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#### Asymmetric Catalysis

# **Catalytic Asymmetric Epoxidation of Aldehydes with Two Different Borate Catalysts of VANOL**

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

Abstract. A highly diastereoselective and enantioselective method for the epoxidation of aldehydes with  $\alpha$ -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 made to the side-chain of taxol.

The tactical repertoire for the conversion of an aldehyde or ketone to an epoxide largely consists of two transformations indicated in Scheme 1: i) the Darzens condensation of an  $\alpha$ -halo stabilized carbanion with the a carbonyl compound,<sup>1,2</sup> ii) the Corey-Chaykovsky reaction which involves a sulfur ylide as a carbene surrogate in the synthesis of epoxides.<sup>3-7</sup> A third method involving the formation of epoxides from the reactions of diazo compounds are not that common and have not been particularly useful.<sup>8,9,10</sup> However, efficient catalytic asymmetric versions have been more recently reported by Gong and coworkers for the reactions of aldehydes with secondary  $\alpha$ -diazoacetamides.<sup>1</sup> 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.  $^{\rm 11c,d}$  We report here 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 have not been engaged in aldehyde activation other than for a Diels-Alder reactions.<sup>12,13</sup>

We have 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. The diazo ester **4** reacts to give *cis*-aziridines,<sup>14</sup> whereas, the diazo acetamide **2** reacts with the same imine and with the exact same catalyst

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Scheme 1. Epoxides from Ketones and Aldehydes



EWG = electron withdrawing group

(either VANOL or VAPOL) to give *trans*- aziridines.<sup>15,16</sup> The structure of the BOROX catalyst **8**/9 for the aziridination reactions was determined to have a boroxine ring by NMR, X-ray analysis, and KIE and computational studies.<sup>15b,17a,c</sup> The BOROX catalyst can be assembled in-situ by the imine substrate from the ligand by a number of methods but the most common is either with B(OPh)<sub>3</sub> or BH<sub>3</sub>•SMe<sub>2</sub> and phenol.<sup>14e,17,18</sup> Most amines and imines are basic enough to cause assembly of the BOROX catalyst.

Scheme 2. Cis and Trans Aziridines from Imines



Attempts to utilize the BOROX catalyst for the generation of epoxides from aldehydes and ethyl diazoacetate have been unsuccessful and this is undoubtedly due to the fact that neither substrate is capable of generating the BOROX catalyst.<sup>14e</sup> First an aldehyde is not a strong enough base to assemble a BOROX catalyst. Second, ethyl diazoacetate reacts with VAPOL and B(OPh)<sub>3</sub> to only give the alkylated VAPOL derivative **14a** in 80% yield which 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)<sub>3</sub> has been previously carried out for a different purpose and the epoxide **12** (R=Ph) was only produced, inter alia, in 3% yield.<sup>14e</sup>

Scheme 3. Epoxides from Aldehydes with a BOROX catalyst?



The question remains whether the epoxidation of an aldehyde with a diazo acetamide can be effected with a BOROX catalyst. VAPOL and B(OPh)<sub>3</sub> do not react by themselves, but in the presence of diazoacetamide 2a, a reaction occurs but, 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. A number of bases were screened and many were found to be efficacious in the reaction of benzaldehyde 15 and diazoacetamide 2a including aniline and DMSO (dimethyl sulfoxide) with VANOL the optimal ligand (see supporting information).

10 mol%	<ol> <li>30 mol% BH<sub>3</sub>•SMe<sub>2</sub></li> <li>20 mol% PhOH</li> <li>30 mol% H<sub>2</sub>O</li> </ol>		3) 10 mol% DMSO	VANOL
VANOL	toluene, 1 2) 0.5 mm H	00 °C, 1 h g, 100 °C, 0.5 h	toluene, 25 °C, 1 h	catalyst A
0 ↓ +	O ↓ NH- <i>n</i> -Bu	(S)-VANOL catalyst A (10 mol%)	Å	o o ↓ ↓
R´ H	N <sub>2</sub> 2a	toluene –60 °C, 24 h	R //NH- <i>n</i> -Bu O epoxide	R NH- <i>n</i> -Bi

