51a**	96	98
17	$4\text{-}BrC_6H_4$	**26**	0.17 (2)	**52a**	99 (72)	> 99 (90)
18	$4\text{-}BrC_6H_4$	**26**	3 (3)	**52c**	98 (91)	99 (97)
19	$3\text{-}ClC_6H_4$	**27**	0.17	**53a**	93	98
20	$3,4\text{-}Cl_2C_6H_3$	**28**	0.25	**54a**	96	99
21	$2\text{-}F\text{-}5\text{-}BrC_6H_3$	**30**	24	**56a**	82	63
22	$4\text{-}CNC_6H_4$	**31**	0.25	**57a**	98	96
23	$4\text{-}NO_2C_6H_4$	**32**	3	**58a**	87	94
24	$3\text{-}NO_2\text{-}4\text{-}ClC_6H_3$	**33**	1	**59a**	98	89
25	*n*-propyl	**34**	0.25	**60a**	87	96
26	*n*-propyl	**34**	12	**60b**	94	90
27	*n*-propyl	**34**	12	**60c**	96	> 99
28	*n*-octyl	**35**	12	**61b**	88	89
29[h]	*n*-octyl	**35**	24	**61b**	72	63
30[i]	*n*-octyl	**35**	24	**61b**	92	83
31	*n*-octyl	**35**	12 (12)	**61c**	93 (82)	> 99 (> 99)
32	cyclohexyl	**36**	12	**62b**	99	98
33	cyclohexyl	**36**	2 (1)	**62c**	99 (93)	> 99 (> 99)
34	*t*-butyl	**37**	36	**63b**	70	92
35[k]	*t*-butyl	**37**	24	**63c**	47	> 99
36	*trans*-PhCH=CH	**38**	24	**64a**	< 5	n.d.
37[j]	PhC≡C	**39**	4	**65a**	53	93
38	$CH_3(CH_2)_{12}C≡C$	**40**	24	**66a**	63	91
39	$CH_3(CH_2)_{12}C≡C$	**40**	24 (1)	**66c**	64 (75)	> 99 (93)

[a] Unless otherwise specified, all reactions were run with 5 mol% (*R*)-VANOL catalyst **B** and 0.5 mmol of **2** as a 0.1 M solution in toluene with 1.2 equiv of aldehyde at −40 °C. Reactions proceeded with 100% completion. No *trans*-epoxides could be detected in the ¹H NMR spectrum of the crude reaction mixture and the amount of ketoamide side-product was ≤ 5% in all reactions. The precatalyst was prepared by heating (*S*)-VANOL (10 mol%) and BH₃·SMe₂ (5 mol%) in toluene at 100 °C for 0.5 h, followed by removal of all volatiles under high vacuum (0.5 mm Hg) for 0.5 h at 100 °C. The precatalyst was mixed with DMSO (10 mol%) at RT in toluene and immediately cooled to −40 °C, then added to a mixture of the aldehyde and **2** and in toluene that had been pre-cooled to −40 °C. [b] Data within parentheses are for reactions runs without DMSO. [c] Yield of isolated product.
[d] Determined by HPLC on purified *cis*-epoxide. [e] Catalyst prepared from (*R*)-BINOL and gave 47% conversion. [f] Catalyst prepared from (*R*)-VAPOL and gave 73% conversion. [g] 65% conversion. [h] 20 mol% phenol added with DMSO. [i] A solution of 25 mol% BH₃·SMe₂, 20 mol% PhOH and 30 mol% H₂O was heated in toluene at 100 °C for 0.5 h and then all volatiles were removed at 100 °C at 0.5 mm Hg for 0.5 h. This mixture was added to the pre-catalyst with the DMSO as described in footnote [a]. [j] An 89% conversion of **2a**. [k] Used 10 mol% catalyst, 78% conversion.

borate species **73** with a trigonal boron (Scheme 5). Alternatively, this species could exist as **74**, which has a tetrahedral boron center that is bound to all four oxygen centers. We investigated the nature of **73/74** by computation at the B3LYP/6–31(d) level and found that this compound prefers the structure **73**, containing a trigonal-planar boron incorporating three of the phenol functions and the fourth was hydrogen bonded to an oxygen of the opposing VANOL ligand (O-H, 2.07 Å; see the Supporting Information). The B−O distance to the fourth phenol unit is too long for any significant interaction (3.47 Å vs. 1.36–1.38 Å for the other three B−O bonds). The structure **74** is higher in energy and is not a local minimum. The borate **73** presumably acts as a Brønsted acid assisted Lewis acid catalyst, or BLA catalyst (i.e., **75**), as pioneered by the group of Yamamoto with BINOL and BINOL derivatives.[12] BLA catalysts have not been previously reported for VANOL (or VAPOL). It should be noted that neither **A** nor **B** prepared from either BINOL or VAPOL are effective in this reaction (Table 1, entries 4 and 5, and Table 2, entries 4 and 5).

same asymmetric induction (99 % *ee*). Finally, it is to be noted that by employing an even simpler procedure involving catalyst formation at 25 °C and eliminating the addition of DMSO, **41c** can be obtained in the 89 % yield with only a small loss of induction from 99 to 95 % *ee*.

