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Controlled Diastereo- and Enantioselection in a Catalytic Asymmetric Aziridination

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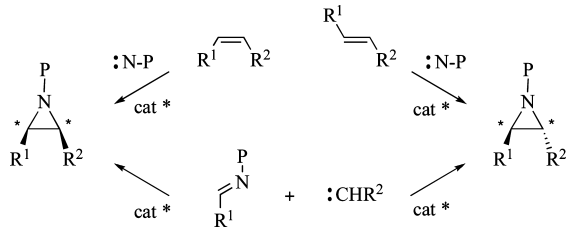
Abstract: Chiral polyborate based Brønsted acids prepared from the VANOL and VAPOL ligands are known to catalyze the reaction of diarylmethyl imines with diazoesters to give *cis*-aziridines. In the present work, this same catalyst is shown to catalyze the reaction of the same imines with diazoacetamides to give *trans*-aziridines with the same high asymmetric inductions as seen with *cis*-aziridines, enabling the development of an unprecedented universal catalytic asymmetric aziridination protocol. The substrate scope is broad and includes imines prepared from both electron-rich and electron-poor aromatic aldehydes and also from 1°, 2°, and 3° aliphatic aldehydes. The face selectivity of the addition to the imine was found to be independent of the diazo compounds. The (*S*)-VANOL or (*S*)-VAPOL derived catalyst will cause both diazoesters and diazoacetamides to add to the *Si*-face of the imine when *cis*-aziridines are formed and both to add to the *Re*-face of the imine when *trans*-aziridines are formed.

The development of methods for the catalytic asymmetric synthesis of aziridines has lagged behind related developments for the synthesis of epoxides.[1] Considerations in design of chiral catalysts for aziridination have focused on two disconnects; formal addition of a nitrene to an olefin or the formal addition of a carbene to an imine (Scheme 1). The nature of these disconnections has consequences for control of enantioselection as well as diastereoselection. In the nitrene approach, control of diastereoselectivity can in principle be exercised by proper selection of the olefin geometry, but in practice this has not been realized in a general way in catalytic asymmetric methods.[2] Control of diastereoselectivity in the formal addition of carbenes to imines would on the surface appear to be more daunting but, nonetheless, could be possible via either catalyst control or substrate control.

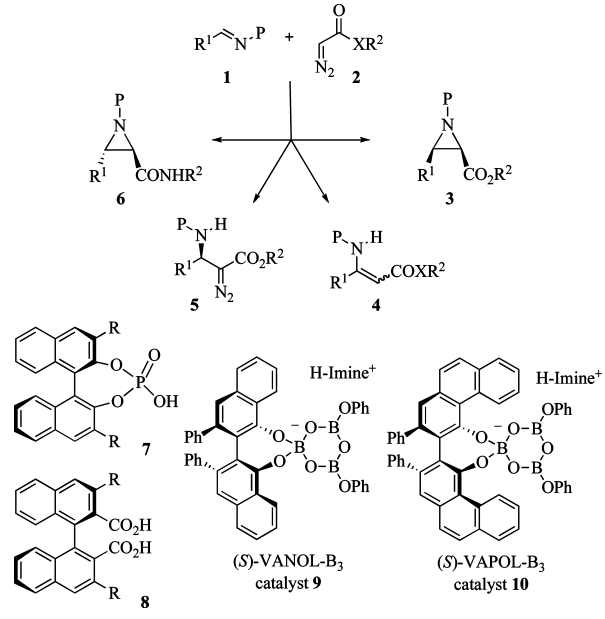
Scheme 1



Within the construct of the formal addition of a carbene to an imine, several efficient asymmetric catalytic systems have been developed for the synthesis of *trans*-aziridines,[3,4] as have those for *cis*-aziridines.[5,6] However, there is no protocol in the literature that can selectively provide access to both *cis*- and *trans*-aziridines from the same imine and the same chiral catalyst.[7] The development of such a universal catalytic asymmetric aziridination protocol has remained an elusive, albeit an actively pursued goal of several research groups.