Table 1. Asymmetric Epoxidation of Aldehydes of VANOL Catalyst A. a

entry	R	aldehyde	epoxide	% yield epoxide <sup>b</sup>	% ee epoxide <sup>c</sup>	cis/trans <sup>d</sup>	% yield ketoamide <sup>e</sup>
1	$C_6H_5$	15	41a	88 (79)	99 (90)	>100:1	< 1 (5)
2 <sup>f</sup>	$C_6H_5$	15	41a	90 (76)	98 (72)	>50 : 1	5
3 g	$C_6H_5$	15	41a	38	90		
4 <sup>h</sup>	$C_6H_5$	15	41a	21	54		51
5 <sup>i</sup>	$C_6H_5$	15	41a	20 <sup>e</sup>	37		52
6	2-MeC <sub>6</sub> H <sub>4</sub>	16	42a	60	80	>100:1	<1
7	4-MeC <sub>6</sub> H <sub>4</sub>	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 <sub>6</sub> H <sub>4</sub>	21	47a	80	90	31:1	6
11	4-AcOC <sub>6</sub> H <sub>4</sub>	23	49a	82	97	>100:1	4
12	3-BrC <sub>6</sub> H <sub>4</sub>	25	51a	88	96	>100:1	4
13	4-BrC <sub>6</sub> H <sub>4</sub>	26	52a	88	99	>100:1	<1
14	2-F-4-BrC <sub>6</sub> H	l <sub>3</sub> 29	55a	70	80	39:1	9
15	4-CNC <sub>6</sub> H <sub>4</sub>	31	57a	84	96	>100:1	<1
16	$4-NO_2C_6H_4$	32	58a	70	92	13:1	8
17	<i>n</i> -propyl	34	60a	65	78	nd	9
18	n-octyl	35	61a	84	90	nd	6

<sup>a</sup> Unless otherwise specified, all reactions were run with 10 mol% (*S*)-VANOL-BOROX catalyst with 0.2 mmol of **2a** as 0.05 M solution in toluene with 1.1 equiv of aldehyde at –60 °C for 24 h and went to 100% completion. The pre-catalyst was prepared by heating (S)-VANOL (10 mol%), (30 mol%), BH<sub>3</sub>-SMe<sub>2</sub> (30 mol%) and PhOH (20 mol%) in toluene at 100 °C for 1 h, followed by removing all volatiles under high vacuum (0.1 mm Hg) for 0.5 h at 100 °C. The pre-catalyst was treated with 1 equiv DMSO (10 mol%) in toluene at 25 °C and then cooled to –60 °C and 2*a* was added as a solution in toluene prior to the addition of the aldehyde. <sup>b</sup> Isolated yield; Data in parentheses are reactions run without DMSO ° Determined by HPLC, Data in parentheses are reactions of the *cis*- and *trans*-epoxides in the <sup>1</sup>H NMR spectrum of the crude reaction mixture. <sup>e</sup> Determined from the <sup>1</sup>H NMR spectrum of the crude reaction mixture. <sup>e</sup> Determined at standard. <sup>I</sup> Reaction at –40 °C for 1 h. <sup>g</sup> Reaction at –40 °C for 10 min with 5 mol% catalyst. <sup>h</sup> Catalyst prepared from (5)-VAPOL.

A suitable protocol for the epoxidation of aldehydes was found which is given in Table 1. The catalyst was prepared by

heating 3 equiv BH3•SMe2, 2 equiv phenol, 1 equiv VANOL and 3 equiv H<sub>2</sub>O in toluene at 100 °C followed by exposure to high vacuum to remove volatiles and then to add 1 equiv of DMSO at With 10 mol% of this catalyst, the 25 °C for an hour. epoxidation of benzaldehyde with diazoacetamide 2a is achieved in 88% yield and 99% ee with >100:1 selectivity for the cisdiastereomer (entry 1). The formation of the cis-epoxide was unexpected since the same diazo compound gives transaziridines with imines (Scheme 2). The origins of this stereochemical outcome is not understood at the present time. Excellent asymmetric inductions were observed for the epoxidation of a number of aldehydes including electron rich and electron poor aryl aldehydes. Slightly lower inductions were observed for o-substituted aryl aldehydes (entries 6 and 14) and for aliphatic aldehydes (entry 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 8/9 that is effective in the aziridination reaction (Scheme 2)? 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 was unaffected (92% yield and 99% ee, see supporting information). This certainly means that the BOROX species 8 can't be the catalyst. After extensive additional optimization studies which are given in 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<sub>3</sub>•SMe<sub>2</sub>. A survey of aldehydes with catalyst **B** is given in Table 2.