Catalysts **B** and **C** are thought to be the same since they both involve a 2:1 ratio of VANOL to boron. In contrast, catalysts **A** and **B** are formed from different stoichiometries of VANOL and boron and thus would be expected to be different. **A** involves a 1:3 ratio of VANOL to boron and **B** a 2:1 ratio. In addition **A** involves the addition of phenol and water. However, just because all ingredients were added, certainly does not mean that all were incorporated into the catalyst. In fact our initial thought was that **A** and **B** are the same since the asymmetric induction for each aldehyde is similar with each catalyst. To probe this issue, nonlinear studies[24] were performed to determine the relationship between the enantiomeric purity of the VANOL ligand and the enantiomeric purity of the epoxide product. We were quite surprised to find that there was a large difference between the two catalysts (Figure 1; see the Supporting
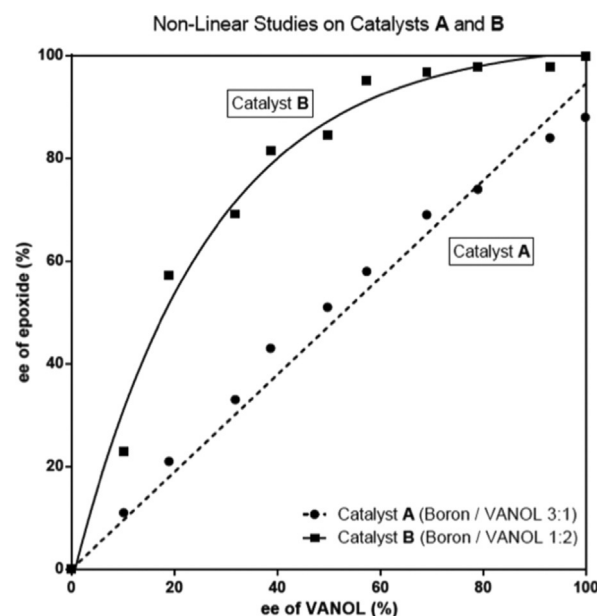

Scheme 6. Catalyst formation from B(OPh)₃ and VANOL.

Triphenylborate is an alternative to BH₃·SMe₂ as a boron source for catalyst formation and, although not always pure from commercial suppliers, it is more convenient to use. As outlined in Scheme 6, commercial B(OPh)₃ was used to generate a catalyst with a 2:1 ratio of VANOL to boron (catalyst **C**). In addition, two different protocols were investigated for catalyst formation, heating VANOL and B(OPh)₃ in toluene at 100 °C and then removal of volatiles, and a much simpler protocol involving stirring in toluene at room temperature without removing volatiles. These different protocols for catalyst formation were evaluated for the epoxidation of **15** with **2a**. The protocol with catalyst formation at 100 °C gives **41a** in greater than 99 % *ee* but with lower yield than that with the catalyst generated from BH₃·SMe₂ [76 versus 99 % (Table 2, entry 1)]. The much simpler protocol for catalyst formation at 25 °C gives the same outcome as that at 100 °C. The yield can be improved from 75 to 92 % by employing **2c** instead of **2a** while maintaining the

Figure 1. Nonlinear studies on the 3:1 and 1:2 catalysts in the reaction of **26** with **2a**.

Information). **A** displayed a linear relationship (squares), which is consistent with **8**, containing one molecule of VANOL. **B** had a strong nonlinear relationship (circles) which is consistent with **73**, containing two molecules of VANOL. The nonlinear study clearly shows that the two catalysts are not the same. The borate **73** may activate the aldehyde by coordination to the boron as in **75**. For **A** two possibilities for aldehyde activation are: 1) the boroxinate anion sequesters the two substrates by hydrogen bonding to give a species of the type **76a**, or 2) the boroxinate core is protonated, giving a neutral pyro-borate which activates the aldehyde by coordination to a Lewis-acidic boron as in structure **76b** (Scheme 7). **76a** is proposed based on similar

76a
Brønsted acid Species

76b
Lewis acid Species
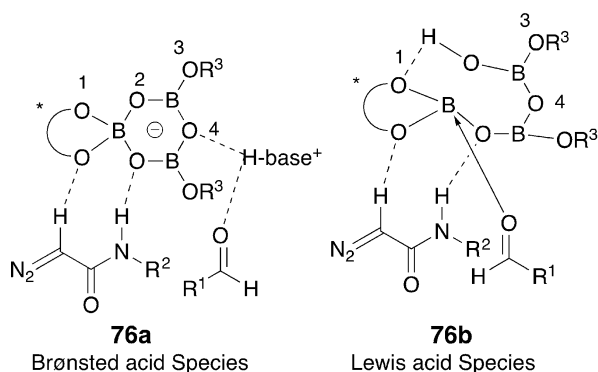
Scheme 7. Possible structures for the catalyst **A**.

hydrogen-bonding interactions observed in KIE and computational studies on BOROX-catalyzed aziridinations.[15b,17c] The structure **76b** is proposed by a similar structure reported for a BINOL borate species.[12a] Experiments will be pursued to differentiate between these two possibilities.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

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