Many of the most successful catalysts for the asymmetric aziridination of imines with diazo carbonyl compounds, to give *trans*-[3e,f] and *cis*-aziridines,[5g,h,6] are chiral Brønsted acids. As a whole, the reactions of imines and diazo compounds mediated by these Brønsted acid catalysts have not necessarily been chemoselective for aziridines.[8] The BINOL hydrogen phosphate catalysts **7** (Scheme 2) will cause the reactions of imines **1** (P = *p*-$Me_2NC_6H_4CO$) with α-diazoacetate esters to give the C−H insertion products **5**.[9a] The same is true for the BINOL bis-carboxylic acid **8** catalyzed reactions of *N*-Boc imines **1** with α-diazoacetate esters.[9b] In contrast, both of the chiral Brønsted acids **7** and **8** give *trans*-aziridines **6** upon catalysis of the reaction of *N*-Boc imines **1** with α-diazoacetamides.[3e,f] The enamines **4** were noted as side products in these reactions. We have developed a catalytic asymmetric synthesis of *cis*-aziridines **3** from the imines **1** and α-diazoacetate esters over the past few years[1c,6] and recently have presented evidence that the VAPOL derived catalyst for these reactions is a chiral Brønsted acid that contains the boroxinate core indicated in structure **10**.[6i,10] Inspired by the work of Hashimoto, Uchiyama, and Maruoka,[3e] we were compelled to examine the effect of this boroxinate catalyst on the reaction of imines **1** with α-diazoacetamides to find a single unprecedented universal protocol that would selectively give both *cis*- and *trans*-aziridines from the same imine with the same chiral catalyst.

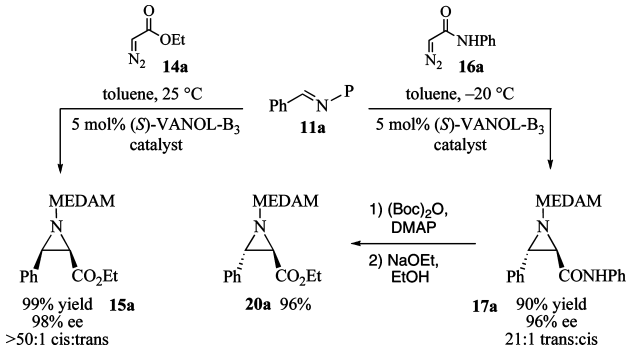
Scheme 2



In the event, the reaction of the imine **11a** with diazoacetamide **16a** gave a 90% yield of isolated pure *trans*-aziridine **17a** in 96% ee

10.1021/ja1038648

Scheme 3



with 5 mol % of the VANOL boroxinate catalyst **9** (Scheme 3).[10] The reaction of the same imine with ethyl diazoacetate **14a** under the aegis of the same catalyst gave a 99% isolated yield of the pure *cis*-aziridine **15a** in 98% ee.[11] The *trans*-aziridine carboxamide **17a** was converted to the *trans*-aziridine carboxylic ester **20a** in 96% yield. Thus, with the proper choice of chirality of the ligand, all four stereoisomers of 3-phenyl-2-carboxylates, synthetic intermediates of seminal importance in organic synthesis,[1a] are now available in high yields as well as high diastereoselectivity and enantioselectivity from the same imine substrate and the same catalyst. The next question is whether this can be extended to all 3-substituted aziridine carboxylates.

The optimized protocol of the *trans*-aziridination of the standard imine **11a** from benzaldehyde with the diazoacetamide **16a** is shown in Scheme 3 and is the culmination of a systematic variation of

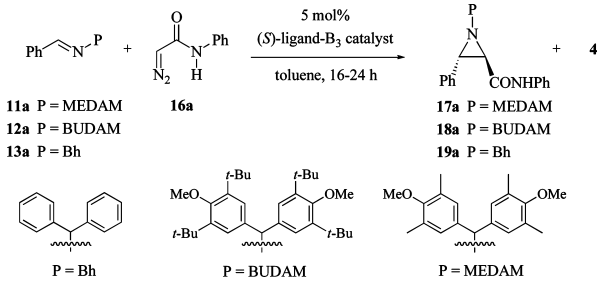


Table 1. Optimization of *Trans*-Aziridination with Boroxinate Catalysts **9** and **10**[a]

entry	P	ligand	temp (°C)	% yield enamines[b]	trans/ cis[b]	% yield *trans*-azir[c]	% ee *trans*-azir[d]
1	MEDAM	(*S*)-VANOL	−20	5	21:1	90	96
2[e]	MEDAM	(*S*)-VANOL	0	8	12:1	84	90
3[f]	MEDAM	(*S*)-VANOL	25	8	5:1	71	88
4[g]	MEDAM	(*R*)-VANOL	0	10	12:1	81	−92
5	MEDAM	(*S*)-VAPOL	0	20	4:1	63	70
6	BUDAM	(*S*)-VANOL	0	10	16:1	75	91
7	BUDAM	(*R*)-VAPOL	0	21	5:1	35	−51
8[h]	Bh	(*S*)-VANOL	0	12	9:1	47	77
9[i]	Bh	(*R*)-VAPOL	0	17	12:1	65	−69