A wide range of electron-poor and electron-rich aryl aldehydes could be epoxidized with excellent asymmetric inductions. The reaction of para-methoxybenzaldehyde is far too slow to be useful, however, its surrogate paraacetoxybenzaldehyde gives the epoxide 49a in 92% yield and 99% ee (entries 12 vs 13). With aliphatic aldehydes, it was found that asymmetric inductions of >99% ee could be realized with unbranched,  $\alpha$ -branched and  $\alpha$ , $\alpha$ -bis-branched aliphatic aldehydes (entries, 27, 31, 33, 35). The reaction could also be extended to acetylenic aldehydes with excellent inductions but not to alkenyl aldehydes (entries 36-39). The absolute configuration of **41b**, **60b** and **62b** are known<sup>10</sup> and that of **41a** was determined by conversion to the taxol side chain 72 (Scheme 4) and the rest were assumed to be homo-chiral. The reaction of diazoacetamide 2a with benzaldehyde could be scaled up ten-fold to 6.0 mmol and in 20 min gives a 95% yield of 41a (1.25 g) with >99% ee. The reaction of benzaldehyde is slightly slower (~5X) with catalyst A than it is with 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 diazo acetamides 2a and 2b, however, for the diazo acetamide 2c there a small or no difference between reactions run with or without DMSO (Table 2, entries 3, 18, 31, 33, 39).

The approach to epoxides involving the formal addition of a carbone to a carbonyl exemplified by the present work is complimentary to that which involves a formal addition of an oxygen to an  $\alpha$ , $\beta$ -unsaturated carbonyl compound (Scheme 4). A significant body of literature exists on the asymmetric epoxidation of electron-deficient alkenes.<sup>19</sup> However, most all methods involve the epoxidation of *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.<sup>20</sup> Two catalysts give both high diastereo- and enantioselection.<sup>21</sup> *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.<sup>14f</sup> A case in point is the taxol side-chain 72.<sup>22</sup> Conversion of the epoxy amide 41a to the ester 71 and then ring-opening with trimethylsilyl azide gives a *syn*-azido-alcohol which is benzoylated on oxygen and

10 mol% VANOL	<ol> <li>5 mol% BH<sub>3</sub>•SN</li> </ol>	le <sub>2</sub> 3) 10 mol%	<ol> <li>3) 10 mol% DMSO</li> </ol>		
	toluene, 100 °C, 2) 0.5 mm Hg, 100	0.5 h toluene, 0 °C, 0.5 h	, 25 °C	catalyst B	
O R <sup>⊥⊥</sup> H	0 +	( <i>R</i> )-VANOL catalyst <b>B</b> (5 mol%)	Å	Å	
	N <sub>2</sub> 2a R <sup>1</sup> = <i>n</i> -Bu	toluene –40 °C, time	R	-NHR <sup>1</sup>	
	<b>2b</b> R <sup>1</sup> = Ph		epoxide	e	
	2c R <sup>1</sup> = Bn				

entry	R	aldehyde	time (h) <sup>b</sup>	epoxide	% yield epoxide b,c	% ee epoxide <sup>b,d</sup>
1	C <sub>6</sub> H <sub>5</sub>	15	0.17 (2)	41a	99 (86)	>99 (93)
2	C <sub>6</sub> H <sub>5</sub>	15	12	41b	93	98
3	C <sub>6</sub> H <sub>5</sub>	15	1 (3)	41c	93 (98)	>99 (97)
4 <sup>e</sup>	C <sub>6</sub> H <sub>5</sub>	15	24	41a	3	_
5 <sup>f</sup>	C <sub>6</sub> H <sub>5</sub>	15	24	41a	13	_
6	2-MeC <sub>6</sub> H <sub>4</sub>	16	2	42a	89	97
7	4-MeC <sub>6</sub> H <sub>4</sub>	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-MeOC <sub>6</sub> H <sub>4</sub>	20	0.17	46a	92	94
11	3-MeOC <sub>6</sub> H <sub>4</sub>	21	0.17	47a	92	97
12 <sup>g</sup>	4-MeOC <sub>6</sub> H <sub>4</sub>	22	24	48a	19	-
13	4-AcOC <sub>6</sub> H <sub>4</sub>	23	0.25	49a	92	>99
14	2-BrC <sub>6</sub> H <sub>4</sub>	24	0.5	50a	94	90
15	2-BrC <sub>6</sub> H <sub>4</sub>	24	(1)	50c	(96)	(97)
16	3-BrC <sub>6</sub> H <sub>4</sub>	25	0.17	51a	96	98
17	4-BrC <sub>6</sub> H <sub>4</sub>	26	0.17 (2)	52a	99 (72)	>99 (90)
18	4-BrC <sub>6</sub> H <sub>4</sub>	26	3 (3)	52c	98 (91)	99 (97)
19	3-CIC <sub>6</sub> H <sub>4</sub>	27	0.17	53a	93	98
20	$3,4-Cl_2C_6H_4$	28	0.25	54a	96	99
21	2-F-5-BrC <sub>6</sub> H <sub>3</sub>	30	24	56a	82	63
22	4-CNC <sub>6</sub> H <sub>4</sub>	31	0.25	57a	98	96
23	$4-NO_2C_6H_4$	32	3	58a	87	94
24	3-NO2-4-CIC6⊦	l <sub>3</sub> 33	1	59a	98	89
25	<i>n</i> -propyl	34	0.25	60a	87	96
26	<i>n</i> -propyl	34	12	60b	94	90
27	<i>n</i> -propyl	34	12	60c	96	>99
28	n-octyl	35	12	61b	88	89
29 <sup>h</sup>	n-octyl	35	24	61b	72	63
30 <sup>i</sup>	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	<i>t</i> -butyl	37	36	63b	70	92
35 <sup>k</sup>	<i>t</i> -butyl	37	24	63c	47	>99
36	trans-PhCH=C	H 38	24	64a	< 5	
37 <sup>j</sup>	PhC <u></u> =C	39	4	65a	53	93
38	$CH_3(CH_2)_{12}C_{\equiv}$	C 40	24	66a	63	91
39	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>12</sub> C≡	C 40	24 (1)	66c	64 (75)	>99 (93)

<sup>a</sup> Unless otherwise specified, all reactions were run with 5 mol% (R)-VANOL catalyst B with 0.5 mmol of 2 as a 0.1 M solution in toluene with 1.2 equiv of aldehyde at -40 °C and went to 100% completion. No trans-epoxides could be detected in the <sup>1</sup>H NMR spectrum of the crude reaction mixture and the amount of ketoamide side-product was ≤5% in all reactions. The pre-catalyst was prepared by heating (S)-VANOL (10 mol%) and BHa•SMea (5 mol%) in toluene at 100 °C for 0.5 h. followed by removing all volatiles under high vacuum (0.5 mm Hg) for 0.5 h at 100 °C. The pre-catalyst was mixed with DMSO (10 mol%) at rt in toluene and immediately cooled to -40 °C and then added to a mixture of the aldehyde and 2 and in toluene that had been pre-cooled to -40 °C. <sup>b</sup> Data in parentheses are for reactions runs without DMSO. <sup>c</sup> Isolated yield. <sup>d</sup> Determined by HPLC on purified *cis*-epoxide. <sup>e</sup> Catalyst prepared from (R)-BINOL and gave 47% conversion. <sup>f</sup> Catalyst prepared from (R)-VAPOL and gave 73% conversion. <sup>9</sup> 65% conversion. <sup>h</sup> 20 mol % phenol added with DMSO. <sup>i</sup> A solution of 25 mol% BH<sub>3</sub>·SMe<sub>2</sub>, 20 mol% PhOH and 30 mol% H<sub>2</sub>O 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. <sup>1</sup>89% conversion of **2a**. <sup>k</sup> 10 mol% catalyst, 78% conversion.

upon azide reduction<sup>23</sup> suffers benzoyl migration giving 72.

It is clear that catalyst B for the reactions in Table 2 is not a BOROX catalyst of the type 8 since neither phenol or water

were added to the catalyst preparation protocol. From the optimized stoichiometry, catalyst B appears to consist of two molecules of VANOL and one boron atom suggesting the Scheme 4



borate species 73 with a trigonal boron (Scheme 5). Alternatively, this species could exist as 74 which has a tetrahedral boron that is bound to all four oxygens. We investigated the nature of 73/74 via computation at the level of B3LYP/6-31(d) and found that this compound prefers the structure 73 containing a trigonal planar boron incorporating three of the phenol functions and the fourth was H-bonded to an oxygen of the opposing VANOL ligand (O-H, 2.07 Å) (see 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. VANOL borate 73 presumably acts as a Brønsted acid assisted Lewis acid catalyst, Scheme 5. Possible Structures of Catalyst B



Scheme 6





Catalyst formation at 25 °C



or BLA catalyst (i.e. **75**), as pioneered by Yamamoto with BINOL and BINOL derivatives.<sup>12</sup> BLA catalysts have not been previously reported for VANOL (or VAPOL). It should be noted

that neither catalysts **A** or **B** prepared from either BINOL or VAPOL are effective in this reaction (Table 1, entries 4 & 5, Table 2, entries 4 & 5).