[a] Unless otherwise specified, all reactions were performed on a 0.2 mmol scale in toluene at 0.2 M in imine with 1.3 equiv of diazoamide for 16−24 h and went to 100% completion at the indicated temperature. Catalyst was prepared by heating 1 equiv of ligand, 3 equiv of $BH_3 \cdot SMe_2$, 2 equiv of PhOH, and 3 equiv of H_2O in toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mm Hg. [b] Determined from the ^1H NMR spectrum of the crude reaction mixture. [c] Isolated yield of pure *trans*-aziridine after silica gel column chromatography. [d] Chiral HPLC. [e] Average of five runs. Reaction complete in 9 h. [f] The *cis*-aziridine **29a** was isolated in 14% yield and 77% ee. [g] 1 mmol scale. [h] 65% completion. [i] 91% completion.

several parameters, some of which are shown in Table 1. Interestingly, the asymmetric induction for the catalyst derived from the VAPOL ligand is significantly lower than that from the VANOL ligand (entry 2 vs 5). This is in stark contrast to the *cis*-aziridinations with ethyl diazoacetate where the two ligands give essentially the same inductions over a range of substrates.[6g,h] The nitrogen substituent plays a larger role in affecting the asymmetric induction for the *trans*-aziridination than for the *cis*-aziridination. The MEDAM and BUDAM groups were both superior to the benzhydryl group which gave aziridine **19a** in only 77% ee with the VANOL catalyst and 69% ee with the VAPOL catalyst (entries 8 and 9). This is in contrast to the reaction of benzhydryl imine **13a** with ethyl diazoacetate which gave the *cis*-aziridine in 93−94% ee with both the VANOL and VAPOL catalysts.[6g] The *trans*-aziridination with the MEDAM and BUDAM imines gave comparable results (entries 2 and 6), but the MEDAM substituent survived selection since it shows higher inductions over a range of substrates in the *cis*-aziridination.[6j]

With the initial optimization complete, attention was turned to the exploration of the generality of this asymmetric catalytic *trans*-aziridination protocol. In the secondary diazoacetamide screen (Table 2), both aryl and alkyl groups performed well. Both electron-rich and electron-deficient phenyl substituents on the nitrogen gave excellent results (entries 3 and 4). Alkyl diazoacetamides **16e** and **16f** were outstanding substrates and gave near perfect asymmetric inductions under their optimized conditions (entries 8 and 10).

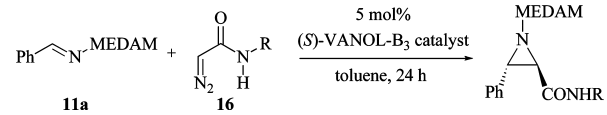


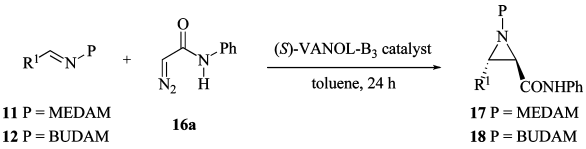
Table 2. *Trans*-Aziridination of Secondary Diazoacetamides[a]

Entry	R (**16**)	temp (°C)	*trans*-aziridine	trans/ cis[b]	% yield *trans*-azir[c]	% ee *trans*-azir[d]
1[e]	Ph (**16a**)	0	**17a**	12:1	84	90
2	Ph (**16a**)	−20	**17a**	21:1	90	96
3[f]	4-$MeOC_6H_4$ (**16b**)	0	**24a**	13:1	80	92
4	4-ClC_6H_4 (**16c**)	0	**25a**	13:1	82	92
5[g]	4-$CF_3C_6H_4$ (**16d**)	0	**26a**	8:1	58	78
6[f]	Bn (**16e**)	0	**27a**	3:1	61	94
7	Bn (**16e**)	−20	**27a**	5:1	78	97
8[h]	Bn (**16e**)	−40	**27a**	10:1	88	98
9[f]	*n*-Bu (**16f**)	0	**28a**	4:1	64	96
10[i]	*n*-Bu (**16f**)	−20	**28a**	8:1	84	−98

[a] Unless otherwise specified, all reactions were performed on a 0.2 mmol scale in toluene at 0.2 M in imine with 1.3 equiv of diazoamide for 24 h and went to 100% completion at the indicated temperature. Catalyst was prepared as indicated in Table 1. The majority of the rest of the mass balance was due to enamines (3−13% as determined by ^1H NMR analysis on the crude reaction mixture). [b] Determined from the ^1H NMR spectrum of the crude reaction mixture. [c] Isolated yield of pure *trans*-aziridine after silica gel column chromatography. [d] Chiral HPLC. [e] Average of five runs. Reaction complete in 9 h. [f] Average of two runs. [g] 10 mol % catalyst. Reaction went to 77% completion in 48 h. [h] 10 mol % catalyst. [i] Reaction with (*R*)-VANOL gives the enantiomer of **28a**.

The scope of the *trans*-aziridination reaction of *N*-phenyl diazoacetamide **16a** is presented in Table 3. A wide range of aromatic imines with varying electronic and steric demands gave excellent diastereoselectivities, yields, and asymmetric inductions for the corresponding *trans*-aziridines. Sterically demanding and functionally rich substrates such as imines **11d** and **11e** worked exceedingly well, with the former providing 74% yield and 95% ee (entry 8) and the latter, 84% yield and 98% ee (entry 10) for their corresponding *trans*-aziridine products. Both electron-rich and electron-deficient aryl imines were tolerated. The imine **11j** bearing

the 4-methoxyphenyl moiety had failed for other *trans*-selective aziridination catalysts giving complex mixtures or low conversions.[3e,f] With the boroxinate catalyst **9**, however, this substrate performed quite well, affording the corresponding *trans*-aziridine **17j** in 66% yield and 94% ee (entry 17).



11 P = MEDAM
12 P = BUDAM
16a
17 P = MEDAM
18 P = BUDAM

Table 3. *Trans*-Aziridination of Aryl and Alkyl Aldimines with **16a**[a]

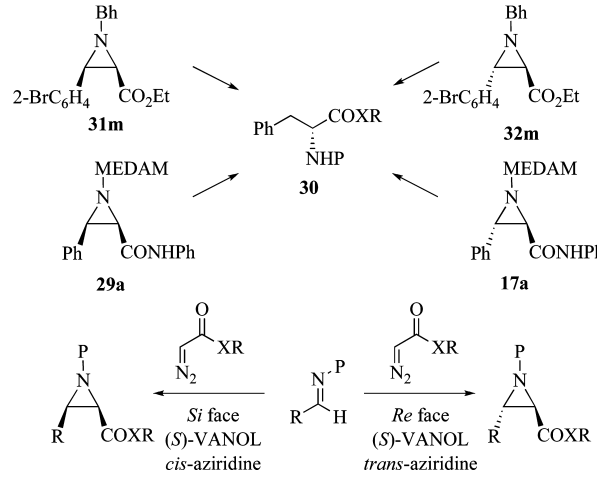
entry	R^1	temp (°C)	mol % catalyst	aziridine	trans/cis[b]	% yield *trans*-azir[c]	% ee *trans*-azir[d]
1[e]	Ph (**11a**)	0	5	**17a**	12:1	84	90
2	Ph (**11a**)	−20	5	**17a**	21:1	90	96
3	4-$NO_2C_6H_4$ (**11b**)	0	5	**17b**	11:1	80	92
4[f,g]	4-$NO_2C_6H_4$ (**11b**)	−20	5	**17b**	19:1	83	93
5[f]	4-BrC_6H_4 (**11c**)	0	5	**17c**	17:1	86	96
6[h]	4-BrC_6H_4 (**11c**)	−20	5	**17c**	36:1	74	99
7[f,i]	4-Br-2-FC_6H_3 (**11d**)	0	5	**17d**	5:1	64	91
8	4-Br-2-FC_6H_3 (**11d**)	−20	10	**17d**	7:1	74	95
9[f]	2-ClC_6H_4 (**11e**)	0	5	**17e**	13:1	77	90
10[j]	2-ClC_6H_4 (**11e**)	−20	10	**17e**	26:1	84	−98
11[f,k,l]	2-naphthyl (**11f**)	0	10	**17f**	7:1	80	81
12[f,j]	4-MeC_6H_4 (**11g**)	0	5	**17g**	14:1	84	−95
13[f,l]	3-MeC_6H_4 (**11h**)	0	5	**17h**	10:1	81	84
14[l]	3-MeC_6H_4 (**11h**)	−20	20	**17h**	12:1	87	90
15[f,l]	3-$MeOC_6H_4$ (**11i**)	0	5	**17i**	10:1	76	93
16[l]	3-$MeOC_6H_4$ (**11i**)	−20	10	**17i**	9:1	74	97
17[f]	4-$MeOC_6H_4$ (**11j**)	0	15	**17j**	7:1	66	94
18[j]	ethyl (**12k**)	0	10	**18k**	nd[m]	67	−82
19[f]	ethyl (**12k**)	0	20	**18k**	nd[m]	67	88
20[f,n]	*iso*-propyl (**12l**)	0	10	**18l**	nd[m]	69	82
21[f,n]	*tert*-butyl (**12m**)	−20	10	**18m**	>50:1	89	90