Triphenylborate is an alternative to BH<sub>3</sub>•SMe<sub>2</sub> 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)<sub>3</sub> was used to generated 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)<sub>3</sub> 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 benzaldehyde with diazo acetamide 2a. The protocol with catalyst formation at 100 °C gives the epoxide 41a in >99% ee but with lower isolated yield that the catalyst generated from BH<sub>3</sub>•SMe<sub>2</sub> (76% vs 99%, Table 2, entry 1). The much simpler protocol for catalyst formation at 25 °C gives the exact same outcome as that at 100 °C. The yield can be improved from 75% to 92% by employing the N-benzyl diazo acetamide 2c instead of 2a while maintaining the same asymmetric induction (99% ee). Finally, it is to be noted that by employing an even simplier procedure that involving catalyst formation at 25 °C and eliminating the addition of DMSO, the epoxide 41c can be obtained in the 89% yield with only a drop in 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. Catalyst A involves a 1:3 ratio of VANOL to boron and Catalyst B a 2:1 ratio. In addition catalyst A involves the addition of phenol and water. However, just because all of these ingredients were added certainly does not mean that all were incorporated into the catalyst. In fact our thought was that catalysts A and B are the same since the asymmetric inductions for each aldehyde are similar with each catalyst. To probe this issue, nonlinear studies<sup>24</sup> were performed to determine the relationship between



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

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, Supporting Information). Catalyst A displayed a linear relationship (squares) which would be consistent with the BOROX catalyst 8 containing one molecule of VANOL. Catalyst **B** had a strong nonlinear relationship (circles) which would be consistent with the VANOL borate 73 which contains two molecules of VANOL. The nonlinear study clearly shows that the two catalysts are not the same. VANOL borate 73 may activate the aldehyde by coordination to the boron as in structure 75. For catalyst A two possibilities for aldehyde activation are: 1) the boroxinate anion sequesters the two substrates via H-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**. The structure **76a** is proposed based on similar H-bonding interactions observed in KIE and computational studies on BOROX catalyzed aziridinations.<sup>15b,17c</sup> The structure 76b is proposed by on an similar structure reported for a BINOL borate species.<sup>12a</sup> Experiments will be pursued that can differentiate between these two possibilities.

#### Scheme 7 Possible Structures for Catalyst A



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#### REFERENCES

(1) T. Rossen in *Comprehensive Organic Synthesis*, B. M. Trost, I. Fleming, Eds.; **1991**, Vol 2, pp 409-441, Pergamon, Oxford.

(2) For recent studies on the Darzens reactions, see: (a) Z. Rapi, P. Bako, G. Keglevich, A. Szollosy, L. Drahos, A. Botyanszki, T. Holczbauer, *Tetrahedron: Asymmetry* 2012, 23, 489-496. (b) M. E. Krafft, S. J. R. Twiddle, J. W. Cran, *Tetrahedron Lett.* 2011, 52, 1277-1280. (c) Y. Liu, B. A. Provencher, K. J. Bartelson, L. Deng, *Chem. Sci.*, 2011, 2, 1301. (d) T. J. R. Achard, Y. N. Belokon, M. Ilyin, M. Moskalenko, M. North, F. Pizzato *Tetrahedron Lett.* 2007, 48, 2965-2969. (e) J.-M. Ku, M.-S. Yoo, H.-G. Park, S.-S. Jew, B.-S. Jeong, *Tetrahedron,* 2007, 63, 8099-8103. (f) S. Arai, K. Tokumaru, T. Aoyama, *Tetrahedron Lett.* 2004, 45, 1845-1848. (g) C. Palomo, M. Oiarbide, A. K. Sharma, M. C. Gonzalez-Rego, A. Linden, J. M. Garcia, A. Gonzalez, *J. Org. Chem.* 2000, 65, 9007-9012. (3) J. Aube in *Comprehensive Organic Synthesis*, B. M. Trost, I. Fleming, Eds.; 1991, Vol 1, pp 819-842, Pergamon, Oxford.
(4) For recent studies with sulfur vlides, see: (a) M. M. Lou, H. Wang, L. Song.

(4) For recent studies with suma yndes, see. (a) M. M. Dou, H. Wang, L. Song,
 H.-Y. Liu, Z.-Q. Li, X.-S. Guo, F.-G. Zhang, B. Wang, J. Org. Chem. 2016, 81,
 5915-5921. (b) F. Sarabia, C. Vivar-Garcia, M. Garcia-Castro, J. Martin-Ortiz, J.
 Org. Chem. 2011, 76, 3139-3150. (c) O. Illa, M. Arshad, A. Ros, E. M.
 McGarrigle, V. K. Aggarwal, J. Am. Chem. Soc. 2010, 132, 1828-1830. (d) T.
 Sone, A. Yamaguchi, S. Matsunaga, M. Shibasaki, J. Am. Chem. Soc. 2008, 130,
 10078. (e) V. K. Aggarwal, J. P. H. Chgarmant, D. Fuentes, J. N. Harvey, G.
 Hynd, D. Ohara, W. Picoul, R. Robiette, C. Smith, J.-L. Vasse, V. Winn, C. L. J.

Am. Chem. Soc. 2006, 128, 2105-2114. (f) M. Davoust, J.-F. Briere, P.-A. Jaffres,
 P. Metzner, J. Org. Chem. 2005, 70, 4166-4169. (g) V.K. Aggarwal, C. L. Winn,
 Acc. Chem. Res. 2004, 37, 611-620.

(5) For recent studies with ammonium ylides, see: (a) M. Waser, R. Herchl, N. Muller, *Chem. Commun.* **2011**, *47*, 2170-2172. (b) H. Kinoshita, A. Ihoriya, M. Ju-ichi, T. Kimachi, *Synlett* **2010**, 2330-2334.

(6) For recent citations to the literature with selenium ylides, see: S.-I. Watanabe, R. Hasebe, J. Ouchi, H. Nagasawa, T. Kataoka, *Tetrahedron Lett.* **2010**, *51*, 5778-5780.

(7) For recent studies with arsenic ylides, see: (a) X.-D. Jiang, S. Matsukawa, Y. Fukuzaki, Y. Yamamoto, *New J. Chem.* 2010, *34*, 1623-1629. (b) V. K. Aggarwal, M. Patel, J. Studley, *Chem. Commun.* 2002, 1514-1515.
(8) See page 832 in reference 3.

(9) (a) T. Liu, Curr. Org. Chem. 2016, 20, 19-28. (b) Z. Wang, J. Wen, Q.-W. Bi, X,-Q. Xu, Z.-Q. Shen, X.-X. Li, L. Chen, Tetrahedron Lett. 2014, 55, 2969-2972. (c) W. Li, J. Wang, X. Hu, K. Shen, W. Wang, Y. Chu, L. Lin, X. Liu, X. Feng, J. Am. Chem. Soc. 2010, 132, 8532-8533. (d) X. Xu, W. Hu, M. P. Doyle, Angew. Chem. Int. Ed. 2011, 50, 11152-11155. (e) T. Hashimoto, H. Miyamoto, Y Naganawa, K. Maruoka, J. Am. Chem. Soc. 2009, 131, 11280-11281, (f) B. M. Trost, S. Malhotra, B. A. Fried, J. Am. Chem. Soc. 2009, 131, 1674-1675. (g) T. Hashimoto, Y. Naganawa, K. Maruoka, J. Am. Chem. Soc. 2008, 130, 2434-2435. (h) K. Hasegawa, S. Arail, A. Nishida, Tetrahedron 2006, 62, 1390-1401. (i) Y. Hari, S. Tsuchida, T. Aoyama Tetrahedron Lett. 2006, 47, 1977-1980. (j) M. E. Dudley, Md. M. Morshed, C. L. Brennan, M. S. Islam, M. S. Ahmad, M.-R. Atuu, B. Branstetter, M. M. Hossain, J. Org. Chem. 2004, 69, 7599-7608. (k) A. E. Russell, J. Brekan, L. Gronenberg, M. P. Doyle, J. Org. Chem. 2004, 69, 5269-5274. (1) W. Tao, J. Wang, Org. Lett. 2003, 5, 1527-1530. (m) M. Curini, F. Epifano, M. C. Marcotullio, O. Rosati, Eur. J. Org. Chem. 2002, 1562-1565. (n) M. P. Doyle, W. H. Hu, D. J. Timmons, Org. Lett. 2001, 3, 933-935. (o) H. M. L. Davies, J. DeMeese, Tetrahedron Lett. 2001, 42, 6803-6805. (p) Z. Zhou, J. H. Espensen, J. Am. Chem. Soc. 1996, 118, 9901-9907. (q) P. De March, R. Huisgen, J. J. Amer. Chem. Soc. 1982, 104, 4952.