[a] Unless otherwise specified, all reactions were typically performed on a 0.2 mmol scale in toluene at 0.2 M in imine with 1.3 equiv of diazoamide for 24 h and went to 100% completion at the indicated temperature. Catalyst was prepared as indicated in Table 1. The majority of the rest of the mass balance for the reactions of aryl imines was due to enamines (3−17%) as determined by ^{1}H NMR analysis on the crude reaction mixture. Enamines not identified for reactions of alkyl imines. [b] Determined from the ^{1}H NMR spectrum of the crude reaction mixture. [c] Isolated yield of pure *trans*-aziridine after silica gel column chromatography. [d] Chiral HPLC. [e] Average of five runs. Reaction complete in 9 h. [f] Average of two runs. [g] 94% completion. [h] 82% completion. [i] 87% completion. [j] Catalyst prepared from (*R*)-VANOL. [k] Reaction went to 62% completion with 5 mol % catalyst. [l] The imine was used without purification. [m] Not determined due to complex alkyl region in the ^{1}H NMR spectrum of the crude reaction mixture. [n] Catalyst prepared from (*S*)-VAPOL.

Imines prepared from 1°, 2°, and 3° aliphatic aldehydes provide excellent results in the *cis*-aziridination[6g,h] with the boroxinate catalysts **9** and **10**; thus in the development of a general *trans*-selective aziridination protocol, inclusion of aliphatic imines was a certain desideratum. It was found that BUDAM was the protecting group of choice for the alkyl substrates. Gratifyingly, the 1° alkyl (ethyl), 2° alkyl (iso-propyl), and 3° alkyl (*tert*-butyl) substrates all performed well and could be optimized (2° and 3° with the VAPOL catalyst) to provide good yields and good to excellent levels of asymmetric inductions for the corresponding *trans*-aziridine products (entries 18−21). The previous reports[3e,f] of asymmetric *trans*-aziridinations with imines were both with *N*-Boc imines, and examples of imines derived from aliphatic aldehydes were not included.

The absolute configurations of the aziridine products were determined as indicated in Scheme 4. The *cis*- and *trans*-aziridine

Scheme 4



carboxamides **29a** and **17a** were both isolated from the reaction with the (*S*)-VANOL catalyst under the conditions shown in entry 3 of Table 1. The absolute configuration of a *trans*-aziridine from the *cis*-selective aziridination reaction with a VANOL or VAPOL catalyst with ethyl diazoacetate has not been previously determined. The only example we have found where a substantial proportion of the *trans*-aziridine is formed is from the benzhydryl imine of 2-bromobenzaldehyde.[6g] As was the case with aziridines **29a** and **17a**, the aziridines **31m** and **32m** were isolated from a reaction promoted by the (*S*)-VANOL catalyst. All of these aziridines were correlated to **30** by catalytic hydrogenation, and all were found to have an *R*-configuration at the 2-position.