(10) For an interesting variation where diazo compounds are used to feed into the Corey-Chaykovsky reaction, see: O. Illa, M. Namutebi, C. Saha, M. Ostovar, C. C. Chen, M. F. Haddow, S. Nocquet-Thibault, M. Lusi, E. M. McGarrigle, V. K. Aggarwal, *J. Am. Chem. Soc.* **2013**, *135*, 11951.

(11) (a) W.-J. Liu, B.-D. Lv, L.-Z. Gong, Angew. Chem. Int. Ed. 2009, 48, 6503-6506. (b) L. He, W.-J. Liu, L. Ren, T. Lei, L.-Z. Gong, Adv. Synth. Catal. 2010, 352, 1123-1127. Two other titanium complex have also been reported; (c) G. Liu, D. Zhang, J. Li, G. Xu, J. Sun, Org. Biomol. Chem. 2013, 11, 900-904. d) G.-L. Chai, J.-W. Han, H. N. C. Wong, Synthesis, 2017, 49, 181-187.

(12) (a) K. Ishihara, M. Miyata, K. Hattori, T. Tada, H. Yamamoto, J. Am. Chem. Soc. 1994, 116, 10520-10524. (b) K. Ishihara, H. Yamamoto, J. Am. Chem. Soc. 1994, 116, 1561-1562. (c) K. Ishihara, H. Kurihara, H. Yamamoto, J. Am. Chem. Soc. 1996, 118, 3049-3050. (d) K. Ishihara, S. Kondo, H. Kurihara, H. Yamamoto, S. Ohashi, S. Inagaki, J. Org. Chem. 1997, 62, 3026-3027. (e) K. Ishihara, H. Kurihara, M. Maatsumoto, H. Yamamoto, J. Am. Chem. Soc. 1998, 120, 6920-6930.

13) a) D. Kaufmann, R. Boese, *Angew. Chem. Int. Ed. Engl.* 1990, 29, 545-546.
b) S. Thormeier, B. Carboni, D. E. Kaufmann, *J. Organometal. Chem.*, 2002, 657, 136-145.

(14) (a) Y. Zhang, Z. Lu, W. D. Wulff, Synlett, 2009, 2715-2739. (b) Y. Zhang, A. Desai, Z. Lu, G. Hu, Z. Ding, W. D. Wulff, Chem. Eur. J. 2008, 14, 3785-3803.
(c) M. Mukherjee, A. K. Gupta, Z. Lu, Y. Zhang, W. D. Wulff, J. Org. Chem. 2010, 75, 5643-5660. (d) A. K. Gupta, M. Mukherjee, W. D. Wulff, Org. Lett. 2011, 13, 5866-5869. (e) A. K. Gupta, M. Mukherjee, G. Hu, W. D. Wulff, J. Org. Chem. 2012, 77, 7932-7944. (f) M. Mukherjee, Y. Zhou, A. K. Gupta, Y. Guan, W. D. Wulff, *Eur. J. Org. Chem.* 2014, 1386-1390.

(15) (a) A. Desai, W. D. Wulff, J. Am. Chem. Soc. 2010, 132, 13100-13103. (b)
M. Vetticatt, A. Desai, W. D. Wulff, J. Am. Chem. Soc. 2010, 132, 13104-14107.
(c) L. Huang, Y. Zhang, R. J. Staples, R. H. Huang, W. D. Wulff, Chem. Eur. J. 2012, 18, 5302-5313.

(16) For related catalytic asymmetric synthesis of *trans*-aziridines, see: (a) T. Hashimoto, N. Uchiyama, K. Maruoka, J. Am. Chem. Soc. 2008, 130, 14380. (b) X. Zeng, X. Zeng, Z. Xu, M. Lu, G. Zhong, Org. Lett. 2009, 11, 3036. (c) T. Hashimoto, A. O. Galvez, K. Maruoka, J. Am. Chem. Soc. 2013, 135, 17667. (17) (a) G. Hu, A. K. Gupta, R. H. Huang, M. Mukherjee, W. D. Wulff, J. Am. Chem. Soc. 2010, 132, 14669-14675. (b) G. Hu, L. Huang, R. H. Huang, W. D. Wulff, J. Am. Chem. Soc. 2009, 131, 15615. (c) Vetticatt, M. J.; Desai, A. A.; Wulff, W. D. J. Org. Chem. 2013, 78, 5142.

(18) W. Zhao, L. Huang, Y. Guan, W. D. Wulff, Angew. Chem. Int. Ed. 2014, 53, 3436-3441.

(19) (a) M. J. Porter, J. Skidmore, *Org. React.* **2009**, *74*, 425-672. (b) See A. Lattanzi in *Catalytic Asymmetric Conjugate Reactions*, A. Cordova, Ed.; WILEY-VCH, **2010**. (c) R. L. Davis, J. Stiller, T. Naicker, H. Jiang, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2014**, *53*, 7406-7426.

(20) For esters and amides see: (a) E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, L. Deng, J. Am. Chem. Soc. 1991, 113, 7063. (b) L. Deng, E. N. Jacobsen, J. Org. Chem. 1992, 57, 4320. (c) E N. Jacobsen, L. Deng, Y. Furukawa, L. E. Martinez, Tetrahedron, 1994, 50, 4323. (d) X.-Y. Wu, X. She, Y. Shi, J. Am. Chem. Soc. 2002, 124, 8792. (e) R. Imashiro, M. Seki, J. Org. Chem. 2004, 69, 4216. (f) S. Matsunga, T. Kinoshita, S. Okada, S. Harada, M. Shibasaki, J. Am. Chem. Soc. 2004, 126, 7559. (g) S. Liao, B. List, B., Angew. Chem. Int. Ed. 2010,

49, 628. (h) O. Cusso, I. Garcia-Bosch, X. Ribas, J. Lloret-Fillol, M. Costas, J.
Am. Chem. Soc. 2013, 135, 14871. For ketones: (i) S. Watanabe, T. Arai, H. Sasai,
M. Bougauchi, M. Shibasaki, J. Org. Chem. 1998, 63, 8090-8091. (j) T. Nemoto,
T. Ohshima, K. Yamaguchi, M. Shibasaki, J. Am. Chem. Soc. 2001, 123, 2725-2732. (k) B. Lygo, S. D. Gardiner, M. C. McLeod, D. C. M. To Org. Biomol. Chem. 2007, 5, 2283-2290.

(21) (a) O. Cusso, I. Garcia-Bosch, X. Ribas, J. Lloret-Fillol, M. Costas, *J. Am. Chem. Soc.* **2013**, *135*, 14871. (b) S. Watanabe, T. Arai, H. Sasai, M. Bougauchi, M. Shibasaki, *J. Org. Chem.* **1998**, *63*, 8090-8091.

(22) For a recent synthesis of 72, see: Y. Jiang, X. Chen, Y. Zheng, Z. Xue, C. Shu, W. Yuan, X. Zhang, *Angew. Chem. Int. Ed.* 2011, *50*, 7304-7307.
(23) D. Lubriks, I. Sokolovs, E. Suna, *J. Am. Chem. Soc.* 2012, *134*, 15436.
(24) C. Girard, H. B. Kagan, *Angew. Chem. Int. Ed.* 1998, *37*, 2922.

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#### Asymmetric Catalysis

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Catalytic Asymmetric Epoxidation of Aldehyde with Two Different Borate Catalysts of VANOL



**A Tale of Two Catalysts** Two different and effective borate catalysts for the epoxidation of aldehydes with diazoacetamides can be generated with either a 3:1 or 1:2 ratio of boron to VANOL. That these catalysts are different is demonstrated by a non-linear study (see graph) on the relationship of the enantiopurity of the product epoxide versus that of the VANOL ligand. Yet despite their structural differences, both catalysts display a strikingly similar substrate scope profile with excellent asymmetric inductions over a series various aryl and aliphatic aldehydes.