This indicates that the face selectivity in addition to the imine is independent of the nature of the diazo compound. With the (*S*)-enantiomer of VANOL, both ethyl diazoacetate **14a** and diazoacetamide **16a** undergo addition to the *Si*-face when the *cis*-aziridine is formed and addition to the *Re*-face when the *trans*-aziridine is formed. Thus, not only was the diastereoselectivity (cis vs trans) completely reversed in going from **14a** to **16a**, the face selectivity to the imine was also reversed on going from *cis*- to *trans*-aziridines. The origins of these stereoselectivity changes are intriguing and not readily obvious and are the subject of the succeeding communication.

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Supporting Information Available: Synthetic procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006. (b) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905–2919. (c) Zhang, Y.; Lu, Z.; Wulff, W. D. *Synlett* **2009**, 2715–2739. (d) Pellissier, H. *Tetrahedron* **2010**, *66*, 1509.
(2) Stereochemical loss has been observed for *cis*-olefins; for a discussion see ref 1b.
(3) (a) Aggarwal, V. K.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Org. Chem.* **1996**, *61*, 8368. (b) Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1433. (c) Aggarwal, V. K.; Ferrara, M.; O'Brien, C. J.; Thompson, A.; Jones, R. V. H.; Fieldhouse, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1635. (d) Aggarwal, V. K.; Vasse, J.-L. *Org. Lett.* **2003**, *5*, 3987. (e) Hashimoto, T.; Uchiyama, N.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 14380–14381. (f) Zeng, X.; Zeng, X.; Xu, Z.; Lu, M.; Zhong, G. *Org. Lett.* **2009**, *11*, 3036.
(4) For an example of azirdination/ring opening, see: Valdez, S. C.; Leighton, J. L. *J. Am. Chem. Soc.* **2009**, *131*, 14638.
(5) (a) Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 676. (b) Rasumussen, K. G.; Jørgensen, K. A. *J. Chem.*

Soc., Perkin Trans. 1 **1997**, 1287. (c) Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2293. (d) Mayer, M. F.; Hossain, M. M. *J. Organomet. Chem.* **2002**, *654*, 202. (e) Krumper, J. R.; Gerisch, M.; Suh, J. M.; Bergman, R. G.; Tilley, T. D. *J. Org. Chem.* **2003**, *68*, 9705. (f) Redlich, M.; Hossain, M. M. *Tetrahedron Lett.* **2004**, *45*, 8987. (g) Wipf, P.; Lyon, A. M. *ARKIVOC* **2007**, *xii*, 91. (h) Akiyama, T.; Suzuki, T.; Mori, K. *Org. Lett.* **2009**, *11*, 2445. (i) Ranocchiari, M.; Mezzetti, A. *Organometallics* **2009**, *28*, 3611.

(6) (a) Antilla, J. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1999**, *121*, 5099–5100. (b) Antilla, J. C.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4518–4521. (c) Loncaric, C.; Wulff, W. D. *Org. Lett.* **2001**, *3*, 3675–3678. (d) Patwardan, A.; Pulgam, V. R.; Zhang, Y.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 6169–6172. (e) Deng, Y.; Lee, Y. R.; Newman, C. A.; Wulff, W. D. *Eur. J. Org. Chem.* **2007**, 2068–2071. (f) Lu, Z.; Zhang, Y.; Wulff, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 7185–7194. (g) Zhang, Y.; Desai, A.; Lu, Z.; Hu, G.; Ding, Z.; Wulff, W. D. *Chem.—Eur. J.* **2008**, *14*, 3785–3803. (h) Zhang, Y.; Lu, Z.; Desai, A.; Wulff, W. D. *Org. Lett.* **2008**, *10*, 5429–5432. (i) Hu, G.; Huang, L.; Huang, R. H.; Wulff, W. D. *J. Am. Chem. Soc.* **2009**, *131*, 15615–15617. (j) Mukherjee, M.; Gupta, A. K.; Lu, Z.; Zhang, Y.; Wulff, W. D. *J. Org. Chem.* **2010**, *75*, 5643.

(7) The same can be said for the catalytic asymmetric synthesis of epoxides from the formal addition of a carbene to a carbonyl compound. For citations to the literature, see: Liu, W.-J.; Lv, B.-D.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2009**, *48*, 6503.

(8) For an expert navigation through this field, see: Johnston, J. N.; Muchalski, H.; Troyer, T. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2290.

(9) (a) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*, 9360. (b) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054.

(10) Spectral data in support of the VANOL-B_3 boroxinate species **9** is presented in the succeeding communication.

(11) See the succeeding communication.

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